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Epidemiology

Obstructive Sleep Apnea Independently Increases the Incidence of Heart Failure and Major Adverse Cardiac Events: A Retrospective Population-Based Follow-Up Study

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Background: Obstructive sleep apnea (OSA) is common in heart failure (HF) patients and exacerbates the outcome of this chronic disease. However, the frequency of HF arising from OSA is varied, with little supporting literature. Here, we aimed to clarify the incidence risk of HF and major adverse cardiac events (MACEs) in OSA patients from the Taiwan large database.

Methods and Results: From 2000-2010, a total of 2699 newly diagnosed OSA patients after polysomnographic study and 13,490 non-OSA patients utilizing 1:5 matching was enrolled and followed to 2011. Compared to the non-OSA cohort, the OSA cohort increased its MACEs incidence 1.95-fold high and HF incidence reached its highest level, up to 2.75-fold [confidential interval (CI): 1.76-4.29; p value < 0.001]. The most common MACE event was stroke, with a 1.75-fold higher risk in the OSA cohort (CI: 1.37-2.20; p value < 0.001). Although the trend is similar, the OSA cohort showed an increased incidence of atrial fibrillation of approximately 1.63-fold high, (CI: 0.78-3.40; p value: 0.193) and 1.44 high, (CI: 0.74-2.79; p value: 0.287) in myocardial infarction. Between genders, HF risk is considerably higher in female OSA cohort than in corresponding males [female: 6.13 (2.68-14.00), p value < 0.01; male: 1.95 (1.11-3.43), p value = 0.020].

Conclusions: OSA patients have nearly triple the HF incidence risk than the non-OSA population, particularly in female OSA patients.

Key Words: Heart failure • Major adverse cardiovascular events • Obstructive sleep apnea

INTRODUCTION

Obstructive sleep apnea (OSA) affects 2-4% of adults worldwide, including Taiwan.[1,2] Cardiovascular complications are the most common and severe consequences of OSA in these patients.[3] Longitudinal studies such as the Wisconsin Cohort Heart Study (WCHS),[4,5] Sleep Heart Health Study (SHHS)[6,7] and Dr. Marin's[8] Spain follow-up study have reported high incidence rates of hypertension (HTN)[9] and major cardiovascular adverse events (MACEs) associated with OSA, including stroke, myocardial infarction (MI) and heart failure (HF), although these studies most included male patients. However, a recent meta-analysis of OSA-related community ran-

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domized controlled trials encompassing 15 populations indicated a high incidence rate of stroke but not MI.[10]

Up to 60% of patients with HF have OSA, and at least two observational studies reported that these patients had worse outcomes. However, few studies have investigated the incidence of HF in patients with OSA.[11-15] Gottlieb et al. reported a higher incidence of HF only in male OSA patients after 8 years of follow-up from the SHHS study.[16] In addition, Ljunggren et al. recently reported the females who snored and had daytime sleepiness may have had a higher incidence of HF in Sweden.[17]

The outcomes of MACEs except for stroke are diverse in patients with OSA, especially in HF. Therefore, we conducted this retrospective nationwide cohort follow-up study to evaluate the risk of HF in patients with OSA in Taiwan.

MATERIALS AND METHODS

Data source

This is a retrospective cohort study that utilized the Longitudinal Health Insurance Database 2000 (LHID2000) in Taiwan, a subset of the National Health Insurance Research Database (NHIRD) (http://nhird.nhri.org.tw/date_01.html), containing all original claims data for one million randomly sampled insured patients in 2000. The NHIRD comprises details of payments involving medical and pharmacy claims including inpatient and outpatient diagnoses and procedures based on International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes. The data are considered reasonably representative of all residents of Taiwan, since > 99% of Taiwan's population are enrolled in the National Health Insurance (NHI) program.[18]

All personal identifiers are encrypted by the Bureau of NHI prior to being released to researchers. The Institutional Review Board of Chang Gung Memorial Hospital approved this retrospective study (#101-5057B) and waived the requirement for informed consent.

