

# Risk of Psychiatric Disorders in Multiple Sclerosis: A Nationwide Cohort Study in an Asian Population

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**Background:** Multiple sclerosis (MS) is a demyelinating disease that can damage neurons in the brain and spinal cord and is associated with several psychiatric disorders. However, few studies have evaluated the risk of psychiatric disorders in patients with MS by using a nationwide database. This study investigated the association between MS and the risk of psychiatric disorders.

**Methods:** Using data from the Taiwan National Health Insurance Research Database from 2000 to 2015, we identified 1066 patients with MS. After adjustment for confounding factors, Fine and Gray's competing risk model was used to compare the risk of psychiatric disorders during 15 years of follow-up.

**Results:** Of the patients with MS, 531 (4622.86 per 10<sup>5</sup> person years) developed psychiatric disorders; by contrast, 891 of the 3198 controls (2485.31 per 10<sup>5</sup> person years) developed psychiatric disorders. Fine and Gray's competing risk model revealed an adjusted hazard ratio (HR) of 5.044 (95% confidence interval = 4.448–5.870,  $p < 0.001$ ) after adjustment for all the covariates. MS was associated with depression, anxiety, bipolar disorder, sleep disorders, schizophrenia, schizophreniform disorder, and other psychotic disorders (adjusted HR: 12.464, 4.650, 6.987, 9.103, 2.552, 2.600, 2.441, and 2.574, respectively; all  $p < 0.001$ ). Some disease-modifying drugs were associated with a lower risk of anxiety or depression.

**Conclusion:** Patients with MS were determined to have a higher risk of developing a wide range of psychiatric disorders.

**Keywords:** multiple sclerosis, psychiatric disorders, depression, anxiety

## Introduction

Although patients with multiple sclerosis (MS) experience considerable challenges and even disability, comprehension of the underlying factors of this disease, including genetics and environmental conditions, has improved.<sup>1</sup> MS often has negative effects on the patients' quality of life as well as their interpersonal relationships, employment, and social life.<sup>2</sup> Neuroimaging research have revealed that symptoms can originate from different brain networks, regardless of the pathological substrate, and from disconnections caused by damage to the strategic white matter tracts.<sup>3</sup>

Previous studies have found that some neuropsychiatric disorders are associated with several immune-mediated inflammatory diseases,<sup>4</sup> such as Guillain-Barre syndrome,<sup>5</sup> fibromyalgia,<sup>6</sup> allergic diseases,<sup>7</sup> and periodontal inflammatory diseases.<sup>8-11</sup> Psychological stressors related to the inflammatory diseases might also contribute to both psychiatric and physical morbidity,<sup>12</sup> and several studies have found that MS is associated with depression, anxiety, bipolar disorder, sleep

disorders, alcohol abuse, substance abuse, and psychosis.<sup>13,14</sup> However, in Taiwan, the prevalence of MS is approximately 2–5 per 100,000,<sup>15–17</sup> which is much lower than the 10-year prevalence of MS in the United States (149.2–309.2 per 100,000).<sup>18,19</sup> Most of the studies about the association between multiple sclerosis and psychiatric disorders are from Western countries, with higher MS prevalence, including anxiety, depression, bipolar disorder, sleep disorder, alcohol abuse, drug abuse, and psychotic disorder, such as schizophrenia.<sup>4,13,14,20–23</sup> Other studies have reported that patients with MS to be at risk for some psychiatric disorders including depression<sup>24</sup> and erectile dysfunction,<sup>25</sup> but no nationwide population-based study has yet been conducted on the correlations of MS with most of the other aforementioned psychiatric disorders. Therefore, a nationwide cohort study must be executed to determine the association of MS with psychiatric disorders in Taiwan. This explored this topic by applying National Health Insurance Research Database (NHIRD)-derived data in order to determine the psychiatric morbidity of patients with MS in Taiwan.

