JCSM
Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

The Impact of Antidepressants on the Risk of Developing Obstructive Sleep Apnea in Posttraumatic Stress Disorder: A Nationwide Cohort Study in Taiwan

Ching-En Lin, MSc[1,2,3]; Chi-Hsiang Chung, PhD[4,5,6]; Li-Fen Chen, MD[7]; Wu-Chien Chien, PhD[3,4,6]; Po-Han Chou[8,9,10,11]

[1]Department of Psychiatry, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Taiwan; [2]School of Medicine, Tzu Chi University, Hualien, Taiwan; [3]Graduate Institute of Life Science, National Defense Medical Center, Taipei, Taiwan; [4]Department of Medical Research, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan; [5]Taiwanese Injury Prevention and Safety Promotion Association, Taipei, Taiwan; [6]School of Public Health, National Defense Medical Center, Taipei, Taiwan; [7]Department of Psychiatry, Hualien Armed Forces General Hospital, Taiwan; [8]Department of Psychiatry, China Medical University Hsinchu Hospital, China Medical University, Taichung, Taiwan; [9]Department of Psychiatry, China Medical University Hospital, China Medical University, Taichung, Taiwan; [10]Department of Biological Science and Technology, National Chiao Tung University, Hsinchu, Taiwan; [11]Biological Optimal Imaging Lab, Department of Photonics, College of Electrical and Computer Engineering, National Chiao Tung University, Hsinchu, Taiwan

Study Objectives: The association between posttraumatic stress disorder (PTSD) and obstructive sleep apnea (OSA) has been reported inconsistently, and the association between antidepressant use and the risk of developing OSA in patients with PTSD has not been previously studied. Therefore, we used the Longitudinal National Health Insurance Database (LHID) to investigate the impact of PTSD and antidepressant use on the risk of OSA development.

Methods: Identified from the LHID, 2,316 individuals aged ≥ 18 years with PTSD, but with no history of OSA, and 23,160 control individuals matched for age, sex, obesity and index date were enrolled between 2000 and 2015 and followed up until the end of 2015 to identify the development of OSA. A two-tailed Bonferroni-corrected $P < .00038$ (.05/13) was considered statistically significant as we examined 13 antidepressants.

Results: Individuals with PTSD had increased risk of developing OSA (adjusted hazard ratio 4.672, 95% confidence interval 2.246–9.787, $P < .001$) after adjusting for demographic data, medical comorbidities, and medication. Treatment with antidepressants was not significantly associated with an increased risk of developing OSA compared to no antidepressant treatment.

Conclusions: Asian patients with PTSD had increased risk of developing OSA, and treatment with antidepressants did not play a key role in increasing the risk of OSA development. Further studies are required to investigate the underlying mechanisms of PTSD and the roles of antidepressants on the risk of developing OSA.

Keywords: antidepressants, obstructive sleep apnea, posttraumatic stress disorder, sleep-disordered breathing

Citation: Lin C-E, Chung C-H, Chen L-F, Chien W-C, Chou P-H. The impact of antidepressants on the risk of developing obstructive sleep apnea in posttraumatic stress disorder: a nationwide cohort study in taiwan. *J Clin Sleep Med*. 2019;15(9):1233–1241.

BRIEF SUMMARY

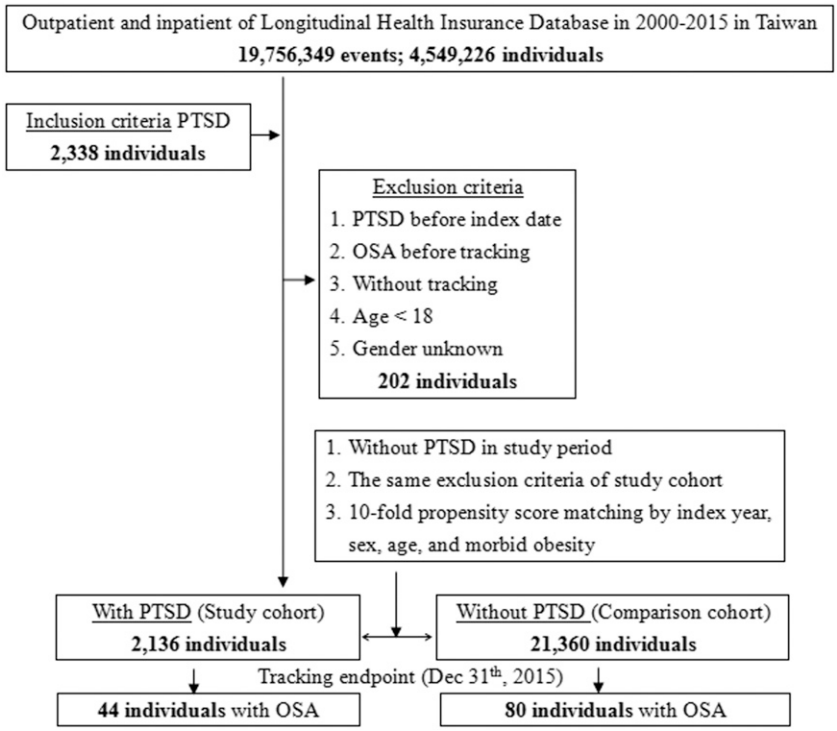
Current Knowledge/Study Rationale: The association between obstructive sleep apnea and posttraumatic stress disorder (PTSD) have been inconsistent, and the impact of antidepressants on the risk of obstructive sleep apnea (OSA) in patients with PTSD still has not been investigated. Therefore, we used a real-world big dataset to investigate the impact of PTSD and antidepressant use on the risk of OSA development.

Study Impact: This study provides extension evidence to the existing literature about the association between PTSD and OSA. In addition, our study results have the potential to impact the development of novel management strategies for patients with PTSD and OSA.

