



Risk of incident hypertension, diabetes, and dyslipidemia after first posttraumatic stress disorder diagnosis: A nationwide cohort study in Taiwan[☆]

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1. 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, and/or avoidance of activities that trigger memories of traumatic events. Despite abundant Taiwan community-based epidemiological studies of PTSD, which mainly target minor groups that have experienced natural disasters, such as earthquakes and fires [1,2], there has not been an nationwide epidemiological PTSD study in Taiwan. The estimates of the prevalence of PTSD, which is dependent on the features of the population studies and methods for participant recruitment and assessment [3], have been reported to range from 3 to 86% in adult refugees [4,5]. It is known that PTSD is associated with many health problems, including cancer, arthritis, digestive disease, and cardiovascular disease (CVD) [6–8]. Investigators have examined PTSD in relation to a range of health outcomes, and multiple studies have reported an increased risk of developing metabolic syndrome (MetS) in patients with PTSD [9–15]. Diagnosing MetS, which is identified by abnormal glucose and insulin

metabolism, overweight and abdominal fat distribution, dyslipidemia, and hypertension, is of extreme importance because of its association with the development of type 2 diabetes mellitus and CVD [16,17]. Indeed, MetS reportedly occurs in 31.9–38.1% of patients with war-induced PTSD [18]. Despite the high prevalence of MetS among patients with PTSD, the exact causal relationship between PTSD and MetS remains unclear, mainly owing to methodological problems within previous studies, including small sample sizes [12,14], cross-sectional designs [11,12], short follow-up periods [19], and the evaluation of limited clinical variables [9,13,14]. Furthermore, the under-representation of women and minority groups (most of the studies were conducted in western countries) [11,13] may limit the generalizability of the study results. In addition, most of the previous studies that examined the link between PTSD and MetS used a composite outcome, such as MetS development, as the study outcome, instead of examining the risk of developing hypertension, diabetes, or dyslipidemia individually. Therefore, the specific risk of developing individual parameters of MetS in patients with PTSD, particularly in Asian populations, is still unknown.

Accumulating evidence indicates that elevated inflammation may

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play a causal role in the PTSD-related increased risk for the development of cardiometabolic diseases [20]. Some antidepressants, especially SSRIs, which are the predominant pharmacotherapy for PTSD [21,22], have been shown to be associated with decreases in inflammatory markers [23]. Studies have also demonstrated that antidepressants may reduce hyperglycemia, normalize glucose homeostasis, and increase insulin sensitivity [24,25]. Therefore, research should investigate the modulatory effects of antidepressants in patients with PTSD who are at a higher risk of developing MetS.

Given that the individual parameters of MetS may play different roles in the pathway linking PTSD to subsequent deleterious health conditions, including CVD [26,27], cognitive impairment [28], and premature mortality [29], further studies clarifying the associations between each metabolic parameter of MetS and PTSD are of paramount importance. Using a population-based prospective study design, we aimed to examine the associations between PTSD and the risk of developing individual MetS parameters, including hypertension, dyslipidemia, and diabetes. We hypothesized that PTSD would be associated with an increased risk of developing any MetS parameter and that antidepressants may modulate MetS in patients with PTSD.

2. Methods

2.1. Data sources

The National Health Insurance (NHI) program was launched in Taiwan in 1995, and nearly 99% of Taiwanese residents were enrolled [30]. In the present study, we used the Longitudinal Health Insurance Database 2005 (LHID2005) released by the Bureau of NHI. The LHID2005 contains all longitudinal claims data from 2000 to 2013 of 1,000,000 individuals who were randomly selected from among the 25.68 million enrollees of the NHI program from January 1, 2005 to January 1, 2006 [31]. The sample was created by the Bureau of NHI using a systematic sampling method to randomly extract a representative database from the entire Taiwan NHI database. No statistically significant differences with regard to age, sex, and medical costs were identified in the LHID 2005. The current study adopted a cohort design to investigate the incidence and risk of developing MetS in patients with PTSD from January 1, 2000 to December 31, 2013. Patient consent was not required to access the LHID 2005, and this study was approved by the Institutional Review Board of Tri-Service General Hospital (No.: 2-105-05-082).