## Methods

### Data Sources

The National Health Insurance (NHI) program, which is Taiwan's single-payer insurance system, was launched in 1995. As of June 2018, it provided medical coverage for an estimated 23 million individuals (>99% of the population in Taiwan), in collaboration with 97% of medical providers.<sup>26,27</sup> Previously executed research has documented the program's details.<sup>28–40</sup>

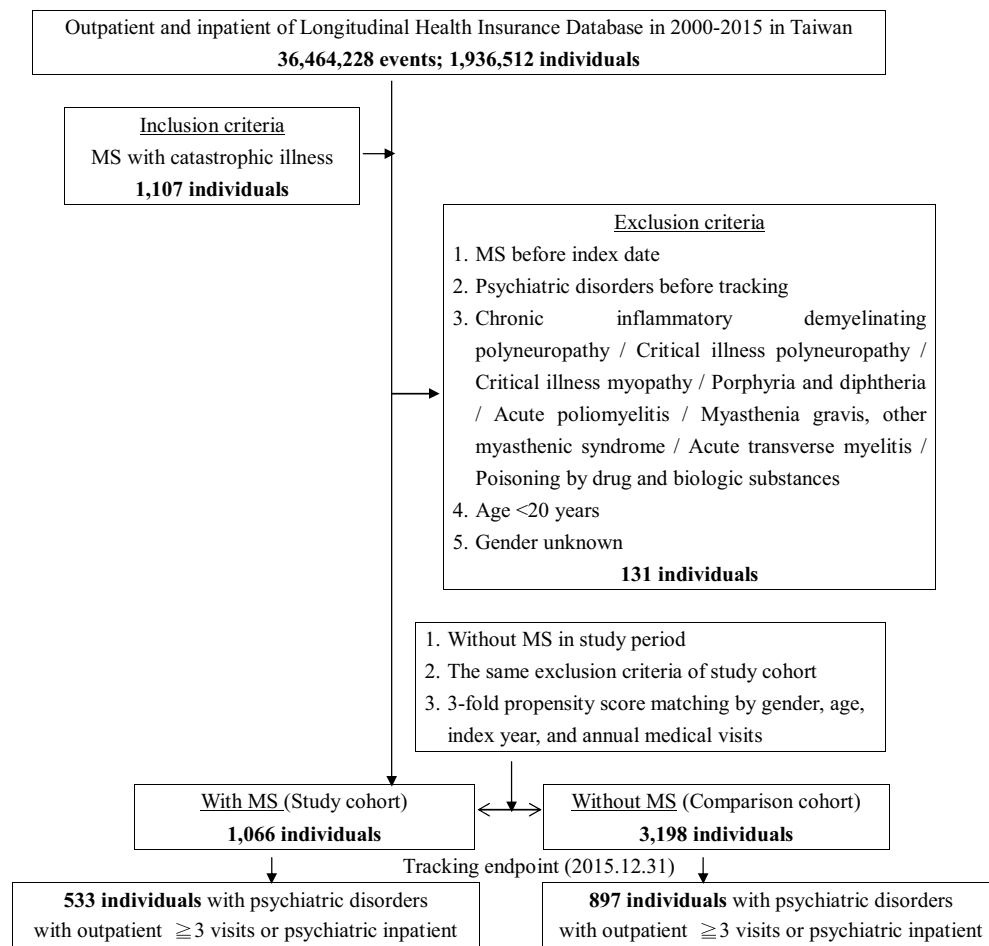
The NHIRD comprises comprehensive data on patients' sex and their date of birth as well as the prescriptions, dental care, outpatient care, and inpatient care that they have received. In accordance with the Personal Information Protection Act, patient identifiers undergo encryption prior to the release of data for use in research. NHIRD-recorded diagnoses are coded in accordance with the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). Board-certified neurologists and board-certified psychiatrists gave all MS diagnoses and all psychiatric disorder diagnoses, respectively. In Taiwan, the diagnosis of MS was according to the McDonald criteria and serial of the revised versions.<sup>41–43</sup>

