Psychiatry Research 273 (2019) 624–630

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Sleep-disordered breathing and Alzheimer's disease: A nationwide cohort study

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A R T I C L E I N F O

Keywords:
Sleep-disordered breathing
Alzheimer's disease
Dementia
Propensity score matching (PSM)

A B S T R A C T

Sleep-disordered breathing (SDB) is common and can lead to significant cognitive decline, such as Alzheimer's disease (AD). Therefore, the present study was conducted to investigate whether SDB is associated with AD onset. This study used the nationwide health check-up cohort data between 2002 and 2015. The study population comprised individuals who were diagnosed with SDB and those without SDB who were matched by using propensity score. The matched cohort was followed up until the onset of AD, death, or end of 2015. A multivariate Cox proportional hazard model was used in the analysis. There were 727 (16.7%) patients in the SDB group between 2002 and 2005 and 3635 subjects (83.3%) in the propensity score-matched non-SDB group. After adjusting for the possible confounding variables, patients with SDB were almost 1.58 times more likely to develop AD than those without SDB (hazard ratio [HR] = 1.575, 95% confidence interval [CI] = 1.013–2.448). The present study showed that SDB was associated with an onset of AD. The findings of this study highlight the importance of the interventions to raise awareness of SDB and the need for the government's support to reduce the barrier in accessing appropriate SDB treatment.

1. Introduction

One person is diagnosed with dementia in Korea every 12 min. According to the Ministry of Health and Welfare, the number of patients with dementia in 2017 was estimated to be about 700,000 and is expected to increase rapidly to 1 million by 2024 (Kim, 2018). The rate of the increase in the number of patients with dementia in Korea has been reported to be 4.5 times faster than that in Organization for Economic Co-operation and Development (OECD) countries (Kim, 2017). According to the OECD report, Alzheimer's disease (AD) is the most common cause of dementia, accounting for approximately 60–80% of cases of dementia (Organization for Economic Co-operation and Development, 2017). According to the Nationwide Survey on the Dementia Epidemiology 2012 in Korea, the prevalence of Alzheimer's disease was 6.5%, accounting for 71.3% of dementia (National Institute of Dementia, 2012). AD is more common in aging populations. There has been a growing interest in AD and its modifiable risk factors, such as cardiovascular disease (CVD), hypertension, Type 2 diabetes mellitus (DM), depression, obesity, smoking, low physical activity, and drinking. Reducing these modifiable risk factors can prevent AD. Recently, an association between sleep-disordered breathing (SDB) and AD has been suggested (Chang et al., 2013; Pan and Kastin, 2014).

SDB, which is a condition characterized by abnormal respiratory patterns or insufficient ventilation during sleep, is a common sleep disorder that can lead to many adverse health outcomes, such as hypertension, diabetes, heart attack, and cognitive impairment (Barsh et al., 1993; Leng et al., 2017; Parati et al., 2016; Sánchez et al., 2017). According to previous studies, the prevalence of SDB is estimated to be 27% and 16% in middle-aged Korean men and women, respectively (Kim et al., 2004), and 24% and 15% in middle-aged American men and women, respectively (Korean Society of Otorhinolaynglolgy-Head and Neck Surgery, 2016). Fortunately, there are highly effective treatments for SDB; they include continuous positive airway pressure (CPAP), which is known as the gold standard therapy for SDB (Carlucci et al., 2015). Although SDB is a treatable condition and can cause many health problems if left untreated, 85% of people with treatable SDB have never been diagnosed (Somers et al., 2008). As the gold standard for diagnosing SDB, polysomnography, is costly and limited accessibility, it is not possible to screen all patients suspected of having SDB. SDB can be classified as mild, moderate, and severe defined by

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https://doi.org/10.1016/j.psychres.2019.01.086
Received 4 July 2018; Received in revised form 24 January 2019; Accepted 25 January 2019
Available online 28 January 2019
0165-1781/