INTRODUCTION

Posttraumatic stress disorder (PTSD) is a psychiatric illness characterized by persistent extreme stress and anxiety responses following a traumatic event. The symptoms of PTSD include hyperarousal, flashbacks, intrusive thoughts, nightmares, or avoidance of activities that trigger memories of traumatic events. PTSD has been associated with a host of health problems, including cancer, arthritis, digestive disease, and cardiovascular disease.[1–3] Investigators have examined PTSD in relation to a range of health outcomes and the studies reporting increased risk for obstructive sleep apnea (OSA) in PTSD are abundant.[4–15] Mild and moderate to severe OSA has been described in 69% and 83% of patients with war-induced PTSD, respectively.[9,16] Despite the very high prevalence of OSA among patients with PTSD, the exact associations between PTSD and OSA remain unclear because of the methodological limitations of previous studies, such as small sample sizes,[5,6,8,11,13,15] cross-sectional designs,[4–9,11] different sleep-testing methods,[12] OSA diagnosis based on survey questionnaires instead of in-laboratory polysomnography (PSG),[8,14,15] and short period of follow up.[14] Moreover, some previous studies have even found a lack of association between OSA and PTSD.[17–20] These studies had similar methodological limitations, such as heterogeneity in the study populations with varied PTSD severity and intensity of traumatic stress exposure and lack of control groups[10,11] and of the numerous different diagnostic tools used for OSA.[17–20] In addition, information with regard to the effects of antidepressant treatment on the risk of OSA in patients with PTSD is scarce. Despite abundant reports on the efficacy of selective serotonin reuptake inhibitors (SSRIs) and the general acceptance of SSRIs as the first-line

Figure 1—The process of study sample selection.



OSA = obstructive sleep apnea, PTSD = posttraumatic stress disorder.

medication interventions for treating PTSD, previous studies have shown that antidepressants may be associated with increased body weight, which is a risk factor for OSA. Finally, most of these studies were conducted in Western countries and whether these findings are applicable to Asian populations remains unknown, given that previous studies have shown that there are specific different patterns in airway structure in Asian populations, and OSA may develop more easily in Asian than in Western individuals despite having similar body mass index (BMI).[21–23]

Therefore, this cohort study aimed to examine the association between PTSD and OSA and to investigate the effect of each type of antidepressant on the risk of developing OSA in patients with PTSD using the Taiwanese Longitudinal Health Insurance Database (LHID) with a large sample size and a long follow-up period. The LHID is a reliable data source and has been used in previous studies investigating issues related to OSA.[24–26]

METHODS

Data Sources

The National Health Insurance (NHI) program was launched in Taiwan in 1995, and nearly 99% of residents were enrolled.[27] In the present study, we used the LHID released by the Bureau of NHI (NHIB). LHID contains all longitudinal claims data from 1995 to 2015 for 2,000,000 individuals randomly selected among the 25.68 million enrollees in the NHI program. The sample was created by the NHIB using a systematic sampling method to randomly extract a representative database from the entire Taiwan NHI database. There were no statistically significant differences with regard to age, sex, and medical costs among the sample groups. The NHIB randomly samples a fixed percentage of claims from every hospital each year to ensure diagnostic validity through reviewing the symptomatologies documented in the medical records by an independent group of professional experts, and false claims are fined.

In the present study, we adopted a cohort design to investigate the incidence and risk of OSA in patients with PTSD from January 1, 2000 to December 31, 2015. Patient consent was not required to access the LHID, as data were analyzed anonymously. Although the study was entirely based on register data, ethical permission was still required according to Taiwanese law. This study was approved by the Institutional Review Board of Tri-Service General Hospital (IRB No.: 2-105-05-082).

Inclusion Criteria for PTSD and Control Cohorts

Individuals aged 18 years or older who were newly diagnosed with PTSD (ICD-9-CM codes 309.81) by board-certified psychiatrists between 2000 and 2015 and had no history of any PTSD or OSA before the index date were included as the PTSD cohort. The time of first PTSD diagnosis was defined as the index date. The propensity score matched (1:10) control cohort by age, sex, obesity (ICD-9-CM code: 780), and index date was identified among 2,000,000 individuals, after excluding people who had received a diagnosis of PTSD at any time during the follow-up period and those who had been diagnosed with OSA before the index date. The first time the patient in the control cohort sought medical consultation during 2000–2015 was considered the index date. Patients with

Table 1—Baseline characteristics of the PTSD and comparison cohorts.

	Total (n = 23,496)		PTSD (n = 2,136)		Comparison (n = 21,360)		*P*
	n	%	n	%	n	%	
OSA							< .001
Without	23,372	99.47	2,092	97.94	21,280	99.63	
With	124	0.53	44	2.06	80	0.37	
Sex							.999
Male	6,534	27.81	594	27.81	5,940	27.81	
Female	16,962	72.19	1,542	72.19	15,420	72.19	
Age (years), mean ± SD	42.05 ± 16.24		41.54 ± 16.89		42.10 ± 16.17		.129
Age group (years)							.999
< 40	12,628	53.75	1,148	53.75	11,480	53.75	
40–59	7,282	30.99	662	30.99	6,620	30.99	
≥ 60	3,586	15.26	326	15.26	3,260	15.26	
Insured premium (NTD)							.786
< 18,000	20,518	87.33	1,872	87.64	18,646	87.29	
18,000–34,999	1,930	8.21	175	8.19	1,755	8.22	
≥ 35,000	1,048	4.46	89	4.17	959	4.49	
Urbanization level							< .001
1 (highest)	8,630	36.73	738	34.55	7,892	36.95	
2	9,695	41.26	982	45.97	8,713	40.79	
3	1,928	8.21	154	7.21	1,774	8.31	
4 (lowest)	3,243	13.80	262	12.27	2,981	13.96	
Medical comorbidities							
Hypertension	4,264	18.15	552	25.84	3,712	17.38	< .001
Coronary artery disease	2,162	9.20	224	10.49	1,938	9.07	.027
Cerebrovascular disease	2,741	11.67	316	14.79	2,425	11.35	< .001
Obesity	275	1.17	25	1.17	250	1.17	.999
Diabetes mellitus	2,829	12.04	316	14.79	2,513	11.76	< .001
COPD	1,958	8.33	286	13.39	1,672	7.83	< .001
Depression	2,103	8.95	1,428	66.85	675	3.16	< .001
Dyslipidemia	1,542	6.56	254	11.89	1,288	6.03	< .001
Asthma	1,064	4.53	170	7.96	894	4.19	< .001
Alcohol/substance abuse	531	2.26	210	9.83	321	1.50	< .001
Antidepressants	2,110	8.98	428	20.04	1,682	7.87	< .001
Anxiety	1,678	7.14	1,012	47.38	666	3.12	< .001
Headache	1,438	6.12	141	6.60	1,297	6.07	.803
Musculoskeletal pain	5,402	22.99	501	23.46	4,901	22.94	.792
Frequency of health care utilization							.966
1–5	7,958	33.87	725	33.94	7,233	33.86	
6–10	9,550	40.65	864	40.45	8,686	40.66	
11–20	4,332	18.44	391	18.31	3,941	18.45	
≥ 21	1,656	7.05	156	7.30	1,500	7.02	
Frequency of PSG examinations (n = 296)							.092
1–5	250	84.46	49	75.38	201	87.01	
6–10	45	15.20	15	23.08	30	12.99	
≥ 11	1	0.34	1	1.54	0	0	