2.2. Inclusion criteria for patients with PTSD and the control cohort

Since Taiwan's NHI was launched in 1995, patients' medical claims before 1995 are unavailable. Therefore, information related to patients diagnosed with PTSD before 1995 was not available; thus, the duration of illness could not be determined. Therefore, we chose to include patients who were newly diagnosed with PTSD as our study cohort in order to prevent survival bias. To establish this cohort, we excluded patients with a diagnosis of PTSD before 2000 or diagnoses of hypertension, dyslipidemia, and diabetes before the first diagnosis of PTSD. Patients with an unspecified sex and those < 18 years of age were also excluded from this study ($n = 129$). The enrollment date was considered the index date. A total of 953 individuals ≥ 18 years of age who were newly diagnosed with PTSD (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 309.81) by board-certified psychiatrists (using the DSM-5 criteria) between January 1, 2000 and December 31, 2013 and who did not have a history of the metabolic parameters of MetS, including diabetes mellitus (ICD-9-CM code 250), hypertension (ICD-9-CM codes 401–405), or dyslipidemia (ICD-9-CM code 272), before enrollment, were included in the PTSD cohort.

Our control cohort was selected from the remaining patients during the same period (January 1, 2000 to December 31, 2013). Similar

exclusion criteria that were applied for the PTSD cohort were also applied for the control cohort, namely patients with a diagnosis of PTSD before 2000 and/or during the study period, patients of an unspecified sex, and/or those < 18 years of age. We randomly selected a control cohort from the remaining eligible subjects ($n = 3812$) and matched the subjects according to the index year. The first time the patients in the control cohort sought medical consultation during 2000–2013 was considered the index date.

2.3. Main outcome

All study participants were followed from the index date until the development of any new-onset metabolic parameter of MetS, including hypertension, dyslipidemia, and diabetes mellitus, or until the end of 2013. In order to achieve diagnostic validity, all diagnoses had to be specified at least once in inpatient or outpatient medical records with concomitant medication prescriptions for patients with MetS.

2.4. Possible confounding variables

Medical comorbidities at enrollment and during the entire follow-up period, including nephritis, nephrotic syndrome, and nephrosis (ICD-9-CM codes 580–589); thyroid disease (ICD-9-CM codes 242–244); systemic autoimmune diseases (ICD-9-CM codes shown in Table S); and chronic obstructive pulmonary disease (ICD-9-CM 490–496), were also identified in our study. All diagnoses were given at least twice by corresponding board-certified physicians after related laboratory examinations to achieve diagnostic validity. We also assessed the psychiatric comorbidity of depression (ICD-9-CM codes 296.2–296.3, 311, 300.4). In order to achieve diagnostic validity, patients required ≥ 2 diagnoses of depression by board-certified psychiatrists. Other variables, including the level of urbanization (from the most urbanized [level 1] to the least urbanized [level 4]) [32], season, hospital type (medical center, regional hospital, or district hospital), residential location (northern Taiwan, central Taiwan, southern Taiwan, eastern Taiwan, and the outer islands), and income-related insurance premiums, were also assessed in our study. The following medications used by patients during the follow-up period were considered in the analysis: steroids, antidepressants, antipsychotics, and mood stabilizers.

2.5. Antidepressant exposure

In the present study, we investigated the associations between the risk of developing MetS and the cumulative dosage of antidepressants during the study period in patients with PTSD. Patients who did not use a specified drug contributed to “zero” dose of the drug. The defined daily dose (DDD), recommended by the World Health Organization, is the assumed average maintenance dose per day of a drug, and the daily dose of each antidepressant was based on the international standard DDD.

(ATC/DDD Index 2018. <http://www.whocc.no/atc-ddd-index/> [accessed February 23, 2018]). In this study, we used the DDD to prescribe 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 (cDDD), that is, the sum of DDDs of any antidepressant, served as the index of cumulative dosage of an antidepressant. This method has been adopted in many previous pharmacological studies [33]. 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 assess the duration or continuation of antidepressant usage precisely.