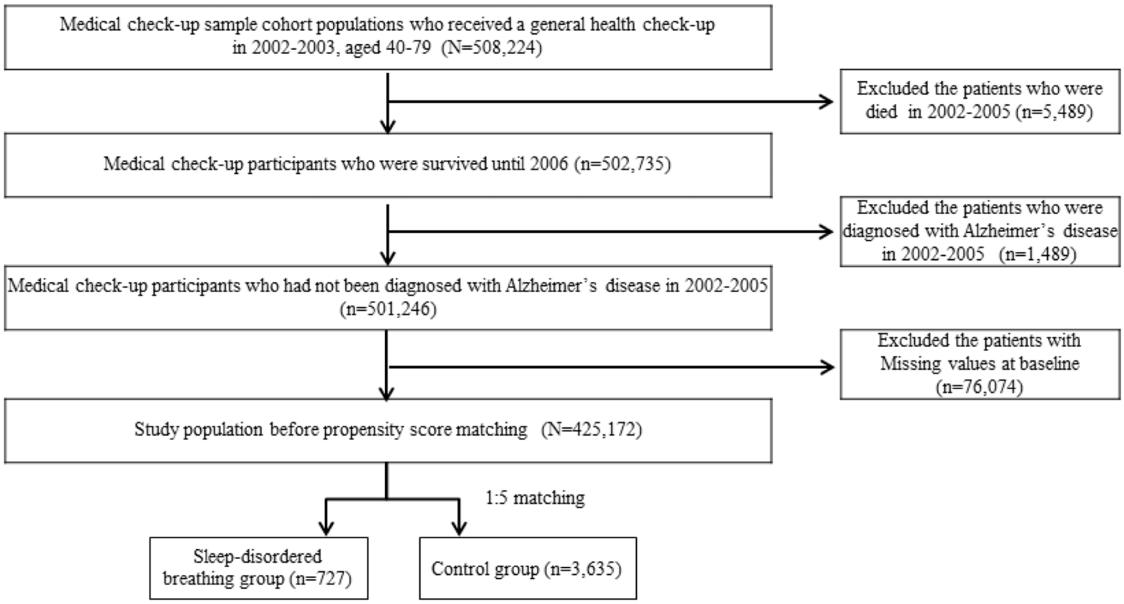

Fig. 1. Flow chart of study population selection.

breathing stoppages 5–15 per hour, 15–30 per hour, and over 30 per hour. Untreated SDB can lead to increased healthcare expenditures amounting to billions of dollars worldwide (AlGhanim et al., 2008).

Recent studies have shown a direct association between SDB and cognitive impairment (Aoki et al., 2014; Osorio et al., 2015). However, the association between SDB and AD remains controversial, and only few longitudinal studies have been performed in an Asian population (Gottlieb et al., 2010; Kendzerska et al., 2014). Similar results were obtained between Western and Asian studies, most studies showed SDB patients were more likely to have cognitive impairment (Chang et al., 2013; Osorio et al., 2015; Yaffe et al., 2011) while some studies that showed no significant association (Blackwell et al., 2015; Foley et al., 2003) On the other hand, SDB is more prevalent among Asian people than Caucasians (Al Lawati et al., 2009; Dudley and Patel, 2016). Despite people with the similar age and body mass index (BMI), Asian people tend to have more severe SDB than Caucasians (Lee et al., 2010). Most of the previous studies have investigated the cross-sectional relationship between SDB and cognitive decline in patients at sleep clinics (Ju et al., 2012; Liguori et al., 2017b; Saunamäki et al., 2009). Recently, there have been few population-based studies on the association between SDB and AD. However, these recent studies have investigated longitudinal cohorts with short-term follow-up and have not evaluated the health behaviors that are known to be risk factors for AD (Osorio et al., 2015; Yaffe et al., 2011).

Therefore, the present study was conducted to investigate whether SDB is associated with the onset of AD, using representative nationwide cohort data with a 14-year follow-up. Both SDB and AD are of crucial national concern, but SDB is a social problem that is in the medical blind spot; it is important to investigate whether SDB, which is treatable, increases the risk of AD. By estimating the association between SDB and AD, this study can provide useful evidence for the need for AD prevention strategy, such as intervention to treat SDB.

2. Methods

2.1. Participants

The present study used the health check-up cohort data from the National Health Insurance Service (NHIS) claims between 2002 and 2015. The study population comprised about 10% of the 5.15 million subjects aged 40–79 years who participated in the national medical check-up between 2002 and 2003. The NHIS cohort data includes all claims data; general health examination results, which are updated every 2 years; and health examination results specified for life-turning points, such as reaching the age of 40 or 66 years between 2002 and 2015. Subjects who were diagnosed with AD ($N = 1489$) or died ($N = 5489$) between 2002 and 2005 were excluded from the cohort sample (Fig. 1). The study groups comprised the SDB group ($N = 727$) and the control group ($N = 3635$). The SDB group comprised patients who were diagnosed with SDB between 2002 and 2005. On the other hand, subjects without SDB were randomly selected to form the control group. Subjects without SDB were matched to subjects with SDB at a ratio of 5:1 by sex, age, index date (the date of first diagnosis), CVD, hypertension, type 2 DM, depression, BMI, smoking status, physical activity, and drinking by using propensity scoring and the stepwise algorithm. The matched cohort was followed up until onset of AD, death, or end of 2015. The cohort data included information on demographic characteristics, medical utilization, medical check-up, and health behavior.

2.2. Variables

The outcome variable was the incidence of AD. In this study, incidence of AD was identified using the 10th revision of the International Classification of Diseases (ICD) codes in the medical records (ICD-10: G30). The present study tried to measure the risk of SDB to the development of AD patients except the existing patients. Therefore, patients who had AD during the first 4 years (2002–2005) were excluded, to estimate the incidence of AD, the outcome variable. SDB, which was the primary independent variable, was identified using the SDB diagnosis (ICD-10: G47.3) or surgical intervention for SDB, CPAP treatment, or bilevel positive airway pressure treatment. Other independent variables were sex, age, income level, CVD, hypertension, type 2 DM, depression, BMI, smoking status, physical activity, and alcohol drinking. CVD included coronary heart disease, cerebrovascular disease, heart failure, and peripheral arterial disease. BMI was classified as underweight

Table 1
Baseline characteristics of patients with sleep-disordered breathing (SDB) and control group subjects in 2002–2005.