COPD = chronic obstructive pulmonary disease, NTD = new Taiwan dollar, OSA = obstructive sleep apnea, PSG = polysomnography, PTSD = posttraumatic stress disorder, SD = standard deviation.

unidentified sex were excluded from this study. In order to achieve full diagnostic validity, PTSD was diagnosed by psychiatrists at least twice in an outpatient setting or once in an inpatient setting, as performed in previous studies using the Taiwanese LHID.[28,29] The reason for the requirement of two consecutive diagnoses from outpatient medical records was to minimize the possibility of recruiting patients who were erroneously coded during a single outpatient visit. Inpatient diagnoses are highly reliable; therefore, a single record was sufficient. A flow chart of the study selection process is provided in **Figure 1.**

Main Outcome

All study participants were followed from the index date until developing any new-onset OSA (ICD-9-CM codes 327.23,780.51,780.53,780.57), withdrawal from the NHI program, or the end of 2013. In order to achieve diagnostic validity, OSA was diagnosed at least twice in an outpatient setting or once in an inpatient setting following a diagnostic PSG (examination codes 1708A and 1708B in LHID). The reason for the requirement of repeat OSA diagnoses was the same as the reason for the requirement of repeat PTSD diagnoses.[28,29] As the diagnostic criteria for OSA are not only based on clinical signs and symptoms but also on findings identified by sleep testing such as PSG,[30] we used the findings of a PSG examination to diagnose OSA.

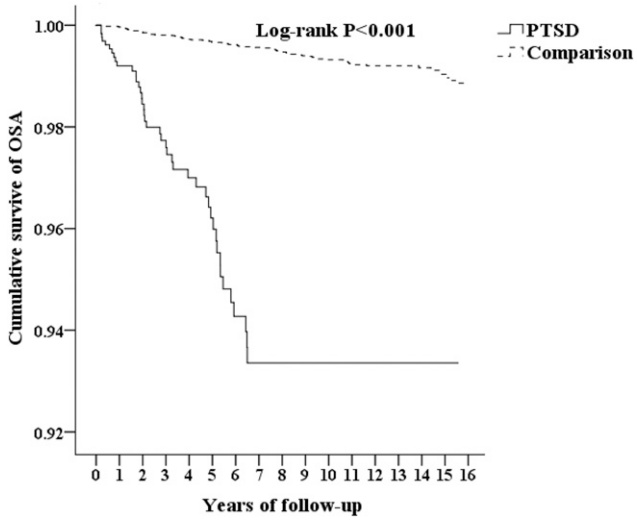
Possible Confounding Variables

We individually assessed medical comorbidities associated with OSA at enrollment and during the entire follow-up period, including hypertension, coronary artery disease, cerebrovascular disease,[31] obesity,[32] diabetes,[33] dyslipidemia,[34,35] chronic obstructive pulmonary disease,[36,37] and asthma[38] in our study. In the LHID, obesity is defined by a cutoff BMI of 24 kg/m^2, in accordance with the criteria for being overweight defined by the Department of Health Promotion, Ministry of Health and Welfare, Taiwan.[39] Therefore, obesity is coded as a dichotomous variable and thus, we could not ascertain its severity among participants in the study. Furthermore, depression, anxiety disorder, alcohol/substance abuse, headache, and musculoskeletal pain as psychiatric comorbidities associated with OSA,[40–43] diagnosed by board-certified psychiatrists, were also assessed in our study. In order to achieve full diagnostic validity, diagnoses of any psychiatric comorbidity had to be specified at least twice for consecutive outpatients or once for inpatient medical records. Other variables, including urbanization level of residence, from level 1 (most urbanized) to level 4 (least urbanized),[44] and income-related insured premium (in New Taiwan Dollars [NTDs]: < 18,000, 18,000–34,999, > 35,000) were also assessed in our study.

Antidepressant Exposure

Antidepressants in medical claims during the entire follow-up period were considered in the analysis, including fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram, venlafaxine, duloxetine, imipramine, clomipramine, amitriptyline, mirtazapine, and bupropion. In this study, we used the defined daily dose (DDD) to determine certain amounts of antidepressants, which were calculated using the following formula: (total amount of the individual drug) / (DDD of the drug) = number of DDDs. Cumulative DDDs (cDDDs), that is, the DDD sum of any antidepressant, served as the index of the cumulative dosage of the antidepressant. This method has been adopted in many previous pharmacological studies.[45] The DDD data were obtained from the World Health Organization Collaborating Centre for Drug Statistics Methodology (https://www.whocc.no/), and the duration of the use of antidepressant medications was calculated by dividing the cDDDs by the DDD of the antidepressant medications. The DDD was divided into 1–29 days and ≥ 30 days. Because the LHID is a medical claims database, the DDD can only represent the number of drug prescription days rather than actual use; therefore, we could not precisely assess the duration or continuation of antidepressant usage.

Figure 2—Comparison of Kaplan-Meier survival curve estimates of OSA between the PTSD and comparison cohorts.



OSA = obstructive sleep apnea, PTSD = posttraumatic stress disorder.

Statistical Analysis

All statistical analyses were performed using SPSS for Windows, version 22.0 (IBM, Armonk, New York). The chi-square and *t* tests were used to evaluate the distributions of the categorical and continuous variables, respectively. The Fisher exact test for categorical variables was used to statistically examine the differences between the two cohorts. A Cox proportional hazards regression model was used to investigate the relationship between PTSD and OSA, and the results are presented as hazard ratio (HR) with 95% confidence interval (CI). The difference in the risk of OSA between the PTSD and comparison cohorts was estimated using the Kaplan-Meier method with the log-rank test. Sensitivity analysis was used to investigate the robustness of study results after excluding the first 1 year and the first 3 years of OSA development during the study period. Each individual antidepressant medication was used to analyze the risk ratio of OSA development between patients with PTSD who were using and not using antidepressants. Bonferroni correction for multiple comparisons was applied.[46] A two-tailed Bonferroni-corrected $P < .00038$ (.05/13) was considered statistically significant, as we examined 13 antidepressants.

Table 2—The incidence rates and risks of developing OSA between the PTSD and comparison cohorts, stratified by variables.