Study and comparison cohorts

The study cohort consisted of adult patients (age ≥ 18 years) with newly-diagnosed OSA (ICD-9-CM 78057, 78053, 78051, 32723) after polysomnographic studies (ICD-9-CM code 17008B, 17008A) between 2000 and 2010.[19,20] Patients who had visited the outpatient care clinic with a previous MACE, and those hospitalized with a diagnosis of MI (ICD-9-CM code 410), HF (ICD-9-CM code, 4280, 4281), cerebrovascular accident (stroke) (ICD-9-CM code 430-437),[21] malignant dysrhythmia (ICD-9-CM code 426, 427, 246), cardiac shock (ICD-9-CM code 785.51), implantable cardiac defibrillator (ICD) (ICD-9-CM code v4502, v4501) and sudden cardiac death (SCD) (427.5, 798.1, 798.2)[22] were excluded. Confounding factors including diabetes mellitus (DM) (ICD-9-CM 250), HTN (ICD-9-CM 401.0, 401.1, 401.9) and Charlson Comorbidity Index (CCI) (according to D'Hoore's CCI, 1993) one year before the index date were recorded. Data on baseline medications and disease history including chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), dyslipidemia and HTN drugs including angiotensin receptor blockers/angiotensin converting enzyme inhibitors (ARBs/ACEIs), calcium channel blocker, beta-blockers, and diuretics were also recorded.

The comparison cohort consisted of adults (age ≥ 18 years) without OSA (non-OSA group) were randomly selected from the remaining individuals in the LHID2000 database. All of the subjects in the comparison cohort were matched with the study cohort for age, sex, DM, HTN, and index year. None of the comparison cohort had a previously diagnosed MACE before the index year. Both the study and comparison cohorts were followed up for at least 1 year (Figure 1 and Table 1).

MACEs

The primary endpoint for the study cohort was a newly-diagnosed MACE during the study period. Newly-diagnosed cases of MACE were defined as the patients who were hospitalized or visited the emergency room with a diagnosis of MI (ICD-9-CM 410-410.9), HF (ICD-9-CM 428.0, 428.10), stroke (ICD-9-CM 430-437), percutaneous cardiac intervention (PCI) (ICD-9-CM code 36.0-36.03, 36.05-36.09), coronary artery bypass grafting (CABG) (ICD-9-CM 36.1-36.99, V45.81), atrial fibrillation (AFib) (ICD-9-CM code 427.3),[23-25] cardiac shock (ICD-9-CM code 785.51), ICD (ICD-9-CM code v4502, v4501), ventricular fibrillation (VF) (427.41) and SCD (427.5, 798.1, 798.2). Newly-diagnosed cases of MACEs including MI (ICD-9-CM code 410-410.9), HF (ICD-9-CM 428.0, 428.10), stroke (ICD-9-CM code 430-437) and

AFib (ICD-9-CM code 427.3) were also identified from the outpatient clinic if they were recorded to have persisted over 3 clinic visits in 1 year.

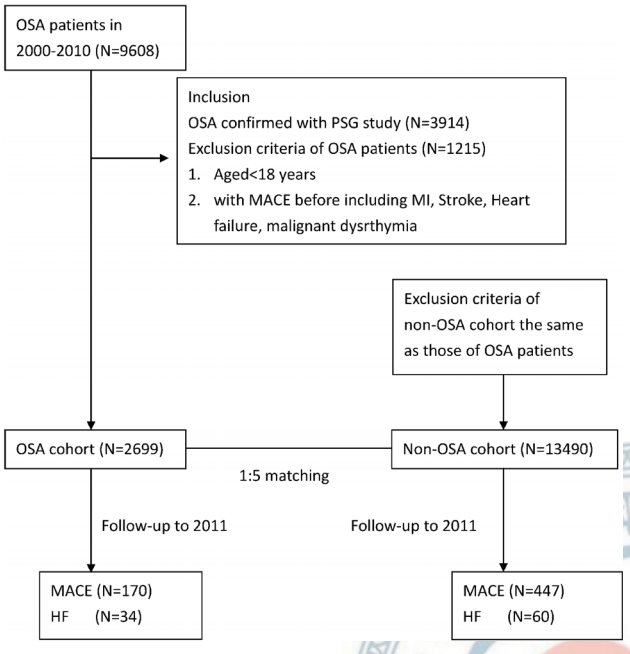

Figure 1. *Flow chart of ascertainment of the OSA and non-OSA cohorts. HF, heart failure; MACEs, major adverse cardiovascular events; OSA, obstructive sleep apnea; PSG, polysomnographic.*