	Controls		Patients with SDB		*p* -value
	N(%)	Mean ± SD	*N*(%)	Mean ± SD	
Sex					
Men	2772	(83.2)	560	(16.8)	0.6902
Women	863	(83.8)	167	(16.2)	
Age (years)					
40–49	1805	(83.6)	355	(16.4)	0.5317
50–59	1214	(82.7)	254	(17.3)	
60–69	509	(83.2)	103	(16.8)	
≥70	107	(87.7)	15	(12.3)	
Income level					
~30%	500	(83.3)	100	(16.7)	0.7944
31–60%	677	(82.7)	142	(17.3)	
61–80%	689	(82.6)	145	(17.4)	
81–100%	1769	(83.9)	340	(16.1)	
CVD					
No	2688	(82.9)	553	(17.1)	0.2515
Yes	947	(84.5)	174	(15.5)	
Hypertension					
No	2122	(82.9)	438	(17.1)	0.3714
Yes	1513	(84.0)	289	(16.0)	
DM					
No	2639	(82.9)	543	(17.1)	0.2658
Yes	996	(84.4)	184	(15.6)	
Depression					
No	3195	(83.0)	656	(17.0)	0.0843
Yes	440	(86.1)	71	(13.9)	
Body mass index (BMI) (kg/m^2)					
<18.5	15	(75.0)	5	(25.0)	0.7947
18.5–22.9	645	(83.6)	127	(16.5)	
23–24.9	1023	(83.3)	205	(16.7)	
≥25	1952	(83.4)	390	(16.7)	
Smoking status					
Never smoked	2055	(83.7)	399	(16.3)	0.6633
Former smoker	527	(82.3)	113	(17.7)	
Current smoker	1053	(83.0)	215	(17.0)	
Physical activity					
Low	2793	(83.3)	560	(16.7)	0.9836
Moderate	479	(83.6)	94	(16.4)	
High	363	(83.3)	73	(16.7)	
Drinking					
Non-drinker	1772	(82.9)	365	(17.1)	0.7708
Moderate drinker	1028	(83.8)	199	(16.2)	
Heavy drinker	835	(83.7)	163	(16.3)	
Total	3635	(83.3)	727	(16.7)	

Matched by sex, age, index date, CVD, hypertension, DM, depression, BMI, smoking status, physical activity, drinking, and index date for SDB (the date of first diagnosis).
CVD, cardiovascular disease; DM, diabetes mellitus.

(BMI < 18.5 kg/m^2), normal (18.5–22.9 kg/m^2), overweight (23–24.9 kg/m^2), and obese (≥25 kg/m^2) (Barba et al., 2004). Smoking status was categorized as never smoked, former smoker, and current smoker. Physical activity was classified as low (less than 3 days per week), moderate (3 to less than 5 days per week), and high (more than 5 days per week) (Seong et al., 2017; Shin et al., 2018). Alcohol drinking was classified as no alcohol drinking, moderate drinking (up to 14 drinks per week for men and up to 7 drinks per week for women), or heavy drinking (15 drinks or more per week for men and 8 drinks or more per week for women).

2.3. Statistical analysis

To reduce bias, propensity score matching (PSM) was performed. The propensity score matching eliminates systematic differences between groups (Austin et al., 2007). For all covariates that matched the propensity score, the sample that matched the propensity score was found to be similar (Stuart, 2010). Therefore, propensity score matching can reduce the selection bias in observational studies. After PSM, the chi-square test was used to assess differences in the proportions between the SDB and control groups. To estimate the influence of SDB on AD onset, Kaplan–Meier survival curves and Cox proportional hazard models were used. All analyses in this study were performed using SAS 9.4 version.

3. Results

The baseline characteristics of patients with SDB and the matched controls are shown in Table 1. Of all participants who had national health check-up in 2002–2005, the patients who were diagnosed with SDB were 0.17% (Appendix Table A.1). There were 727 (16.7%) subjects diagnosed with SDB between 2002 and 2005 and 3635 (83.3%) propensity score-matched subjects in the non-SDB group. After matching, 3332 (76.4%) were men and 1030 (23.6%) were women. Almost half (49.5%) of subjects in the baseline population were 40–49 years old, 33.7% were 50–59 years old, 14.0% were 60–69 years old, and 2.8% were older than 70 years; subjects with AD and those who died were excluded. Patients with SDB tended to have comorbidities such as CVD (25.7%), hypertension (41.3%), and diabetes (27.1%). About 53.7% were obese, 28.2% were overweight, 17.7% had normal weight, and 0.5% were underweight. In addition, most patients (76.9%) tended to have low physical activity, 13.1% had moderate activity, and 10.0% had high activity. Because the SDB and control groups were matched for socioeconomic characteristics, comorbidities, and health behaviors, the proportions of these variables in the two groups were similar.

Kaplan–Meier curves of the incidence of AD based on the presence of SDB showed differences. The log-rank test showed that the SDB group had a higher risk of AD than the non-SDB group (log-rank test $p < 0.0422$) (Fig. 2).

Table 2 shows the results of the Cox proportional hazard model of AD incidence. After adjusting for the possible confounding variables, the incidence of AD was significantly higher among patients with SDB than in those without SDB (hazard ratio [HR] = 1.575, 95% confidence interval [CI] = 1.013–2.448). In addition, the elderly people had a higher incidence of AD than the younger ones (HR = 4.527, 95% CI = 2.133–9.609 for patients in the 50s; HR = 19.404, 95% CI = 9.406–40.028 for patients in the 60s; HR = 49.190, 95% CI = 22.352–108.252 for patients older than 70 years). Furthermore, patients who were underweight had a higher incidence of AD (HR = 5.963, 95% CI = 1.394–25.505).