2.6. Statistical analysis

All statistical analyses were performed using SPSS for Windows,

version 22.0 (IBM Corp., Armonk, NY). Chi-square and *t*-tests were used to evaluate the distributions of the categorical and continuous variables, respectively. Cox proportional hazards models were used to investigate the relationships between PTSD and hypertension, diabetes, or dyslipidemia. The results are presented as the adjusted hazard ratio (aHR) with a 95% confidence interval (CI). A stratified analysis was conducted to compare the effects of sex and age on the development of hypertension, diabetes, or dyslipidemia. Additionally, 2 sensitivity analyses were conducted: 1) we excluded patients who developed metabolic syndrome within 1–3 years of the index date of PTSD diagnoses, which was based on previous studies of the Taiwan LHID [34,35], and 2) we included patients who later developed hypertension, diabetes, or hyperlipidemia without concomitant use of anti-hypertensives, anti-diabetic medications, or lipid lowering medications. Further, we analyzed the risk of hypertension, diabetes, or dyslipidemia development in patients with PTSD individually. Among the PTSD cohort, each antidepressant was investigated to analyze the risk of developing any parameter of MetS using Cox proportional hazards models. Differences in the hypertension-, diabetes-, or dyslipidemia-free survival curves between the PTSD and control cohorts are illustrated by Kaplan-Meier plots with the log-rank test. The level of statistical significance was set at a two-tailed *P* value of < 0.05.

3. Results

3.1. Baseline characteristics of the study population

There were 953 subjects in the PTSD cohort and 3812 subjects in the control cohort.

There were no significant differences with regard to frequency of health care utilization between the PTSD and control groups (*P* = .130; Table 1). The mean age in the PTSD cohort was younger than it was in the control cohort (*P* < .001), the percentage of women was higher in the PTSD cohort than it was in the control cohort (*P* < .001), and individuals in the PTSD cohort had significantly more comorbidities of depression (*P* < .001), thyroid disease (*P* = .038), and systemic autoimmune diseases (*P* = .005) than individuals in the control cohort. Further, significantly more individuals in the PTSD cohort were treated with antidepressants, antipsychotics, and mood stabilizers than in the control cohort (all *P* < .001). Other sociodemographic characteristics of the study population are shown in Table 1.

3.2. Association between PTSD and MetS

A significantly higher percentage of patients in the PTSD cohort developed hypertension, diabetes, or hyperlipidemia than in the control cohort (*P* = .001, Table 1). After adjusting for age, sex, and all of the covariates, the Cox proportional hazards model revealed that the adjusted hazard ratio (aHR) for developing any metabolic parameter of MetS was 4.451 (95% CI: 2.109–5.001, *P* < .001; Table 2) for patients in the PTSD cohort as compared to patients in the control cohort. The results of the 2 sensitivity analyses showed similar findings (Table 2, Table S1). The Kaplan-Meier analysis showed that the PTSD cohort was associated with a lower cumulative survival rate for developing diabetes (log-rank *P* = .022), hypertension, dyslipidemia, or any metabolic parameter of MetS (all log-rank *P* < .001) than the control cohort during the follow-up period (Fig. 1).

3.3. Risk of MetS stratified by sex and age

We analyzed the data stratified by sex and age. The risk for developing MetS in male subjects with PTSD (aHR: 6.742, 95% CI: 4.184–7.233, *P* < .001) was higher than that in female subjects with PTSD (aHR: 3.611, 95% CI: 2.064–4.951, *P* < .001). Among the different age groups, we found that younger adults (< 40 years; aHR: 3.196, 95% CI: 1.976–4.119, *P* < .001), middle-aged adults

Table 1
Characteristics of study population.

Characteristics	With PTSD (n = 953)		Without PTSD (n = 3812)		<i>P</i>
	n	%	n	%	
Overall metabolic parameters	123	12.91	357	9.37	0.001**
Diabetes	29	3.04	142	3.73	0.311
Hypertension	51	5.35	120	3.15	0.001**
Dyslipidemia	54	5.67	104	2.73	< 0.001***
Sex					< 0.001***
Male	356	37.36	2014	52.83	
Female	597	62.64	1798	47.17	
Age (yrs)	36.93 ± 13.18		49.15 ± 14.97		< 0.001***
Age groups (years)					< 0.001***
< 40	601	63.06	1100	28.86	
40–59	295	30.95	1268	33.26	
≥60	57	5.98	1444	37.88	
Insured premium (NTD)					< 0.001***
< 18,000	891	93.49	3327	87.28	
18,000–34,999	46	4.83	371	9.73	
≥35,000	16	1.68	114	2.99	
Comorbidities					
Depression	653	68.52	297	7.79	< 0.001***
Nephritis/Nephrotic syndrome/Nephrosis	21	2.20	140	3.67	0.025*
Thyroid disease	27	2.83	68	1.78	0.038*
Chronic obstructive pulmonary disease,	79	8.29	361	9.47	0.260
Systemic autoimmune disease	55	5.77	142	3.73	0.005**
Medications					
Steroids	112	11.75	489	12.83	0.371
Antidepressants	641	67.26	1276	33.47	< 0.001***
Antipsychotics	480	50.37	1034	27.12	< 0.001***
Mood stabilizers	567	59.50	1102	28.91	< 0.001***
Season					< 0.001***
Spring (Mar–May)	189	19.83	920	24.13	
Summer (Jun–Aug)	256	26.86	991	26.00	
Autumn (Sep–Nov)	310	32.53	943	24.74	
Winter (Dec–Feb)	198	20.78	958	25.13	
Location					< 0.001***
Northern Taiwan	423	44.39	1012	26.55	
Middle Taiwan	186	19.52	876	22.98	
Southern Taiwan	285	29.91	933	24.48	
Eastern Taiwan	55	5.77	802	21.04	
Outlets islands	4	0.42	189	4.96	
Urbanization level					< 0.001***
1 (The highest)	363	38.09	1014	26.60	
2	414	43.44	1250	32.79	
3	76	7.97	735	19.28	
4 (The lowest)	100	10.49	813	21.33	
Hospital type					< 0.001***
Hospital center	325	34.10	1011	26.52	
Regional hospital	470	49.32	1345	35.28	
Local hospital	158	16.58	1456	38.20	
Frequency of health service utilization (Visits)					0.130
1–5	222	23.29	1008	26.44	
6–10	598	62.75	2301	60.36	
11–20	101	10.60	407	10.68	
≥21	32	3.36	96	2.52	