Stratified		PTSD (n = 2,136)			Comparison (n = 21,360)			PTSD vs Comparison (Reference)		Multivariable Cox Regression	
		Events	PYs	Rate (per 10^3 PYs)	Events	PYs	Rate (per 10^3 PYs)	Adjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
Overall		44	24,315.45	1.81	80	261,186.36	0.31	4.672 (2.246–9.787)	< .001	4.672 (2.246–9.787)	< .001
Sex	Male	10	5,929.22	1.69	35	71,301.46	0.49	2.715 (1.305–5.688)	< .001	0.982 (0.197–4.998)	.295
	Female	34	18,386.23	1.85	45	189,884.90	0.24	6.172 (2.967–12.930)	< .001	Reference	
Age group (years)	< 40	27	10,354.43	2.61	38	92,594.01	0.41	5.025 (2.416–10.526)	< .001	Reference	
	40–59	11	8,632.15	1.27	21	94,641.99	0.22	4.542 (2.184–9.515)	< .001	0.672 (0.485–0.973)	.012
	≥ 60	6	5,328.87	1.13	21	73,950.36	0.28	3.135 (1.507–6.567)	< .001	0.312 (0.121–0.752)	< .001
Hypertension	Without	27	16,194.35	1.67	51	176,750.46	0.29	4.569 (2.197–9.572)	< .001	Reference	
	With	17	8,121.10	2.09	29	84,435.90	0.34	4.820 (2.317–10.098)	< .001	1.792 (0.565–2.793)	.451
Coronary artery disease	Without	30	20,407.19	1.47	59	219,273.49	0.27	4.321 (2.077–9.051)	< .001	Reference	
	With	14	3,908.26	3.58	21	41,912.87	0.50	5.653 (2.718–11.843)	< .001	1.862 (1.024–3.975)	.033
Cerebrovascular disease	Without	24	21,116.97	1.14	50	229,853.26	0.22	4.132 (1.986–8.655)	.003	Reference	
	With	20	3,198.48	6.25	30	31,333.10	0.96	5.165 (2.483–10.819)	< .001	1.121 (0.792–2.865)	.386
Obesity	Without	33	23,859.01	1.38	75	259,734.80	0.29	3.792 (1.823–7.944)	< .001	Reference	
	With	11	456.45	24.10	5	1,451.56	3.44	4.462 (2.145–9.346)	< .001	1.783 (1.116–2.725)	< .001
Diabetes mellitus	Without	34	19,505.77	1.74	34	205,888.90	0.17	8.352 (4.015–17.495)	< .001	Reference	
	With	10	4,809.69	2.08	46	55,297.45	0.83	1.973 (0.948–4.132)	.096	0.864 (0.025–7.683)	.896
COPD	Without	33	19,535.06	1.69	53	227,216.23	0.23	5.727 (2.753–11.998)	< .001	Reference	
	With	11	4,780.39	2.30	27	33,970.12	0.79	2.289 (1.100–4.795)	.003	0.662 (0.159–1.195)	.134
Depression	Without	6	7,217.21	0.83	73	247,017.91	0.30	2.225 (1.069–4.660)	.015	Reference	
	With	38	17,098.25	2.22	7	14,168.45	0.49	3.558 (1.710–7.453)	< .001	1.986 (1.005–3.374)	.044
Dyslipidemia	Without	37	19,896.38	1.86	70	230,448.37	0.30	4.842 (2.328–10.142)	< .001	Reference	
	With	7	4,419.07	1.58	10	30,737.99	0.33	3.850 (1.851–8.065)	.196	0.963 (0.422–2.865)	.273
Asthma	Without	35	21,551.48	1.62	64	242,785.83	0.26	4.872 (2.342–10.206)	< .001	Reference	
	With	9	2,763.97	3.26	16	18,400.53	0.87	2.961 (1.424–6.203)	< .001	0.501 (0.033–1.794)	.267
Alcohol / substance abuse	Without	34	21,439.12	1.59	75	253,004.16	0.30	4.232 (2.034–8.865)	< .001	Reference	
	With	10	2,876.33	3.48	5	8,182.20	0.61	4.458 (2.143–9.338)	< .001	1.124 (0.856–1.973)	.870
Antidepressants	Without	41	20,187.36	2.03	67	194,055.38	0.35	4.652 (2.236–9.745)	< .001	Reference	
	With	3	4,128.10	0.73	13	67,130.98	0.19	2.968 (1.427–6.217)	< .001	0.677 (0.335–1.012)	.064
Anxiety	Without	17	5,744.21	2.96	49	149,505.30	0.33	7.140 (3.433–14.958)	< .001	Reference	
	With	10	10,450.15	0.96	2	27,245.16	0.07	10.309 (4.956–21.596)	< .001	2.010 (1.137–6.389)	.007
Headache	Without	20	13,724.07	1.46	48	170,919.66	0.28	4.103 (1.973– 8.596)	< .001	Reference	
	With	7	2,470.28	2.83	3	5,830.80	0.51	4.356 (2.094–9.124)	< .001	1.000 (0.767–1.835)	.299
Musculoskeletal pain	Without	17	13,489.25	1.26	47	170,780.19	0.28	3.621 (1.741–7.586)	< .001	Reference	
	With	10	2,705.10	3.70	4	5,970.26	0.67	4.364 (2.098–9.141)	< .001	1.207 (0.685–2.973)	.331

Adjusted for variables listed in Table 1. Multivariable Cox regression: reference in overall was comparison cohort. CI = confidence interval, COPD = chronic obstructive pulmonary disease, HR = hazard ratio, OSA = obstructive sleep apnea, PTSD = posttraumatic stress disorder, PYs = person-years.

RESULTS

The baseline characteristics of the study population are shown in **Table 1**. There were 2,316 individuals in the PTSD group and 23,160 individuals in the control group, with a similar distribution of sex, age, and income-related insurance premiums. There were no significant differences with regard to the frequency of health care utilization ($P = .966$) and PSG examinations received ($P = .092$) between the PTSD and control groups (**Table 1**). There were also no significant differences with regard to the PSG examinations among the patients with OSA between the PTSD and control groups (**Table S2** in the supplemental material). The mean age of the PTSD cohort was 41.54 ± 16.89 years, and 72.19% were women. Patients with

Table 3—Sensitivity tests for the risk of developing OSA using Cox proportional hazards model.

PTSD vs Comparison (Reference)	Adjusted HR (95% CI)	*P*
All OSA cases	4.672 (2.246–9.787)	< .001
OSA in the first year excluded	3.825 (1.763–8.167)	.001
OSA in the first 3 years excluded	3.011 (1.125–7.672)	.009

Adjusted for variables listed in Table 1. CI = confidence interval, HR = hazard ratio, OSA = obstructive sleep apnea, PTSD = posttraumatic stress disorder.