4. Discussion

Reducing the prevalence of AD can be a powerful strategy to minimize the burden of AD (World Health Organization, 2015). Although the Korean government's economic support for dementia has greatly improved, there is little interest or support for the prevention of dementia. To reduce the economic burden on patients with dementia, the government pays for 90% of the medical cost of dementia (Ministry of Health and Welfare, 2017). However, if the government is only urged to reduce the burden of patients with dementia (including AD), it may be trying to fill a bottomless pit (Lee, 2017). AD has no cure or effective treatment, but the risk of AD can be reduced by addressing the modifiable risk factors for AD. A major trend in major OECD countries' policies on dementia is precautionary community protection and home-care services (World Health Organization, 2015). Some countries have prioritized the reduction of the incidence and prevalence

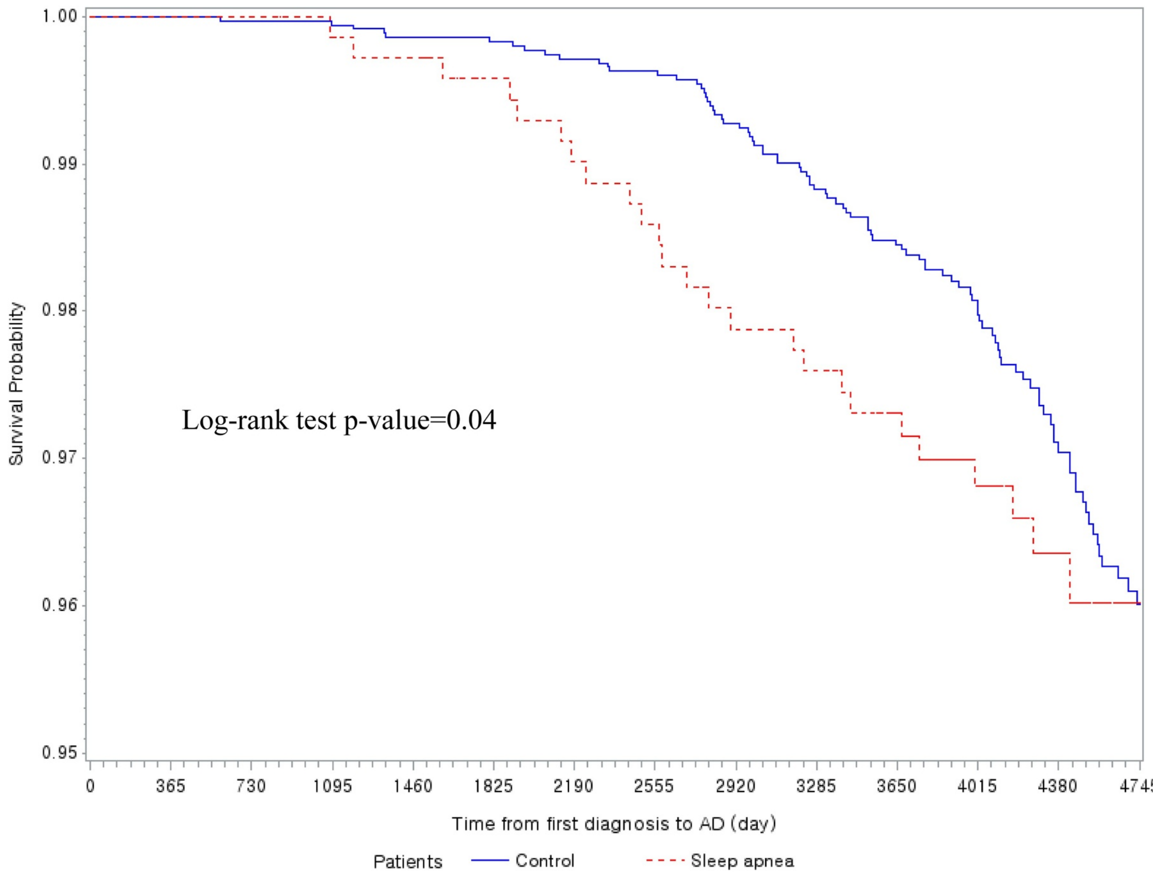

Fig. 2. Kaplan–Meier curves of the incidence of Alzheimer's disease in subjects with and without sleep-disordered breathing.

of dementia; however, recognition of the modifiable risk factors for AD among policymakers and the general population is insufficient in many countries, including Korea.

Age is the greatest risk factor for AD, but recent studies have showed that SDB can play a role in AD pathology (Liguori et al., 2017a; Lucey and Bateman, 2014). SDB can bring out early amendable neuropathological AD biomarker changes, such as amyloid-β (Liguori et al., 2017b). Amyloid-β is a major component of amyloid plaques found in the brain of Alzheimer's patients and is critically involved in Alzheimer's disease (Hamley, 2012). Recently, it has been hypothesized that SDB can be regarded as a preclinical condition of AD (Liguori et al., 2017a).

This study investigated whether SDB is associated with the onset of AD using the national cohort data because SDB is common as well as treatable. The results of this study indicate that SDB is associated with a higher risk of AD onset after matching and adjusting for other risk factors.