NTD, New Taiwan Dollar; PTSD, posttraumatic stress disorder; *P*: Chi-square test on category variables and *t*-test on continue variables.

* *P* < .05.

** *P* < .01.

*** *P* < .001..

(40–59 years; aHR: 4.311, 95% CI: 2.001–5.003, *P* < .001), and older adults (≥60 years; aHR: 6.184, 95% CI: 3.503–6.974, *P* < .001) with PTSD all had a significantly higher risk of developing MetS than controls. The interactive effects of age and sex revealed that older male patients had the highest risk of developing any parameter of MetS (aHR: 6.501, 95% CI: 4.001–7.013, *P* < .001; Table 2).

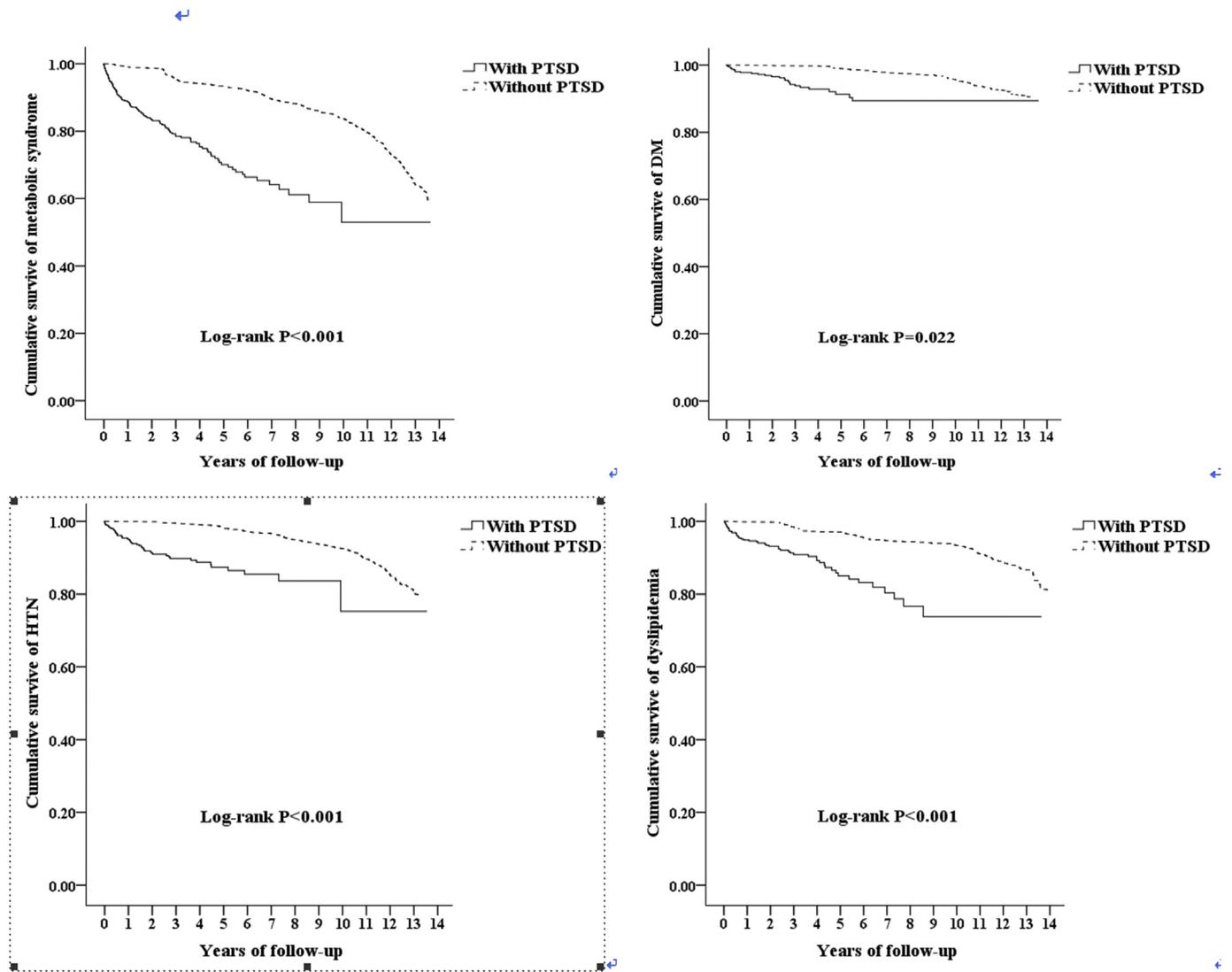


Fig. 1. Comparison of Kaplan-Meier survival curve estimates of metabolic syndrome (total/subgroups) between the study groups. Left-upper: Metabolic syndrome (Diabetes, hypertension, or dyslipidemia). Right-upper: Diabetes mellitus (DM). Left-bottom: Hypertension (HTN). Right-bottom: Dyslipidemia.

Table 2

Incidence and risk of developing any metabolic parameters of MetS using multivariable Cox proportional hazard regression model, stratified by sex and age groups.

Stratified		With PTSD (n = 953)			Without PTSD (n = 3812)			With PTSD vs. Without PTSD (Reference)	
		Events	PYs	Rate (per 10 ³ PYs)	Events	PYs	Rate (per 10 ³ PYs)	aHR ^{***} (95% CI)	P
Overall		123	8977.17	13.701	357	45,248.44	7.890	4.451 (2.109–5.001)	< 0.001 ^{***}