In the present study, inpatients determined to have received an MS diagnosis (ICD-9-CM code: 340) at discharge during 2000–2015 were identified from the 2-

million Longitudinal Health Insurance Database, a subset of the NHIRD. Clinic and hospital reimbursement claims were reviewed by licensed medical record technicians for coding verification.<sup>27</sup> Senior external specialists in psychiatry and neurology are selected by the National Health Insurance Administration (NHIA) to periodically conduct random reviews of records pertaining to outpatient care visits as well as inpatient claims in order to confirm accurate diagnoses.<sup>44</sup>

### Study Design and Sampling

In our executed population-based, matched-cohort study, we identified from the inpatient data set adults who had recently received an MS diagnosis during the period from January 1, 2000, to December 31, 2015. To restrict our sample to only patients with newly registered MS, we excluded patients who had received an MS diagnosis prior to 2000. Additionally, patients who had received a diagnosis of depressive, bipolar, anxiety, sleep, schizophrenia, schizophreniform disorder, other psychotic disorder, or substance-related disorders (disorders pertaining to alcohol use or illicit drug use) before 2000 were excluded. All patients under the age of 20 years were also excluded so that only adult patients were included. The patients' catastrophic illness certificates (CICs) were used to ensure the accuracy of the MS diagnosis because in accordance with NHI regulations, patients with a CIC are exempted from copayment for MS-related medical care after their medical records and imaging and laboratory results have been rigorously reviewed. With reference to other research involving the use of the NHIRD to study MS, we estimated patients' follow-up durations by using CIC registration dates as the index dates.<sup>45</sup> The NHIA review committee assesses applications according to both the Posner criteria and McDonald criteria.<sup>46</sup> Among the patients included in this study, the average time from the first inpatient diagnosis to the CIC registration date was 14.06 (standard deviation [SD] = 18.25) days. We excluded patients who had other neurological disorders and were admitted due to conditions that were comparable to MS, including critical illness polyneuropathy, chronic inflammatory demyelinating polyneuropathy, polyneuropathy caused by other diseases (eg, diphtheria or porphyria), critical illness myopathy, acute poliomyelitis, myasthenic syndromes, myasthenia gravis, acute transverse myelitis, or poisoning from drugs or biological substances (Figure 1).



**Figure 1** The flowchart of study of multiple sclerosis (MS) sample selection from National Health Insurance Research Database in Taiwan.

## Ethics

The tenets of the Declaration of Helsinki were adhered to, following the Code of Ethics of the World Medical Association. Since the identifiable database of individuals included in the NHIRD were all encrypted in order to protect individual privacy,<sup>27,47,48</sup> the NHI Administration has given general approval for their data to be used in this research.<sup>48</sup> Because the NHIRD has the advantage of providing a large-scale, longitudinal, reliable dataset, leading to extensive usage for population-based researches in Taiwan.<sup>48–51</sup> Therefore, the Tri-Service General Hospital's Institutional Review Board ratified our executed study (IRB No. 2-107-05-026); in addition, the necessity of written informed consent from individuals was waived.

## Covariates

The covariates in this study consisted of sex, age group (20–49, 50–64, or ≥65 years), marital status, education (<12 years or ≥12 years), monthly income (<NT\$18,000,

NT\$18,000–34,999, ≥NT\$35,000), urbanization level (levels 1–4), and region of residence (central, northern, eastern, or southern Taiwan). Population as well as several indicators of development level constituted the basis for the definition of urbanization level; the definition is detailed as follows. Level 1: population of >1,250,000 with designated economic, political, metropolitan, and cultural development. Level 2: population of 500,000–1,249,999 with prominent political, cultural, and economic influence. Level 3: population of 149,999–499,999. Level 4: population of <149,999. Usage of the NHI-reimbursed disease-modifying drugs (DMDs) that include, natalizumab, interferon β-1a, interferon β-1b, and teriflunomide were also recorded.