The association between SDB and cognitive impairment or AD remains controversial, and few longitudinal studies have been conducted in an Asian population. The main finding of the present study is similar to findings from previous studies, which have indicated that SDB patients are at a higher risk of developing cognitive impairment or incident AD. Most of these studies were performed as case-control studies in sleep clinic patients (Ancoli-Israel et al., 2008; Liguori et al., 2017b; Pan and Kastin, 2014). Some of the studies were community-based studies, but these were limited by a cross-sectional analysis or a shortage of clinical information, such as the presence of comorbidities (Dlugaj et al., 2014; Ramos et al., 2015; Spira et al., 2008). On the other hand, there have been other studies that have found no association between SDB and cognitive decline (Foley et al., 2003; Lutsey et al., 2016; PROOF study group, 2015).

This study has several limitations. First, the data used in the present study consisted of a population aged 40–79 years between 2002 and 2003. Therefore, this study could not determine whether the findings in middle-aged and elderly populations are applicable in all age groups (including the youth). However, SDB and AD are mostly incident in the middle-aged and elderly populations. In addition, recent findings have indicated there is a relationship between SDB and AD in the elderly people. Second, general health check-ups are typically performed every 2 years, but the risk factors that are measured in health check-ups may be measured at different times because the timing and frequency of screening may vary between individuals. However, since the cohort comprised only participants who had a national medical check-up between 2002 and 2003, the difference in the measurement period was up to 2 years. In addition, because this study identified the main variables using the claim data with diagnosis dates, the limitation of the data would have had little effect. Third, this study could not include F00 code, because the claim data used in this study masked some sensitive patients' information such as mental and behavior disease (F00-F99). Therefore, only G30 code was available to identify Alzheimer's disease in this study. Fourth, there might have been a selection bias because the cohort data included data from participants who underwent general health check-up between 2002 and 2003. However, this study used the nationwide representative cohort data, and PSM was conducted to

Table 2
Multivariate Cox proportional hazard model of the incidence of Alzheimer's disease in 2006–2013.

	Alzheimer's disease (AD)		
	HR	95% CI	
Sleep-disordered breathing			
No	1.000		
Yes	1.575	1.013	2.448
Sex			
Men	1.000		
Women	1.085	0.710	1.658
Age (years)			
40–49	1.000		
50–59	4.527	2.133	9.609
60–69	19.404	9.406	40.028
≥70	49.190	22.352	108.252
Income level			
~30%	1.062	0.643	1.756
31–60%	1.205	0.782	1.857
61–80%	0.602	0.335	1.082
81–100%	1.000		
CVD			
No	1.000		
Yes	1.392	0.913	2.122
Hypertension			
No	1.000		
Yes	1.116	0.708	1.758
DM			
No	1.000		
Yes	1.134	0.780	1.648
Depression			
No	1.000		
Yes	1.422	0.942	2.147
Body mass index (BMI) (kg/m^2)			
<18.5	5.963	1.394	25.505
18.5–22.9	1.000		
23–24.9	0.996	0.604	1.642
≥25	0.722	0.447	1.166
Smoking status			
Never smoked	1.000		
Former smoker	0.870	0.482	1.572
Current smoker	1.061	0.614	1.831
Physical activity			
Low	1.001	0.606	1.653
Moderate	0.778	0.375	1.614
High	1.000		
Drinking			
Non-drinker	1.000		
Moderate drinker	0.720	0.423	1.224
Heavy drinker	0.977	0.560	1.706

CVD, cardiovascular disease; DM, diabetes mellitus.

reduce the bias. Fifth, the prevalence of SDB in the claim data was low compared with the prevalence of SDB determined using the apnea-hypopnea index ≥5(Jee and Jeon, 2016; Young et al., 1993). This might be because the prevalence of SDB in this study was based on SDB diagnosed by physicians only. Therefore, the effect of SDB might have been underestimated if the percentage of subjects with undiagnosed SDB was high. In particular, the prevalence of doctor-diagnosed SDB was lower in subjects with a low income level in this study population. Last, definition of SDB would have been more refined if we used the 3rd Edition International Classification of Sleep Disorders (ICSD). However, 6th edition of Korean Standard Classification of Diseases (KCD) used in the data is operated on the basis of ICD-10 and unlike the subdivision of ICD-10-CM, this study could not apply ICSD-3rd Edition. The ICD tends to cluster different disorders together while the ICSD divides related disorders into multiple categories.

Despite these limitations, the present study has important strengths. First, to our knowledge, this study is the first longitudinal study with a large sample size and long-term follow-up in Korea. Few longitudinal studies with Asian population have been conducted compared to those involving Western populations (Chang et al., 2013; Foley et al., 2003). Only cross-sectional studies or longitudinal studies with small sample sizes in sleep clinic patients have been conducted in Korea (Ju et al., 2012; Kang et al., 2012; Kim et al., 2013). Second, this study considered both diagnosed comorbidities and important health behaviors. Because this study used claims data, information about diseases and treatments was more reliable than self-reported data. In addition to the accuracy of claims data, the data used in this study also included information on health behaviors that are modifiable risk factors for AD. Therefore, the present study could obtain reliable and robust findings compared to findings from prior studies in Korea. Third, to reduce potential bias, PSM was performed. The patients with SDB and subjects in the control group were matched by confounders such as sex, age, index date (the date of first diagnosis), CVD, hypertension, type 2 DM, depression, BMI, smoking status, physical activity, and drinking by using propensity score and stepwise algorithm.