PTSD lived in more urbanized regions ($P < .001$). The PTSD group had more medical comorbidities with hypertension, cerebrovascular disease, diabetes mellitus, chronic obstructive pulmonary disease, depression, dyslipidemia, asthma, alcohol/substance abuse (all $P < .001$), coronary artery disease ($P = .027$), and anxiety disorder ($P < .001$) than those in the control group. In the PTSD group, 44 (2.06%) individuals developed OSA compared to 80 (0.37%) in the control group during the follow-up period ($P < .001$; **Table 1**). The cumulative survival rate of OSA in the PTSD group was significantly lower than that in the control group (log-rank test, $P < .001$; **Figure 2**).

Table 2 shows the Cox regression analysis of factors associated with the risk of developing OSA. After adjusting for age, sex, geographical area of residence, urbanization level of residence, monthly income, OSA-related medical comorbidities and antidepressants, the adjusted HR (aHR) was 4.672 (95% CI 2.246–9.787, $P < .001$). In stratified analyses, the aHR became nonsignificant in patients with diabetes mellitus and dyslipidemia.

Table 3 shows that PTSD was still associated with increased risk of OSA even after we excluded individuals with a diagnosis of OSA within the first year (aHR 3.825, 95% CI 1.763–8.167, $P < .001$) and the first 3 years (aHR 3.011, 95% CI 1.125–7.672, $P = .009$).

Table 4 shows that the most commonly prescribed antidepressant in PTSD in Taiwan was fluvoxamine, followed by citalopram, mirtazapine, and clomipramine in this order. In addition, it shows that all antidepressants were not associated with an increased risk of OSA development after Bonferroni correction for multiple comparisons (aHR 0.988, 95% CI 0.464–1.231, $P = .201$).

DISCUSSION

In our study, we found that Taiwanese patients with PTSD had an almost 5-fold increased risk of developing OSA compared to the control group. The Kaplan-Meier analysis revealed that patients with PTSD had a significantly lower 16-year OSA-free survival rate than did the control group. Even when the individuals with a diagnosis of OSA within the first year and the first 3 years were excluded, PTSD was still associated with increased risk of developing OSA. Several previous local cohort studies have revealed that PTSD increased the risk of OSA.[4–15] However, this is the first nationwide matched cohort study to examine the association between PTSD and the risk of OSA. It is worth noting that the overall treatment effect of antidepressants was not associated with an increased risk of OSA development in the present study.

The prevalence rates of the national sample of PTSD and OSA were 19.30 and 330.19 per 100,000 persons in 2005, respectively (**Table S1** in the supplemental material). The estimate of the prevalence rates of PTSD and OSA in our study were lower than the prevalence reported by previous studies.[47–49] There are several possible explanations for the lower prevalence rates of PTSD and OSA in our study. First, previous studies have reported a low rate of help-seeking behaviors for mental health services in Taiwanese people due to stigmatization,[50] which may lead to underestimation of PTSD prevalence. Second, we only extracted cases of OSA from the probably underestimated pool of patients with PTSD, which may have resulted in further underestimation of cases of OSA. Third, we only included patients with incident PTSD and excluded those who already had a history OSA before the study baseline. Therefore, the risk of OSA in patients with PTSD may have been underestimated in the current study.

Although the mechanism underlying the associations between PTSD and OSA has not been fully elucidated. Emerging evidence suggests that both PTSD and OSA share pathophysiological features, including biological effects on rapid eye movement sleep disturbance,[51] derangement within the neuroendocrine and neuroanatomical pathways,[52] and psychological causes such as sleep-related comorbid anxiety or depression.[53,54] In addition, patients with PTSD have more physical comorbidities such as hypertension, diabetes, and dyslipidemia than has the general population,[55] which are all risk factors for OSA.[56,57] Associations between PTSD and OSA are probably due to the physical comorbidities of patients with PTSD. Furthermore, prior studies have shown that women with PTSD with a history of sexual abuse or rape in childhood may display high levels of eating disorder behavior, resulting in weight gain,[58,59] which in turn may lead to obesity and hence increased risk of developing OSA. In addition, it is noteworthy that obesity may be a mediating variable in the causal relationship between PTSD and OSA. However, due to the limitations of the statistical methods (ie, Cox proportional hazard model[60]) we used in the present study and because variables such as BMI and body weight were not included in the health claims database, we could not precisely evaluate the mediating effects of obesity on the causal pathway between PTSD and OSA by adopting structure equation modeling[61] or causal mediation analysis.[62] Future studies with more variables are warranted to investigate this causality.

Our study found that treatment with antidepressants did not have significant negative effects on the development of OSA in patients with PTSD, although there is some evidence that specific antidepressants are associated with a greater risk of weight gain,[63] which is a risk factor for OSA development. The impact of antidepressant use on the risk of developing OSA has not been previously studied even though antidepressants are used as the first line treatment for PTSD. Further clinical studies are warranted to confirm our findings.

Table 4—Percentages of use of medications, treatment duration, and increased or decreased OSA risk for each antidepressant, and adjusted HR of antidepressants among the PTSD cohort (n = 2,136).