Sex	Male	47	2632.75	17.852	171	22,972.81	7.444	6.742 (4.184–7.233)	< 0.001 ^{***}
	Female	76	6344.42	11.979	174	23,155.44	7.514	3.611 (2.064–4.951)	< 0.001 ^{***}
Age groups (yrs)	< 40	49	6305.81	7.771	93	14,232.49	6.534	3.196 (1.976–4.119)	< 0.001 ^{***}
	40–59	49	3877.77	12.636	122	14,997.10	8.135	4.311 (2.001–5.003)	< 0.001 ^{***}
	≥60	25	1075.71	23.240	142	16,018.85	8.865	6.184 (3.503–6.974)	< 0.001 ^{***}
Sex × age groups (yrs)	Male, < 40	19	1297.07	14.648	45	7024.93	6.406	6.501 (4.001–7.013)	< 0.001 ^{***}
	Male, 40–59	18	900.97	19.978	59	7650.13	7.712	6.674 (4.154–7.099)	< 0.001 ^{***}
	Male, ≥60	10	434.71	23.004	67	8297.75	8.074	6.893 (4.306–7.287)	< 0.001 ^{***}
	Female, < 40	30	5008.74	5.990	48	7207.56	6.660	2.298 (1.248–3.862)	< 0.001 ^{***}
	Female, 40–59	31	2976.80	10.414	63	7346.97	8.575	3.574 (1.987–4.443)	< 0.001 ^{***}
	Female, ≥60	15	641.00	23.401	75	7721.10	9.714	5.977 (3.302–6.678)	< 0.001 ^{***}

Abbreviations: aHR, adjusted hazard ratio; MetS, metabolic syndrome; PTSD, posttraumatic stress disorder, PYs, person-years; CI, confidence interval.

* P < .05.

** P < .01.

*** P < .001..

Table 3

Percentages, duration, decreased risk ratio per day, and risk of developing any metabolic parameters of MetS using multivariable Cox proportional hazard regression model among the PTSD cohort (n = 953), stratified by each antidepressant.