5. Conclusion

The present study showed that SDB is associated with the onset of AD based on the results from a nationwide representative cohort data. The study findings suggest that there is a need for interventions to raise awareness that SDB is not just snoring but can cause adverse health consequences, such as AD. Furthermore, the government's support for reducing the barrier in accessing appropriate SDB treatment is necessary, because the investigation of SDB and its treatment, such as CPAP, are expensive. Although it is well known that health-related behaviors are difficult to change, medical treatment of disease that has a gold standard treatment such as CPAP is relatively easy, and it can be powerful in the public health approach to modify health-related risk factors. The findings of this study highlight the need for improved preventive strategy for AD, such as intervention to treat SDB, which is a treatable risk factor; these strategies are necessary to delay the onset of AD or to slow the progression of AD.

Ethics approval

Institutional review board (IRB) of Ajou Hospital (IRB No.:AJIRB-SBR-EXP-18-087)

Consent for publication

The authors declared no conflicts of publication of this article.

Availability of data and material

The data used in this study are available at https://nhiss.nhis.or.kr/bd/ay/bdaya001iv.do.

Conflicts of interest

None declared.

Funding

The present study received no financial support.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.01.086.

Appendix

Table A.1

Table A.1
Baseline characteristics for patients with SDB and control group in 2002–2005 before propensity score matching.

	Controls		Patinets with SDB		*p* -value
	N(%)	Mean ± SD	*N*(%)	Mean ± SD	
Sex					
Men	210,162	(99.73)	560	(0.27)	< 0.0001
Women	214,283	(99.92)	167	(0.08)	
Age					
40–49	187,006	(99.81)	355	(0.19)	< 0.0001
50–59	122,008	(99.79)	254	(0.21)	
60–69	87,666	(99.88)	103	(0.12)	
≥70	27,765	(99.95)	15	(0.05)	
Income level					
~30%	97,264	(99.90)	100	(0.10)	< 0.0001
31 ~ 60%	99,165	(99.86)	142	(0.14)	
61 ~ 80%	87,939	(99.84)	145	(0.16)	
81 ~ 100%	140,077	(99.76)	340	(0.24)	
CVD					
No	344,098	(99.84)	553	(0.16)	< 0.0001
Yes	80,347	(99.78)	174	(0.22)	
hypertension					
No	285,275	(99.85)	438	(0.15)	< 0.0001
Yes	139,170	(99.79)	289	(0.21)	
DM					
No	326,591	(99.83)	543	(0.17)	< 0.0001
Yes	97,854	(99.81)	184	(0.19)	
Depression					
No	388,616	(99.83)	656	(0.17)	< 0.0001
Yes	35,829	(99.80)	71	(0.20)	
Body mass index (BMI)					
< 18.5	10,082	(99.95)	5	(0.05)	< 0.0001
18.5–22.9	151,217	(99.92)	127	(0.08)	
23–24.9	114,764	(99.82)	205	(0.18)	
≥25	148,382	(99.74)	390	(0.26)	
Smoking status					
Never smoker	297,962	(99.87)	399	(0.13)	< 0.0001
Former smoker	32,608	(99.65)	113	(0.35)	
Current smoker	93,875	(99.77)	215	(0.23)	
Physical activity					
Low	346,776	(99.84)	560	(0.16)	0.0021
Moderate	37,484	(99.75)	94	(0.25)	
High	40,185	(99.82)	73	(0.18)	
Drinking					
Non-drinker	272,131	(99.87)	365	(0.13)	< 0.0001
Moderate drinker	90,343	(99.78)	199	(0.22)	
Heavy drinker	61,971	(99.74)	163	(0.26)	
Total	424,445	(99.83)	727	(0.17)	

References

Al Lawati, N.M., Patel, S.R., Ayas, N.T., 2009. Epidemiology, risk factors, and consequences of obstructive sleep apnea and short sleep duration. Prog. Cardiovasc. Dis. 51 (4), 285–293.

AlGhanim, N., Comondore, V.R., Fleetham, J., Marra, C.A., Ayas, N.T., 2008. The economic impact of obstructive sleep apnea. Lung 186 (1), 7–12.

Ancoli-Israel, S., Palmer, B.W., Cooke, J.R., Corey-Bloom, J., Fiorentino, L., Natarajan, L., Liu, L., Ayalon, L., He, F., Loredo, J.S., 2008. Cognitive effects of treating obstructive sleep apnea in Alzheimer's disease: a randomized controlled study. J. Am. Geriatr. Soc. 56 (11), 2076–2081.

Aoki, K., Matsuo, M., Takahashi, M., Murakami, J., Aoki, Y., Aoki, N., Mizumoto, H., Namikawa, A., Hara, H., Miyagawa, M., 2014. Association of sleep-disordered breathing with decreased cognitive function among patients with dementia. J. Sleep Res. 23 (5), 517–523.

Austin, P.C., Grootendorst, P., Anderson, G.M., 2007. A comparison of the ability of different propensity score models to balance measured variables between treated and untreated subjects: a Monte Carlo study. Stat. Med. 26 (4), 734–753.

Barba, C., Cavalli-Sforza, T., Cutter, J., Darnton-Hill, I., 2004. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 363 (9403), 157.