Statistical analysis

The follow-up period began on the index date of OSA and ended at the time of the diagnosis of a MACE, when the patient withdrew from the NHI program, or January 31, 2011, which ever came first. Descriptive results were reported as the number of baseline characteristics of the OSA and non-OSA cohorts. The incidence of MACEs was calculated based upon person-years of follow-up from 2000-2011. Person-years of follow-up were estimated for each individual from the index date until the date of diagnosis of a MACE, when the patient withdrew from the NHI program, or January 31, 2011. Survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test. Cox proportional hazards models were used to analyze associations between baseline OSA and the risk of a MACE with or without adjustments for age, sex, DM, and HTN at baseline. Stratified Cox proportional analysis was also used for subgroups including age, sex and the presence or lack of DM/HTN during follow-up. Proportional hazards assumption was not violated, and hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated. Two-tailed tests were used, and p values < 0.05 were considered to be significant. The statistical analyses were performed using SAS version 9.2

Table 1. Demographic and clinical characteristics in obstructive sleep apnea (OSA) and non-OSA at baseline of follow-up

	Non-OSA (n = 13490)	OSA (n = 2699)	p-value
Age	43.8 ± 12.1	43.9 ± 12.2	0.747
Gender			0.993
Male	10710 (79.4%)	2142 (79.4%)	
Female	2780 (20.6%)	557 (20.6%)	
Diabetes	1820 (13.5%)	366 (13.6%)	0.948
Hypertension	3805 (28.2%)	763 (28.3%)	0.965
Baseline medications			
ARB/ACEI	212 (1.57%)	37 (1.37%)	0.492
CCB	403 (2.99%)	88 (3.26%)	0.488
Beta-blockers	1047 (7.76%)	250 (9.26%)	0.010
Diuretics	163 (1.21%)	53 (1.96%)	0.002
Chronic kidney disease	66 (0.5%)	7 (0.3%)	0.142
Chronic obstructive lung disease	51 (0.4%)	30 (1.1%)	< 0.001
Dyslipidemia	713 (5.3%)	244 (9.0%)	< 0.001
Charlson comorbidity index			< 0.001
Mean (SD)	0.25 (1.06)	0.17 (0.72)	
0	12309 (91.3%)	2479 (91.9%)	
1-2	709 (5.3%)	161 (6.0%)	
3-4	270 (2.0%)	43 (1.6%)	
≥ 5	202 (1.5%)	16 (0.6%)	

ARB/ACEI, angiotensin receptor blockers/angiotensin converting enzyme inhibitor; CCB, calcium channel blockers; OSA, obstructive sleep apnea; SD, standard deviation.

(SAS Institute Inc., Cary, NC, USA).

RESULTS

Participant characteristics

In this study, 2,699 patients were enrolled in the OSA group and 13,490 patients were enrolled in the non-OSA group (matched 1:5 to the OSA group). The mean age was 43 years most (79%) patients were male, as expected in an OSA population. The baseline demographics and clinical characteristics of both cohorts are listed in Table 1. The prevalence rates of DM and HTN were 13.5% and 28.5%, respectively, which is consistent with the national rates in Taiwan except for a higher prevalence of DM. The average CCI was 0.17 in the OSA cohort and 0.25 in the non-OSA cohort.

Outcome measurements

In follow-up through 2011, 170 (6.3%) MACEs occurred in the OSA cohort compared to 447 (3.1%) in the non-OSA cohort. The mean (median) follow-up periods in the patients overall and in the OSA and non-OSA groups were 47.5 (39.9), 46.5 (38.7) and 47.7 (40.5) months, respectively.

The OSA cohort had a 1.95-fold higher incidence of MACEs compared to the non-OSA cohort (CI: 1.63-2.34; p < 0.001). Details of the MACEs are reported in Table 2 and Figure 2. Compared to the non-OSA cohort, the OSA cohort had a 2.75-fold higher risk of HF (CI: 1.76-4.29; p < 0.001). The most common MACE was stroke, with a 1.74-fold higher risk in the OSA cohort (CI: 1.37-2.20; p < 0.001). In addition, the OSA cohort had a 1.63-fold increased risk of AFib (CI: 0.78-3.40; p = 0.193) and a 1.44-fold increased risk of MI (CI: 0.74-2.79; p = 0.287) compared to the non-OSA cohort, and although the trend was similar to stroke, the differences did not reach statistical significance.