Antidepressants					With vs Without Antidepressants (Reference)		
Type	n	%	Duration (days)		n% Increase or Decrease of Risk / Day	Adjusted HR (95% CI)	*P*
			Mean	SD			
Overall	428		95.38	134.52	−0.013	0.988 (0.464–1.231)	.201
Fluoxetine	104	0.24	113.51	135.03	−0.140	0.841 (0.552–1.029)	.176
1–29 days	45	0.11	28.45	37.45	0.225	1.065 (0.679–1.568)	.309
≥ 30 days	59	0.14	178.38	209.45	−0.138	0.753 (0.438–1.008)	.056
Paroxetine	136	0.32	105.91	136.44	−0.089	0.906 (0.568–1.501)	.267
1–29 days	59	0.14	29.78	38.95	−0.027	0.994 (0.805–1.772)	.204
≥ 30 days	77	0.18	164.25	211.14	−0.121	0.801 (0.412–1.244)	.373
Sertraline	215	0.50	113.81	125.98	0.046	1.052 (0.773–1.889)	.786
1–29 days	101	0.24	27.86	33.45	0.083	1.023 (0.708–1.701)	.836
≥ 30 days	114	0.27	189.96	207.95	0.041	1.077 (0.806–1.989)	.713
Fluvoxamine	241	0.56	86.86	130.95	−0.117	0.898 (0.459–1.126)	.133
1–29 days	104	0.24	28.45	34.12	0.148	1.042 (0.685–1.643)	.266
≥ 30 days	137	0.32	131.20	204.45	−0.143	0.812 (0.364–1.005)	.052
Citalopram	233	0.54	99.94	143.29	−0.261	0.739 (0.561–1.094)	.068
1–29 days	89	0.21	27.65	29.87	−0.495	0.863 (0.667–1.174)	.144
≥ 30 days	144	0.34	144.62	213.39	−0.344	0.503 (0.301–0.910)	.028
Escitalopram	211	0.49	104.40	145.62	−0.131	0.863 (0.508–1.248)	.324
1–29 days	79	0.18	26.98	39.96	−0.033	0.991 (0.683–1.721)	.493
≥ 30 days	132	0.31	150.73	208.86	−0.165	0.751 (0.442–0.891)	.012
Venlafaxine	191	0.45	81.51	120.88	0.076	1.062 (0.883–1.989)	.254
1–29 days	88	0.21	25.97	28.45	−0.474	0.877 (0.456–1.324)	.186
≥ 30 days	103	0.24	128.96	199.85	0.080	1.103 (0.905–2.013)	.288
Duloxetine	191	0.45	73.16	139.65	−0.025	0.982 (0.305–2.010)	.484
1–29 days	92	0.21	24.42	29.01	0.008	1.002 (0.678–2.114)	.796
≥ 30 days	99	0.23	118.45	242.46	−0.062	0.926 (0.519–1.453)	.463
Imipramine	193	0.45	86.65	119.39	−0.156	0.865 (0.227–1.046)	.211
1–29 days	84	0.20	28.80	30.42	−0.125	0.964 (0.410–1.840)	.108
≥ 30 days	109	0.25	131.24	187.96	−0.144	0.811 (0.343–0.926)	.009
Amitriptyline	167	0.39	86.21	121.03	−0.117	0.899 (0.441–1.883)	.263
1–29 days	76	0.18	22.11	25.94	0.538	1.119 (0.828–1.753)	.313
≥ 30 days	91	0.21	139.75	200.44	−0.258	0.639 (0.296–0.877)	.005
Clomipramine	225	0.53	77.22	146.32	−0.157	0.879 (0.454–1.073)	.222
1–29 days	108	0.25	27.65	31.65	−0.116	0.968 (0.593–1.382)	.312
≥ 30 days	117	0.27	122.98	252.16	−0.225	0.723 (0.230–0.989)	.018
Mirtazapine	226	0.53	110.33	148.08	−0.081	0.911 (0.453–1.769)	.563
1–29 days	99	0.23	25.42	32.45	−0.389	0.901 (0.331–1.983)	.659
≥ 30 days	127	0.30	176.52	238.21	−0.042	0.925 (0.562–1.623)	.482
Bupropion	176	0.41	100.39	136.17	−0.156	0.843 (0.603–1.089)	.268
1–29 days	80	0.19	28.11	33.04	−0.103	0.971 (0.777–1.156)	.334
≥ 30 days	96	0.22	160.62	222.11	−0.135	0.783 (0.515–0.924)	.021

Adjusted for variables listed in Table 1. CI = confidence interval, HR = hazard ratio, OSA = obstructive sleep apnea, PTSD = posttraumatic stress disorder, SD = standard deviation.

The major strength of our study is its population-based design. However, a major limitation stems from the lack of certain data excluded from the LHID. First, due to the limitations of the LHID claims database, we were unable to obtain the detailed characteristics of PTSD, such as type of trauma, duration of trauma, or severity of symptoms, OSA, and obesity. In particular, information on the severity of obesity, such as BMI and related laboratory data, could not be obtained. Therefore, we could not precisely investigate the association between PTSD severity and the risk of developing OSA. Further clinical studies would be required to elucidate this association. Second, other residual confounding factors such as genetics, smoking, dietary habits, and other lifestyle factors were also not included in the LHID. Third, the DDD did not represent the actual use of antidepressants, and changes in the exposure to antidepressants is a complex issue in the LHID. Therefore, we could not precisely estimate the effect of antidepressants on OSA, and future studies are warranted to confirm our findings. Fourth, the incidence of PTSD and OSA may have been underestimated because only individuals who sought medical help were enrolled. Even though there were no significant differences between the frequency of health care utilization and PSG examinations between the two groups, the possibility of ascertainment bias remains. Fifth, due to the limitations of health insurance claims database and the statistical analysis we adopted in the present study, we could not investigate the possibility of a causal relationship among PTSD, obesity, and OSA. Finally, as previously mentioned, due to the structural airway differences facilitating the development of OSA between Asian and Western individuals,[21–23] the generalizability of our findings may be limited.

CONCLUSIONS

Patients with PTSD may have a 4.67-fold increased risk of developing OSA. The usage of antidepressants in the treatment of PTSD was not associated with an increased risk of developing OSA. These findings might be of use to the clinicians caring for patients with PTSD. Further research is necessary to explore the underlying mechanisms of this association.