Type and cDDD	Antidepressants			With antidepressants vs. without antidepressants (Reference)		
	n	%	Duration (days)	Decreased risk ratio per day	aHR (95% CI)	P
Overall	641		92.12 ± 110.19	0.328	0.698 (0.495–0.862)	< 0.001***
Fluoxetine	119	17.47	105.44 ± 127.40	0.207	0.782 (0.592–0.913)	0.005**
1–29 days	35	5.14	28.45 ± 36.45	0.612	0.826 (0.624–1.015)	0.097
≥30 days	84	12.33	137.52 ± 165.29	0.228	0.687 (0.402–0.836)	< 0.001***
Paroxetine	141	20.70	97.30 ± 112.96	0.341	0.668 (0.422–0.897)	0.001**
1–29 days	46	6.75	26.78 ± 35.92	1.210	0.676 (0.438–0.913)	0.004**
≥30 days	95	13.95	131.44 ± 150.26	0.265	0.652 (0.402–0.811)	< 0.001***
Sertraline	130	19.09	104.86 ± 113.44	0.275	0.712 (0.602–0.906)	0.001**
1–29 days	41	6.02	27.95 ± 30.25	0.809	0.774 (0.686–0.977)	0.025*
≥30 days	89	13.07	140.29 ± 151.77	0.284	0.602 (0.545–0.810)	< 0.001***
Fluvoxamine	101	14.83	114.63 ± 147.26	0.452	0.482 (0.264–0.562)	< 0.001***
1–29 days	31	4.55	28.02 ± 33.98	1.792	0.498 (0.304–0.646)	< 0.001***
≥30 days	70	10.28	152.98 ± 197.42	0.350	0.465 (0.230–0.512)	< 0.001***
Citalopram	141	20.70	73.99 ± 91.16	0.968	0.284 (0.186–0.358)	< 0.001***
1–29 days	52	7.64	26.11 ± 30.25	2.689	0.298 (0.201–0.384)	< 0.001***
≥30 days	89	13.06	101.96 ± 126.74	0.752	0.233 (0.154–0.306)	< 0.001***
Escitalopram	133	19.53	84.87 ± 123.41	0.694	0.411 (0.302–0.621)	< 0.001***
1–29 days	51	7.49	27.97 ± 34.62	2.052	0.426 (0.378–0.676)	< 0.001***
≥30 days	82	12.04	120.26 ± 178.64	0.504	0.394 (0.269–0.566)	< 0.001***
Venlafaxine	80	11.75	105.04 ± 142.90	0.349	0.633 (0.402–0.843)	< 0.001***
1–29 days	23	3.38	25.92 ± 38.42	1.265	0.672 (0.424–0.896)	< 0.001***
≥30 days	57	8.37	136.97 ± 185.06	0.297	0.593 (0.384–0.811)	< 0.001***
Duloxetine	126	18.50	72.67 ± 77.44	0.643	0.533 (0.345–0.777)	< 0.001***
1–29 days	44	6.46	22.01 ± 28.96	1.899	0.582 (0.398–0.798)	< 0.001***
≥30 days	82	12.04	99.86 ± 103.45	0.500	0.501 (0.287–0.713)	< 0.001***
Imipramine	63	9.25	79.09 ± 86.88	0.741	0.414 (0.206–0.602)	< 0.001***
1–29 days	28	4.11	26.90 ± 30.52	2.152	0.421 (0.259–0.709)	< 0.001***
≥30 days	35	5.14	120.84 ± 131.97	0.496	0.401 (0.181–0.590)	< 0.001***
Clomipramine	60	8.81	85.84 ± 99.12	0.532	0.543 (0.364–0.735)	< 0.001***
1–29 days	19	2.79	28.30 ± 34.52	1.530	0.567 (0.398–0.799)	< 0.001***
≥30 days	41	6.02	112.51 ± 129.06	0.434	0.512 (0.342–0.672)	< 0.001***
Amitriptyline	42	6.17	91.05 ± 99.96	0.354	0.678 (0.482–0.897)	< 0.001***
1–29 days	15	2.21	27.52 ± 33.08	0.967	0.734 (0.533–1.020)	0.134
≥30 days	27	3.96	126.35 ± 137.12	0.355	0.551 (0.302–0.712)	< 0.001***
Mirtazapine	81	11.89	89.44 ± 97.24	0.787	0.296 (0.184–0.426)	< 0.001***
1–29 days	26	3.82	25.12 ± 30.81	2.460	0.382 (0.201–0.486)	< 0.001***
≥30 days	55	8.08	119.84 ± 128.64	0.667	0.201 (0.111–0.389)	< 0.001***
Bupropion	68	9.99	94.39 ± 101.99	0.249	0.765 (0.712–1.098)	0.121
1–29 days	20	2.94	27.06 ± 32.45	0.510	0.862 (0.737–1.163)	0.256
≥30 days	48	7.05	122.45 ± 130.96	0.243	0.703 (0.622–1.004)	0.053