## Comorbidity

Comorbidities in this study included the following: coronary artery, peripheral vascular, chronic pulmonary, cerebrovascular, peptic ulcer, rheumatologic, liver, and renal

diseases. Other comorbidities included were diabetes mellitus, hemiplegia or paraplegia, malignancy, metastatic solid tumor, congestive heart failure, myocardial infarction, acquired immune deficiency syndrome/human immunodeficiency virus, infectious mononucleosis, hypertension, hyperlipidemia, lower leg fracture or surgery, systemic lupus erythematosus, rheumatoid arthritis, deficiency anemias, fluid or electrolyte disorders, smoking habit, and obesity. The reasons for the inclusion of these comorbidities in this analysis were that they are either clinical risk factors for MS, or have been suspected of being associated with development of MS.<sup>22,52–56</sup> [Table S1](#) lists all the ICD-9-CM codes for these comorbidities.

## Outcome Measures

Psychiatric, or mental disorders, are defined as clinically significant behavioral or psychological syndromes, which are associated with present distress, disability, or an increased risk of suffering death, pain, or disability, and subsequent behavioral, psychological, or biological dysfunctions.<sup>57,58</sup> The included patients were all followed from the index date until the occurrence of any of the following events: onset of anxiety, depressive, bipolar, sleep, schizophrenia, schizophreniform disorder, other psychotic disorder, or substance-related (namely alcohol use or illicit drug use) disorders; withdrawal from the NHI program; or the end of 2015. All of the ICD-9-CM codes for the outcomes are listed in [Table S1](#). In this study, we have separated these diagnoses by the first identified ICD codes in the subjects in these two cohorts.

## Statistical Analysis

SPSS for Windows, version 22.0 (IBM Corp., Armonk, NY, USA) was applied in this study to execute all statistical analyses. The distribution of categorical variables was assessed using the  $\chi^2$  test; in addition, that of continuous variables was determined by applying a *t* test, with the Fisher exact test. On the basis of the model presented by Fine and Gray, this study executed a survival analysis to compare estimated hazards for patients with diseases that had a potential outcome of death, such as MS, with those for the controls.<sup>59</sup> To perform this analysis, the SPSS value-added module, including competing risks survival analysis, was applied (<https://www.asia-analytics.com.tw/en/product/p-asia-analytics-2.jsp>). Accordingly, we could employ the competing risk analysis approach put forward by Fine and Gray to identify the risk of psychiatric disorders (competing with death) in patients with MS.<sup>60</sup> The

results that were derived from the mentioned analysis are presented herein as hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs). We compared the control and study groups with respect to the risk of psychiatric disorders by executing the Kaplan–Meier method in conjunction with a Log rank test. A two-tailed *p* value of <0.05 was deemed in this study as denoting statistical significance.

## Results

### Sample Characteristics

As indicated in [Table 1](#), 1:3 matching was performed on the enrolled patients (1066 patients with MS and 3198 controls without MS) with respect to index year, sex, and age. There were statistically significant differences in hemiplegia or paraplegia, rheumatologic disease, liver disease, hyperlipidemia, lower leg fracture or surgery, systemic lupus erythematosus, deficiency anemias, and fluid and electrolyte disorders between the MS and control groups. The MS group tended to have a higher percentage of patients living in Northern or Eastern Taiwan, residing in areas with urbanization levels of 1 and 2, and seeking medical care from a medical center.

### Cumulative Risk of Psychiatric Disorders as Assessed Using the Kaplan–Meier Model

Of the MS patients, 531 (4622.86 per 10<sup>5</sup> person years) were determined to develop psychiatric disorders; by contrast, whereas 891 of the 3198 individuals in the control group (2,85.31 per 10<sup>5</sup> person years) were determined to develop psychiatric disorders. This difference reached statistical significance, as determined through the execution of Kaplan–Meier survival analysis (log rank, *p* < 0.001, [Figure 2](#)).