Blackwell, T., Yaffe, K., Laffan, A., Redline, S., Ancoli-Israel, S., Ensrud, K.E., Song, Y., Stone, K.L., 2015. Associations between sleep-disordered breathing, nocturnal hypoxemia, and subsequent cognitive decline in older community-dwelling men: the osteoporotic fractures in men sleep study. J. Am. Geriatr. Soc. 63 (3), 453–461.

Carlucci, A., Ceriana, P., Mancini, M., Cirio, S., Pierucci, P., Lupo, N.D.A., Gadaleta, F., Morrone, E., Fanfulla, F., 2015. Efficacy of bilevel-auto treatment in patients with obstructive sleep apnea not responsive to or intolerant of continuous positive airway pressure ventilation. J. Clin. Sleep Med. JCSM Off. Publ. Am. Acad. Sleep Med. 11 (9), 981.

Chang, W.-P., Liu, M.-E., Chang, W.-C., Yang, A.C., Ku, Y.-C., Pai, J.-T., Huang, H.-L., Tsai, S.-J., 2013. Sleep apnea and the risk of dementia: a population-based 5-year follow-up study in Taiwan. PLoS One 8 (10), e78655.

Dlugaj, M., Weinreich, G., Weimar, C., Stang, A., Dragano, N., Wessendorf, T.E., et al., 2014. Sleep-disordered breathing, sleep quality, and mild cognitive impairment in the general population. J. Alzheimer's Dis. 41 (2), 479–497.

Dudley, K.A., Patel, S.R., 2016. Disparities and genetic risk factors in obstructive sleep