MetS, metabolic syndrome; PTSD, posttraumatic stress disorder; DDD, defined daily dose; cDDD, cumulative DDD; CI, confidence interval; aHR, adjusted hazard ratio; Adjusted for sex, age, insured premium, comorbidities, medications, season, location, urbanization level, and level of care.

* $P < .05$.

** $P < .01$.

*** $P < .001$.

3.4. Association between antidepressant use and the risk of developing MetS

Table 3 shows that patients with PTSD who were treated with antidepressants had a significantly lower risk of developing any metabolic parameter of MetS than those who were not treated with antidepressants (aHR: 0.698, 95% CI: 0.495–0.862, $P < .001$). Treatment with antidepressants, including fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram, venlafaxine, duloxetine, imipramine, clomipramine, amitriptyline, and mirtazapine, in patients with PTSD was associated with a decreased risk of developing MetS (all $P < .05$). In particular, patients treated with these antidepressants for ≥ 30 days had an even lower risk of developing MetS than those treated with antidepressants for < 30 days.

4. Discussion

To our knowledge, this is the first study to use a population-based dataset from an Asian country to investigate the risk of MetS in patients with PTSD. Consistent with the findings of previous studies, we found that patients with PTSD had an increased risk of developing MetS as

compared to control subjects [9–15]. Sensitivity analyses for the risk of developing any parameter of MetS after excluding the first year and the first three years of observation remained significant. More specifically, we found an increased risk of new-onset hypertension [36–38], dyslipidemia [39–41], and diabetes [42–45] in patients with PTSD as compared to controls during the follow-up period, which is consistent with previous findings. It is worth noting that the age of the PTSD group was significantly lower than the control group. Lin et al. (2011) reported that the utilization rate of medical services in young people is substantially lower than that of the elderly [46], which implies that the disease detection rate of MetS in the PTSD group may be lower than the control group. Therefore, the risk of developing of MetS in patients with PTSD in the present study may be underestimated. On the other hand, in the present study, patients with PTSD were prone to living in urban areas. It was probably due to that urbanization can lead to increased rates of trauma exposure because of higher concentrations of poverty, substance abuse, and crime [47] or that individuals living in areas with the higher urbanization levels are more likely to have access to medical services compared to those living in areas with the lower urbanization levels [46].

The proportion of the national sample of PTSD is roughly 0.1% (987/1,000,000). The estimate of the prevalence of PTSD in our study was lower than the prevalence in previous studies [4,5]. There were several possible reasons that may help explain the lower prevalence of PTSD in our study. First, to increase the diagnostic validity, only the cases of PTSD that were diagnosed by board-certified psychiatrists were included. Secondly, previous studies have reported a low rate of help-seeking behaviors for mental health services in Taiwanese people due to stigmatization [48]. Third, we excluded PTSD patients who had a history of the metabolic parameters of MetS, including diabetes mellitus, hypertension, or dyslipidemia, before the study baseline. Therefore, the risk of MetS in patients with PTSD may have been underestimated in the current study.

Our study results demonstrated increased risks of developing MetS in patients with PTSD, which are compatible with previous reports [8,36,49–54]. The mechanism underlying the associations between PTSD and MetS has not been fully elucidated. Emerging evidence suggests that both PTSD and MetS share pathophysiological features, including hypothalamic-pituitary-adrenal (HPA) and sympathoadrenomedullary dysfunction [55,56], inflammation [57], common genetic links, and epigenetic interactions [58,59]. Furthermore, patients with PTSD may be at an increased risk for developing depression, substance use disorders, or an unhealthy lifestyle, which may also increase the risk of developing MetS [60]. Although studies report that there are biological, psychological, and behavioral factors mediating the association between PTSD and MetS, data regarding behavioral and biological mediating factors are not recorded in the NHI database. Therefore, further studies are required to elucidate the complicated factors underlying the association between PTSD and MetS.