REFERENCES

1. Boscarino JA. Diseases among men 20 years after exposure to severe stress: implications for clinical research and medical care. *Psychosom Med*. 1997;59(6):605–614.
2. Boscarino JA. External-cause mortality after psychologic trauma: the effects of stress exposure and predisposition. *Compr Psychiatry*. 2006;47(6):503–514.
3. Wentworth BA, Stein MB, Redwine LS, et al. Post-traumatic stress disorder: a fast track to premature cardiovascular disease? *Cardiol Rev*. 2013;21(1):16–22.
4. Krakow B, Germain A, Tandberg D, et al. Sleep breathing and sleep movement disorders masquerading as insomnia in sexual-assault survivors. *Compr Psychiatry*. 2000;41(1):49–56.
5. Lavie P, Katz N, Pillar G, Zinger Y. Elevated awaking thresholds during sleep: characteristics of chronic war-related posttraumatic stress disorder patients. *Biol Psychiatry*. 1998;44(10):1060–1065.
6. Engdahl BE, Eberly RE, Hurwitz TD, Mahowald MW, Blake J. Sleep in a community sample of elderly war veterans with and without posttraumatic stress disorder. *Biol Psychiatry*. 2000;47(6):520–525.
7. Sharafkhaneh A, Giray N, Richardson P, Young T, Hirshkowitz M. Association of psychiatric disorders and sleep apnea in a large cohort. *Sleep*. 2005;28(11):1405–1411.
8. Ocasio-Tascón ME, Alicea-Colón E, Torres-Palacios A, Rodríguez-Cintrón W. The veteran population: one at high risk for sleep-disordered breathing. *Sleep Breath*. 2006;10(2):70–75.
9. Yesavage JA, Kinoshita LM, Kimball T, et al. Sleep-disordered breathing in Vietnam veterans with posttraumatic stress disorder. *Am J Geriatr Psychiatry*. 2012;20(3):199–204.
10. Williams SG, Collen J, Orr N, Holley AB, Lettieri CJ. Sleep disorders in combat-related PTSD. *Sleep Breath*. 2015;19(1):175–182.
11. Krakow B, Melendrez D, Pedersen B, et al. Complex insomnia: insomnia and sleep-disordered breathing in a consecutive series of crime victims with nightmares and PTSD. *Biol Psychiatry*. 2001;49(11):948–953.
12. Krakow B, Melendrez D, Johnston L, et al. Sleep-disordered breathing, psychiatric distress, and quality of life impairment in sexual assault survivors. *J Nerv Ment Dis*. 2002;190(7):442–452.
13. Krakow B, Haynes PL, Warner TD, et al. Nightmares, insomnia, and sleep-disordered breathing in fire evacuees seeking treatment for posttraumatic sleep disturbance. *J Trauma Stress*. 2004;17(3):257–268.
14. Webber MP, Lee R, Soo J, et al. Prevalence and incidence of high risk for obstructive sleep apnea in World Trade Center-exposed rescue/recovery workers. *Sleep Breath*. 2011;15(3):283–294.
15. Arnetz BB, Templin T, Saudi W, Jamil H. Obstructive sleep apnea, posttraumatic stress disorder, and health in immigrants. *Psychosom Med*. 2012;74(8):824–831.
16. Kinoshita LM, Yesavage JA, Noda A, et al. Modeling the effects of obstructive sleep apnea and hypertension in Vietnam veterans with PTSD. *Sleep Breath*. 2012;16(4):1201–1209.
17. Klein E, Koren D, Arnon I, Lavie P. No evidence of sleep disturbance in post-traumatic stress disorder: a polysomnographic study in injured victims of traffic accidents. *Isr J Psychiatry Relat Sci*. 2002;39(1):3–10.
18. Breslau N, Roth T, Burduvali E, Kapke A, Schultz L, Roehrs T. Sleep in lifetime posttraumatic stress disorder: a community-based polysomnographic study. *Arch Gen Psychiatry*. 2004;61(5):508–516.
19. Capaldi VF, Guerrero ML, Killgore WD. Sleep disruptions among returning combat veterans from Iraq and Afghanistan. *Mil Med*. 2011;176(8):879–888.
20. Mysliwiec V, Gill J, Lee H, et al. Sleep disorders in US military personnel: a high rate of comorbid insomnia and obstructive sleep apnea. *Chest*. 2013;144(2):549–557.
21. Darvall K, Sam R, Silverman S, Bradbury A, Adam D. Obesity and thrombosis. *Eur J Vasc Endovasc Surg*. 2007;33(2):223–233.
22. Drager LF, Togeiro SM, Polotsky VY, Lorenzi-Filho G. Obstructive sleep apnea: a cardiometabolic risk in obesity and the metabolic syndrome. *J Am Coll Cardiol*. 2013;62(7):569–576.
23. Li KK, Kushida C, Powell NB, Riley RW, Guilleminault C. Obstructive sleep apnea syndrome: a comparison between Far-East Asian and white men. *Laryngoscope*. 2000;110(10):1689–1693.
24. Shen T-C, Lin C-L, Wei C-C, et al. Risk of obstructive sleep apnea in adult patients with asthma: a population-based cohort study in Taiwan. *PLoS One*. 2015;10(6):e0128461.
25. Kao L-T, Lee H-C, Lin H-C, Tsai M-C, Chung S-D. Healthcare service utilization by patients with obstructive sleep apnea: a population-based study. *PLoS One*. 2015;10(9):e0137459.
26. Shen T-C, Hang L-W, Liang S-J, et al. Risk of obstructive sleep apnoea in patients with rheumatoid arthritis: a nationwide population-based retrospective cohort study. *BMJ Open*. 2016;6(11):e013151.
27. Cheng T-M. Taiwan's National Health Insurance system: high value for the dollar. In: Okma KG, Crivelli L, eds. *Six Countries, Six Reform Models: The Healthcare Reform Experience of Israel, The Netherlands, New Zealand, Singapore, Switzerland and Taiwan*. Singapore. World Scientific; 2010: 171-204.