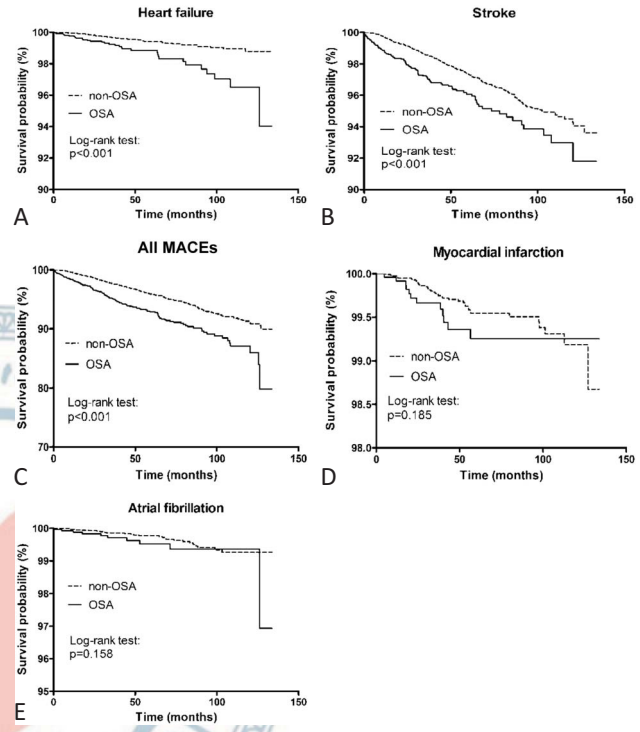

Figure 2. Kaplan-Meier estimates of (A) heart failure; (B) stroke; (C) all major adverse cardiac events; (D) myocardial infarction; (E) atrial fibrillation. MACEs, major adverse cardiovascular events; OSA, obstructive sleep apnea.

Table 2. Incidence and hazard ratios of major adverse cardiac events for obstructive sleep apnea (OSA) patients compared with non-OSA patients

Outcomes	Groups	Incident events (%)	Incidence rate (95% CI)*	HR (95% CI)#	p-value
All MACEs	OSA	170 (6.30%)	13.52 (11.60, 15.67)	1.95 (1.63, 2.34)	< 0.001
	non-OSA	447 (3.31%)	6.94 (6.32, 7.61)	1.00	
Heart failure	OSA	34 (1.26%)	2.70 (1.90, 3.73)	2.75 (1.76, 4.29)	< 0.001
	non-OSA	60 (0.44%)	0.93 (0.72, 0.12)	1.00	
Stroke	OSA	95 (3.52%)	7.56 (6.15, 9.20)	1.74 (1.37, 2.20)	< 0.001
	non-OSA	285 (2.11%)	4.43 (3.94, 4.97)	1.00	
Atrial fibrillation	OSA	10 (0.37%)	0.80 (0.41, 1.43)	1.63 (0.78, 3.40)	0.193
	non-OSA	31 (0.23%)	0.48 (0.33, 0.67)	1.00	
Myocardial infarction	OSA	12 (0.44%)	0.95 (0.51, 0.16)	1.44 (0.74, 2.79)	0.287
	non-OSA	40 (0.30%)	0.62 (0.45, 0.84)	1.00	

CI, confidence intervals; HR, hazard ratio; MACE, major adverse cardiovascular events; OSA, obstructive sleep apnea.
* Incidence rate per 10000 person-years. # Adjustment for age at index date, gender, and Charlson comorbidity index.

Subgroup analyses

A borderline significant interaction between OSA and sex (p = 0.0459) suggested that sex might modify the effect of OSA on the risk of HF. Therefore, separate models were constructed for the male and female patients (Table 3). In the female patients, a significant effect of OSA was detected after adjusting for age and CCI (OR = 6.13; 95% CI: 2.68-14.00, p = 0.03). In addition, the risk of HF was significantly higher in the female patients with OSA than in the male patients with OSA (OR = 1.95; 95% CI: 1.11-3.43, p = 0.03).

The HR for stroke was nearly the same in both genders, with the males having a 1.72-fold increased risk (CI: 1.32-2.25; p < 0.001), and the females a 1.84-fold increased risk (CI: 1.08-3.13, p = 0.024). However, there were no significant differences in AFib or MI between gender.

In age subgroups, few MACEs were noted in patients younger than 30 years of age in the OSA group except for stroke. In the patients under 30 years of age, only 2 new strokes (0.54%) were recorded in the OSA group and 5 new strokes (0.27%) in the non-OSA group, without statistical significance. Details of the MACEs in age subgroup analysis are shown in Table 4. Increased risks of both HF and stroke remained in different age groups. Although there were no significant differences in MI among the age groups, the risk of Afib in the patients between 30-49 years was significantly higher in the OSA group, with a 3.58-fold-higher risk (95% CI: 1.05-12.25; p = 0.042).