Here, we demonstrated that antidepressant treatment in patients with PTSD was associated with a decreased risk of developing MetS. A prior study by van Reedt Dortland et al. (2010) [61] indicated that tricyclic antidepressants (TCAs) independently increased the odds ratio (OR) for the development of MetS (OR: 2.30, 95% CI: 1.21–4.36, $P = .01$), while selective serotonin reuptake inhibitors (SSRIs), serotonergic and noradrenergic reuptake inhibitors (SNRIs), or other antidepressant types did not. However, there were methodological concerns associated with this previous study. Specifically, the cross-sectional design of the study did not permit the authors to make causative inferences regarding the relationship between psychopathological characteristics and MetS alterations. Moreover, the inclusion of a relatively small number of TCA users lowered the statistical power of the results. Finally, the study population did not focus on patients with PTSD; therefore, we cannot directly compare these findings to our own, and the association between antidepressant treatment and an increased risk of developing MetS remains controversial.

Another prospective study conducted by Hiles et al. (2016) [62] showed that antidepressants, including TCAs, SSRIs, or other antidepressants, are independently associated with dyslipidemia and a number of metabolic abnormalities, such as hypertension and blood glucose intolerance. Nevertheless, limited research on long-term prospective relationships (*i.e.*, from 2- to 6-year follow-up periods) indicates that the effects of psychopathology and antidepressants on MetS may be explained by other unmeasured factors, including lifestyle or other enduring behavioral or biological factors. Furthermore, methodological problems existed in the study by Hiles et al. [62], including the small number of TCA users and the lack of focus on patients with PTSD. In contrast, the results of our study indicated that treatment with SSRIs, SNRIs, or TCAs (*vs.* no treatment) was associated with a lower risk of developing MetS, especially in the long-term users (≥ 30 days). With regard to the association between antidepressants and MetS, most types of antidepressants, including SSRIs [63–66] or SNRIs [67–69], have little effect on blood glucose levels, blood pressure, and lipid profiles in patients with depression. In contrast to the findings of prior studies showing that paroxetine (an SSRI) or TCA use is associated with dyslipidemia or glucose intolerance in patients with depression

[70–72], our study demonstrated that paroxetine or TCA use was associated with a decreased risk of developing MetS. However, the main population of these studies was patients with depression, not patients with PTSD; therefore, we cannot directly compare the findings of these studies to our own.

The mechanism underlying the association between antidepressants and the development of metabolic syndrome remains unknown. However, it has been shown that the amygdala in patients with PTSD demonstrates hypersensitivity to emotional stimulus [73], and long-term amygdala hyperactivity is associated with increased arterial inflammation, which may lead to an increased risk of cardiometabolic diseases in patients with PTSD [74]. Therefore, antidepressants may reduce the risk of MetS in patients with PTSD by reducing amygdala activity [75].

The current study had multiple strengths, including the utilization of real-world data with a large sample size, a long follow-up period, a longitudinal follow-up design, and adjustments for comorbid conditions. However, the present study also had several limitations that warrant consideration. First, due to limitations of the LHID claims database, we were unable to obtain detailed characteristics of the PTSD group, such as type of trauma, duration of trauma, or severity of symptoms. Therefore, we could not thoroughly investigate the association between PTSD and the risk of developing any parameter of MetS. Further clinical studies are required to elucidate this association. Second, other residual confounding factors, such as genetic, dietary, biological, and behavioral factors, were not included in the NHI database. 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 MetS, and future studies are warranted to confirm our findings. Finally, the incidence of PTSD may be underestimated because only patients who visited psychiatrists were recorded in the LHID. However, as shown in Table 1, there were no significant differences regarding the frequency of healthcare utilization between the two groups. Even though, there is still possible ascertainment bias as we did not have data on the number of laboratory measurements.

5. Conclusions

Overall, PTSD is a devastating medical syndrome that is associated with clinical and biochemical abnormalities that are associated with the parameters of MetS. Abnormalities in the metabolic parameters contribute to the burden of CVD [6–8], the largest cause of premature mortality in this population [76]. Antidepressant medications may exert beneficial effects on metabolic physiology. Clinicians are encouraged to familiarize themselves with the effects of antidepressant medications on metabolic profiles to provide a balanced view of the benefits and risks that are associated with these treatments for their patients with PTSD.

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Declaration of interest

None.

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