28. Lin C-E, Chung C-H, Chen L-F, Chi M-J. Increased risk of dementia in patients with Schizophrenia: a population-based cohort study in Taiwan. *Eur Psychiatry*. 2018;53:7–16.
29. Chou P-H, Lin C-C, Lin C-H, Loh E-W, Chan C-H, Lan T-H. Prevalence of allergic rhinitis in patients with attention-deficit/hyperactivity disorder: a population-based study. *Eur Child Adolesc Psychiatry*. 2013;22(5):301–307.
30. Epstein LJ, Kristo D, Strollo PJ, Jr, et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *J Clin Sleep Med*. 2009;5(3):263–276.
31. Kasai T, Floras JS, Bradley TD. Sleep apnea and cardiovascular disease: a bidirectional relationship. *Circulation*. 2012;126(12):1495–1510.
32. Tuomilehto H, Seppä J, Uusitupa M. Obesity and obstructive sleep apnea–clinical significance of weight loss. *Sleep Med Rev*. 2013;17(5):321–329.
33. Aurora RN, Punjabi NM. Obstructive sleep apnoea and type 2 diabetes mellitus: a bidirectional association. *Lancet Respir Med*. 2013;1(4):329–338.
34. Li J, Nanayakkara A, Jun J, Savransky V, Polotsky VY. Effect of deficiency in SREBP cleavage-activating protein on lipid metabolism during intermittent hypoxia. *Physiol. Genomics*. 2007;31(2):273–280.
35. Li J, Savransky V, Nanayakkara A, Smith PL, O'Donnell CP, Polotsky VY. Hyperlipidemia and lipid peroxidation are dependent on the severity of chronic intermittent hypoxia. *J Appl Physiol*. 2007;102(2):557–563.
36. Pronzato C. Chronic obstructive pulmonary disease and obstructive sleep apnea. Association, consequences and treatment. *Monaldi Arch Chest Dis*. 2010;73(4):155–161.
37. McNicholas WT. Chronic obstructive pulmonary disease and obstructive sleep apnea: overlaps in pathophysiology, systemic inflammation, and cardiovascular disease. *Am J Respir Crit Care Med*. 2009;180(8):692–700.
38. Teodorescu M, Barnet JH, Hagen EW, Palta M, Young TB, Peppard PE. Association between asthma and risk of developing obstructive sleep apnea. *JAMA*. 2015;313(2):156–164.
39. Wu BY, Wu BJ, Lee SM, Sun HJ, Chang YT, Lin MW. Prevalence and associated factors of comorbid skin diseases in patients with schizophrenia: a clinical survey and national health database study. *Gen Hosp Psychiatry*. 2014;36(4):415–421.
40. Pan M-L, Tsao H-M, Hsu C-C, et al. Bidirectional association between obstructive sleep apnea and depression: a population-based longitudinal study. *Medicine*. 2016;95(37):e4833.
41. Scanlan M, Roebuck T, Little P, Naughton M. Effect of moderate alcohol upon obstructive sleep apnoea. *Eur Respir J*. 2000;16(5):909–913.
42. Saunamäki T, Jehkonen M. Depression and anxiety in obstructive sleep apnea syndrome: a review. *Acta Neurol Scand*. 2007;116(5):277–288.
43. Nampiaparampil DE. Prevalence of chronic pain after traumatic brain injury: a systematic review. *JAMA*. 2008;300(6):711–719.
44. Chang C-Y, Chen W-L, Liou Y-F, et al. Increased risk of major depression in the three years following a femoral neck fracture–a national population-based follow-up study. *PLoS One*. 2014;9(3):e89867.
45. Chou P-H, Chu C-S, Chen Y-H, et al. Antidepressants and risk of cataract development: A population-based, nested case-control study. *J Affect Disord*. 2017;215:237–244.
46. VanderWeele TJ, Mathur MB. Some desirable properties of the Bonferroni correction: is the Bonferroni correction really so bad? *Am J Epidemiol*. 2019;188(3):617–618.
47. Chen Y-L, Weng S-F, Shen Y-C, et al. Obstructive sleep apnea and risk of osteoporosis: a population-based cohort study in Taiwan. *J Clin Endocrinol Metab*. 2014;99(7):2441–2447.
48. Carlson EB, Rosser-Hogan R. Trauma experiences, posttraumatic stress, dissociation, and depression in Cambodian refugees. *Am J Psychiatry*. 1991;148(11):1548–1551.
49. Hauff E, Vaglum P. Chronic posttraumatic stress disorder in Vietnamese refugees: A prospective community study of prevalence, course, psychopathology, and stressors. *J Nerv Ment Dis*. 1994;182(2):85–90.
50. Chou P-H, Lin C-C, Lin C-H, et al. Prevalence of gastroesophageal reflux disease in major depressive disorder: a population-based study. *Psychosomatics*. 2014;55(2):155–162.
51. Ross RJ, Ball WA, Dinges DF, et al. Rapid eye movement sleep disturbance in posttraumatic stress disorder. *Biol Psychiatry*. 1994;35(3):195–202.
52. de Kloet C, Vermetten E, Geuze E, Kavelaars A, Heijnen C, Westenberg H. Assessment of HPA-axis function in posttraumatic stress disorder: pharmacological and non-pharmacological challenge tests, a review. *J Psychiatr Res*. 2006;40(6):550–567.
53. Dow BM, Kelsoe JR, Jr, Gillin JC. Sleep and dreams in Vietnam PTSD and depression. *Biol Psychiatry*. 1996;39(1):42–50.
54. Sateia MJ. Update on sleep and psychiatric disorders. *Chest*. 2009;135(5):1370–1379.
55. Lin C-E, Chung C-H, Chen L-F, You C-H, Chien W-C, Chou P-H. Risk of incident hypertension, diabetes, and dyslipidemia after first posttraumatic stress disorder diagnosis: a nationwide cohort study in Taiwan. *Gen Hosp Psychiatry*. 2019;58:59–66.
56. Sareen J, Cox BJ, Stein MB, Afifi TO, Fleet C, Asmundson GJ. Physical and mental comorbidity, disability, and suicidal behavior associated with posttraumatic stress disorder in a large community sample. *Psychosom Med*. 2007;69(3):242–248.
57. Castaneda A, Jauregui-Maldonado E, Ratnani I, Varon J, Surani S. Correlation between metabolic syndrome and sleep apnea. *World J Diabetes*. 2018;9(4):66–71.
58. Wonderlich SA, Crosby RD, Mitchell JE, et al. Eating disturbance and sexual trauma in childhood and adulthood. *Int J Eat Disord*. 2001;30(4):401–412.
59. Gruber AJ, Pope HG. Compulsive weight lifting and anabolic drug abuse among women rape victims. *Compr Psychiatry*. 1999;40(4):273–277.
60. Wang W, Albert JM. Causal mediation analysis for the Cox proportional hazards model with a smooth baseline hazard estimator. *J R Stat Soc Ser C Appl Stat*. 2017;66(4):741–757.
61. De Stavola BL, Daniel RM, Ploubidis GB, Micali N. Mediation analysis with intermediate confounding: structural equation modeling viewed through the causal inference lens. *Am J Epidemiol*. 2014;181(1):64–80.
62. Taguri M, Featherstone J, Cheng J. Causal mediation analysis with multiple causally non-ordered mediators. *Stat Methods Med Res*. 2018;27(1):3–19.
63. Serretti A, Mandelli L. Antidepressants and body weight: a comprehensive review and meta-analysis. *J Clin Psychiatry*. 2010;71(10):1259–1272.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication January 5, 2019
Submitted in final revised form April 16, 2019
Accepted for publication April 16, 2019
Address correspondence to: Wu-Chien Chien, PhD Department of Medical Research, Tri-Service General Hospital, Taipei, Taiwan, Number 325, Section 2, Chenggong Road, Neihu District, Taipei City 11490, Taiwan; Tel: 886-2-87923100, extension 19189; Fax: 886-2-87927235; Email: chienwu@mail.ndmctsgh.edu.tw and Po-Han Chou, MD, Department of Psychiatry, China Medical University Hospital, China Medical University, No. 2, Yude Road, North District, Taichung City, Taiwan, 40447; Tel: 886-4-22052121-1704; Fax: 886-4-22361230; Email: phchou1980@gmail.com

DISCLOSURE STATEMENT

All authors have seen and approved the manuscript. This study was supported in part by the Tri-Service General Hospital Research Foundation (TSGH-C108-003). The funding agency did not influence the study design, data collection and analysis, decision to publish, or preparation of the manuscript. The authors report no conflicts of interest.