DISCUSSION

The findings of this retrospective cohort follow-up study in Taiwan demonstrated a 2.75-fold higher risk of HF in patients with OSA. Similar to Dr. Wang's report, the patients with OSA had a nearly 2-fold increased risk of overall MACEs,[10] and the most common MACE was HF in both the male and female patients. Surprisingly, the female patients with OSA had a 6-fold higher risk of future HF events, in contrast to Dr. Gottlieb's report.

Parissis and associates reported a gender difference in the ALARM-HF study, in which female patients had a higher prevalence of acute HF and more severe comorbidities. In addition, Lu et al. reported that Malaysian

Table 3. Incidence and hazard ratios of major adverse cardiac events for obstructive sleep apnea (OSA) patients compared with non-OSA patients, stratified by gender

Stratification	Groups	Number of patients	Incident events (%)	Incidence rate (95% CI)*	HR (95% CI)#	p-value
Heart failure						
Male	OSA	2142	20 (0.93%)	1.96 (1.23, 2.97)	1.95 (1.11, 3.43)	0.020
	non-OSA	10710	47 (0.44%)	0.90 (0.67, 1.19)	1.00	
Female	OSA	557	14 (2.51%)	5.87 (3.34, 9.62)	6.13 (2.68, 14.00)	< 0.001
	non-OSA	2780	13 (0.47%)	1.06 (0.59, 1.77)	1.00	
Stroke						
Male	OSA	2142	76 (3.55%)	7.46 (5.92, 9.29)	1.72 (1.32, 2.25)	< 0.001
	non-OSA	10710	224 (2.09%)	4.30 (3.76, 4.89)	1.00	
Female	OSA	557	19 (3.41%)	7.97 (4.94, 12.22)	1.84 (1.08, 3.13)	0.024
	non-OSA	2780	61 (2.19%)	4.95 (3.82, 6.32)	1.00	
Atrial fibrillation						
Male	OSA	2142	9 (0.42%)	0.88 (0.43, 1.62)	1.71 (0.78, 3.73)	0.180
	non-OSA	10710	27 (0.25%)	0.42 (0.28, 0.60)	1.00	
Female	OSA	557	1 (0.18%)	0.52 (0.03, 2.57)	1.19 (0.13, 10.82)	0.881
	non-OSA	2780	4 (0.14%)	0.32 (0.10, 0.77)	1.00	
Myocardial infarction						
Male	OSA	2142	12 (0.56%)	1.18 (0.64, 2.01)	1.58 (0.81, 3.09)	0.185
	non-OSA	10710	37 (0.35%)	0.71 (0.51, 0.97)	1.00	
Female	OSA	557	0 (0%)	0.00	NA†	
	non-OSA	2780	3 (0.11%)	0.24 (0.06, 0.65)		

CI, confidence intervals; HR, hazard ratio; NA, not available; OSA, obstructive sleep apnea.
* Incidence rate per 10000 person-years. # Adjustment for age at index date and Charlson comorbidity index. † No event in the OSA group.

Table 4. Incidence and hazard ratios of major adverse cardiac events for obstructive sleep apnea (OSA) patients compared with non-OSA patients, stratified by age