apnea. Sleep Med. 18, 96–102.
Foley, D.J., Masaki, K., White, L., Larkin, E.K., Monjan, A., Redline, S., 2003. Sleep-disordered breathing and cognitive impairment in elderly Japanese-American men. Sleep 26 (5), 596–599.
Barsh, L.I., 1993. Sleep-disordered breathing. N. Engl. J. Med. 329 (19), 1429–1440.
Gottlieb, D.J., Yenokyan, G., Newman, A.B., O'connor, G.T., Punjabi, N.M., Quan, S.F., Redline, S., Resnick, H.E., Tong, E.K., Diener-West, M., 2010. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. Circulation 122 (4), 352–360.
Hamley, I.W., 2012. The amyloid beta peptide: a chemist's perspective. Role in Alzheimer's and fibrillization. Chem. Rev. 112 (10), 5147–5192.
Jee, S., Jeon, H., 2016. Management of frequent sleep problem after stroke. Brain NeuroRehabil. 9 (1), 20–24.
Ju, G., Yoon, I.Y., Lee, S.D., Kim, T.H., Choe, J.Y., Kim, K.W., 2012. Effects of sleep apnea syndrome on delayed memory and executive function in elderly adults. J. Am. Geriatr. Soc. 60 (6), 1099–1103.
Kang, E.W., Abdel-Kader, K., Yabes, J., Glover, K., Unruh, M., 2012. Association of sleep-disordered breathing with cognitive dysfunction in CKD stages 4-5. Am. J. Kidney Dis. 60 (6), 949–958.
Kendzerska, T., Mollayeva, T., Gershon, A.S., Leung, R.S., Hawker, G., Tomlinson, G., 2014. Untreated obstructive sleep apnea and the risk for serious long-term adverse outcomes: a systematic review. Sleep Med. Rev. 18 (1), 49–59.
Kim, H., Yun, C.-H., Thomas, R.J., Lee, S.H., Seo, H.S., Cho, E.R., Lee, S.K., Yoon, D.W., Suh, S., Shin, C., 2013. Obstructive sleep apnea as a risk factor for cerebral white matter change in a middle-aged and older general population. Sleep 36 (5), 709–715.
Kim, J., In, K., Kim, J., You, S., Kang, K., Shim, J., et al., 2004. Prevalence of sleep-disordered breathing in middle-aged Korean men and women. Am. J. Respir. Crit. Care Med. 170 (10), 1108–1113.
Kim, K.W., 2017. Trends in Research and Policy for Dementia Biotech Policy Research Center. Daejeon, pp. 1–15.
Kim, K.W., 2018. National Institute of Dementia Annual Report 2017. National Institute of Dementia, Gyung-gi, pp. 1–63.
Korean Society of Otorhinolaynglolgy-Head and Neck Surgery, 2016. Sleep apnea. Korea Centers for Disease Control and Prevention.
Lee, M.W., 2017. Problems and Complement of Implementation of Dementia State Responsibility System, Current issue and analysis. National Assembly Research Service.
Lee, R.WW., Vasudavan, S., Hui, D.S., Prvan, T., Petocz, P., Darendeliler, M.A., Cistulli, P.A., 2010. Differences in craniofacial structures and obesity in Caucasian and Chinese patients with obstructive sleep apnea. Sleep 33 (8), 1075–1080.
Leng, Y., McEvoy, C.T., Allen, I.E., Yaffe, K., 2017. Association of sleep-disordered breathing with cognitive function and risk of cognitive impairment: a systematic review and meta-analysis. JAMA Neurol. 74 (10), 1237–1245.
Liguori, C., Chiaravalloti, A., Izzi, F., Nuccetelli, M., Bernardini, S., Schillaci, O., Mercuri, N.B., Placidi, F., 2017a. Sleep apnoeas may represent a reversible risk factor for amyloid-β pathology. Brain 140 (12), e75.
Liguori, C., Mercuri, N.B., Izzi, F., Romigi, A., Cordella, A., Sancesario, G., Placidi, F., 2017b. Obstructive sleep apnea is associated with early but possibly modifiable Alzheimer's disease biomarkers changes. Sleep 40 (5), 1–10.
Lucey, B.P., Bateman, R.J., 2014. Amyloid-β diurnal pattern: possible role of sleep in Alzheimer's disease pathogenesis. Neurobiol. Aging 35, S29–S34.
Lutsey, P.L., Bengtson, L.GS., Punjabi, N.M., Shahar, E., Mosley, T.H., Gottesman, R.F., Wruck, L.M., MacLehose, R.F., Alonso, A., 2016. Obstructive sleep apnea and 15-year cognitive decline: the Atherosclerosis Risk in Communities (ARIC) study. Sleep 39 (2), 309–316.
Ministry of Health and Welfare, (2017). The Government Takes Responsibility for Dementia, in: Policy, D., (Ed.).
National Institute of Dementia, 2012. The Nationwide Survey on the Dementia Epidemiology. National Institute of Dementia.
Organization for Economic Co-operation and Development, 2017. Health at a Glance 2017. Dementia prevalence, pp. 204–205.
Osorio, R.S., Gumb, T., Pirraglia, E., Varga, A.W., Lu, S.-E., Lim, J., Wohlleber, M.E., Ducca, E.L., Koushyk, V., Glodzik, L., 2015. Sleep-disordered breathing advances cognitive decline in the elderly. Neurology 84 (19), 1964–1971.
Pan, W., Kastin, A.J., 2014. Can sleep apnea cause Alzheimer's disease? Neurosci. Biobehav. Rev. 47, 656–669.
Parati, G., Lombardi, C., Castagna, F., Mattaliano, P., Filardi, P.P., Agostoni, P., 2016. Heart failure and sleep disorders. Nat. Rev. Cardiol. 13 (7), 389.
PROOF study group, 2015. Sleep breathing disorders and cognitive function in the elderly: an 8-year follow-up study. The proof-synapse cohort. Sleep 38 (2), 179–187.
Ramos, A.R., Tarraf, W., Rundek, T., Redline, S., Wohlgemuth, W.K., Loredo, J.S., Sacco, R.L., Lee, D.J., Arens, R., Lazalde, P., 2015. Obstructive sleep apnea and neurocognitive function in a Hispanic/Latino population. Neurology 84 (4), 391–398.
Sánchez, B.D.V., Martínez, S.J., Chiches, M.D.O., Vicente, C.D., Sarmiento, E.G., 2017. Obstructive sleep apnoea, type 2 diabetes and cardiovascular risk factors. Eur. J. Intern. Med. 39, e16–e17.
Saunamäki, T., Himanen, S.-L., Polo, O., Jehkonen, M., 2009. Executive dysfunction in patients with obstructive sleep apnea syndrome. Eur. Neurol. 62 (4), 237–242.
Seong, S.C., Kim, Y.-Y., Park, S.K., Khang, Y.H., Kim, H.C., Park, J.H., Kang, H.-J., Do, C.-H., Song, J.-S., Lee, E.-J., Ha, S., Shin, S.A., Jeong, S.-L., 2017. Cohort profile: the national health insurance service-national health screening cohort (NHIS-HEALS) in Korea. BMJ Open 7 (9), e016640.
Shin, W.Y., Lee, T., Jeon, D.-H., Kim, H.C., 2018. Diabetes, frequency of exercise, and mortality over 12 years: analysis of the National Health Insurance Service-Health Screening (NHIS-HEALS) Database. J. Korean Med. Sci. 33 (8), e60.
Somers, V.K., White, D.P., Amin, R., Abraham, W.T., Costa, F., Culebras, A., Daniels, S., Floras, J.S., Hunt, C.E., Olson, L.J., 2008. Sleep apnea and cardiovascular disease: an american heart association/american college of cardiology foundation scientific statement from the american heart association council for high blood pressure research professional education committee, council on clinical cardiology, stroke council, and council on cardiovascular nursing in collaboration with the national heart, lung, and blood institute national center on sleep disorders research (national institutes of health). Circulation 118 (10), 1080–1111.
Spira, A.P., Blackwell, T., Stone, K.L., Redline, S., Cauley, J.A., Ancoli-Israel, S., Yaffe, K., 2008. Sleep-disordered breathing and cognition in older women. J. Am. Geriatr. Soc. 56 (1), 45–50.
Stuart, E.A., 2010. Matching methods for causal inference: a review and a look forward. Stat. Sci. Rev. J. Inst. Math. Stat. 25 (1), 1.
World Health Organization, 2015. First WHO Ministerial Conference on Global Action Against Dementia. World Health Organization, Geneva, Switzerland, pp. 1–78.
Yaffe, K., Laffan, A.M., Harrison, S.L., Redline, S., Spira, A.P., Ensrud, K.E., Ancoli-Israel, S., Stone, K.L., 2011. Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. JAMA 306 (6), 613–619.
Young, T., Palta, M., Dempsey, J., Skatrud, J., Weber, S., Badr, S., 1993. The occurrence of sleep-disordered breathing among middle-aged adults. N. Engl. J. Med. 328 (17), 1230–1235.