Stratification	Groups	Number of patients	Incident events (%)	Incidence rate (95% CI)*	HR (95% CI)#	p-value
Heart failure						
< 30 years	OSA	368	0 (0%)	0.00	NA†	
	non-OSA	1860	0 (0%)	0.00		
30-49 years	OSA	1489	10 (0.67%)	1.42 (0.72, 2.53)	2.88 (1.30, 6.37)	0.009
	non-OSA	7442	18 (0.24%)	0.50 (0.31, 0.77)	1.00	
≥ 50 years	OSA	842	24 (2.85%)	6.24 (4.09, 9.14)	2.70 (1.57, 4.64)	< 0.001
	non-OSA	4188	42 (1.00%)	2.10 (1.53, 2.81)	1.00	
Stroke						
< 30 years	OSA	368	2 (0.54%)	1.20 (0.20, 3.97)	3.62 (0.56, 23.37)	0.176
	non-OSA	1860	5 (0.27%)	0.59 (0.22, 1.31)	1.00	
30-49 years	OSA	1489	26 (1.75%)	3.68 (2.46, 5.32)	1.89 (1.20, 2.99)	0.006
	non-OSA	7442	75 (1.01%)	2.09 (1.66, 2.61)	1.00	
≥ 50 years	OSA	842	67 (7.96%)	17.42 (13.61, 21.99)	1.71 (1.29, 2.27)	< 0.001
	non-OSA	4188	205 (4.89%)	10.26 (8.93, 11.74)	1.00	
Atrial fibrillation						
< 30 years	OSA	368	0 (0%)	0.00	NA†	
	non-OSA	1860	0 (0%)	0.00		
30-49 years	OSA	1489	5 (0.34%)	0.71 (0.26, 1.57)	3.58 (1.05, 12.25)	0.042
	non-OSA	7442	9 (0.12%)	0.25 (0.12, 0.46)	1.00	
≥ 50 years	OSA	842	5 (0.59%)	1.30 (0.48, 0.29)	1.03 (0.38, 2.79)	0.950
	non-OSA	4188	22 (0.53%)	1.10 (0.71, 1.64)	1.00	
Myocardial infarction						
< 30 years	OSA	368	0 (0%)	0.00	NA†	
	non-OSA	1860	0 (0%)	0.00		
30-49 years	OSA	1489	6 (0.40%)	0.85 (0.33, 1.77)	1.82 (0.70, 4.74)	0.223
	non-OSA	7442	17 (0.23%)	0.47 (0.28, 0.74)	1.00	
≥ 50 years	OSA	842	6 (0.71%)	1.56 (0.63, 3.25)	1.27 (0.50, 3.25)	0.621
	non-OSA	4188	23 (0.55%)	1.15 (0.75, 1.70)	1.00	

CI, confidence intervals; HR, hazard ratio; NA, not available; OSA, obstructive sleep apnea.

* Incidence rate per 10000 person-years. # Adjustment for gender and Charlson comorbidity index. † No event in both groups.

females may have a higher risk of previous HF from national registry data.[26,27] In Taiwan, as in most Asian societies, endurance is a kind of virtue to females, and this may result in neglected HF symptoms which are only discovered after admission.

There may also be ethnic differences in the incidence of HF inpatients with OSA, similar to how Taiwanese have a higher reported risk of stroke but a lower risk of MI compared to Western populations. We showed that both HF and stroke were the most significant MACEs in the patients with OSA compared to those without OSA, in both males and females. The incidence of MI had the same trend in the patients with OSA, although the difference did not reach significance, and these findings are different to reports in Western countries.

Furthermore, an older age increased the risk of a MACE in the patients with OSA. Very few MACEs occurred in the patients with OSA under 30 years of age. This may in part be because adult OSA is an acquired disease that needs time to develop, and early screening and prevention may help to eliminate this disease, although further studies are needed to confirm this hypothesis. In addition, although the overall risk of Afib was not significant, the patients aged 30-49 years had a significant 3.5-fold higher risk, which may have increased the incidence of future HF. In the patients older than 30 years, the significant incidence of MACEs was primarily associated with HF and stroke, a pattern that persisted in the patients with OSA aged 50 years. These results may merit further evaluation.

There are several limitations to this study. First, this

was a retrospective population study based on a national claims database, so that data on apnea-hypopnea index, body mass index[28] and smoking were not available. To minimize the effect of these clinical health risk factors, we used the CCI.[29,30] Second, continuous positive airway pressure (CPAP) therapy is the mainstay treatment of OSA patients, however it is not covered under the NHI program in Taiwan. To minimize this limitation, we tried to ascertain CPAP usage (ICD-9 code 93.9), and respiratory failure (ICD-9 code 518), both of which were below 1% in our cohort. Clinically, low CPAP usage may underestimate the risk of MACEs in patients with OSA in the statistical analysis. Third, confounding factors such as DM and HTN though matched initially may have occurred in later follow-up and influenced the risk of MACEs. We checked associations between the diagnoses of DM and HTN and drug usage, and found that approximately 6% of the study population without DM or HTN received medications to treat DM or HTN. However, after excluding these patients, the results were unchanged. Lastly, we also tried to exclude all occurrences of DM or HTN during follow-up and compared them to the patients without OSA, and the results were also the same. Therefore, the patients with OSA had a consistently increased risk of MACEs, and especially HF and stroke, and the younger patients with OSA may have had a higher risk of AFib.

CONCLUSIONS

In conclusion, our findings indicated that the patients with OSA had an increased overall incidence of MACEs, and especially HF. Furthermore, the female patients with OSA had a higher risk of HF than those without OSA.

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CONFLICT OF INTEREST

All the authors declare no conflict of interest.

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