### HR for Psychiatric Disorders in MS Group

[Table 2](#) presents the results derived from the analysis executed using the competing risk model. As revealed by the table, the MS group was determined to exhibit a higher likelihood of developing psychiatric disorders when compared with the control group (crude HR: 4.407; 95% CI = 3.918–5.087, *p* < 0.001). Moreover, the results indicated that after sex, monthly income, urbanization level, geographic region, comorbidities, and age were adjusted for, the adjusted HR was 5.044

**Table I** Characteristics of Study at the Baseline

Variables	MS Cohort		Controls		P
	n	%	n	%	
<b>Total</b>	1066	25.00	3198	75.00	
<b>Sex</b>					0.999
Male	210	19.70	630	19.70	
Female	856	80.30	2568	80.30	
<b>Age (years)</b>	41.20±13.17		40.93±14.78		0.596
<b>Age group (years)</b>					0.999
20–49	788	73.92	2364	73.92	
50–64	224	21.01	672	21.01	
≥ 65	54	5.07	162	5.07	
<b>Marital status</b>					0.868
Single	812	76.17	2428	75.92	
Married	254	23.83	770	24.08	
<b>Education (years)</b>					0.832
<12	500	46.90	1512	47.28	
≥ 12	566	53.10	1686	52.72	
<b>Insurance premium (NT\$)</b>					0.996
<18,000	861	80.77	2579	80.64	
18,000–34,999	139	13.04	420	13.13	
≥ 35,000	66	6.19	199	6.22	
<b>Comorbidities</b>					
Myocardial infarction	3	0.28	10	0.31	0.873
Congestive heart failure	1	0.09	18	0.56	0.046
Peripheral vascular disease	0	0	0	0	–
Cerebrovascular disease	28	2.63	70	2.19	0.409
Hemiplegia or paraplegia	41	3.85	12	0.38	<0.001
Chronic pulmonary disease	14	1.31	65	2.03	0.132
Rheumatologic disease	23	2.16	24	0.75	<0.001
Peptic ulcer disease	31	2.91	124	3.88	0.143
Diabetes	57	5.35	167	5.22	0.874
Renal disease	5	0.47	16	0.50	0.899
Malignancy	60	5.63	232	7.25	0.069
Metastatic solid tumor	6	0.56	32	1.00	0.188
Liver disease	14	1.31	158	4.94	<0.001
AIDS/HIV	1	0.09	0	0	0.083
Infectious mononucleosis	0	0	0	0	–
Hypertension	74	6.94	190	5.94	0.240
Hyperlipidemia	42	3.94	13	0.41	<0.001
Lower leg fracture or surgery	1	0.09	65	2.03	<0.001
Coronary artery disease	26	2.44	81	2.53	0.865
Systemic lupus erythematosus	15	1.41	9	0.28	<0.001
Rheumatoid arthritis	4	0.38	8	0.25	0.504
Deficiency anemias	10	0.94	11	0.34	0.016
Fluid and electrolyte disorders	25	2.35	12	0.38	<0.001
Smoking	0	0	0	0	–
Obesity	1	0.09	0	0	0.083

(Continued)

Table 1 (Continued).

Variables	MS Cohort		Controls		P
	n	%	n	%	
Annual medical visits	9.42±10.12		10.01±11.25		0.129
<b>Location</b>					<0.001
Northern Taiwan	549	51.50	1364	42.65	
Middle Taiwan	206	19.32	845	26.42	
Southern Taiwan	257	24.11	837	26.17	
Eastern Taiwan	54	5.07	138	4.32	
Outlets islands	0	0.00	14	0.44	
<b>Urbanization level</b>					<0.001
1 (The highest)	542	50.84	1233	38.56	
2	448	42.03	1310	40.96	
3	27	2.53	262	8.19	
4 (The lowest)	49	4.60	393	12.29	
<b>Level of care</b>					<0.001
Medical center	786	73.73	1014	31.71	
Regional hospital	239	22.42	1132	35.40	
Local hospital	41	3.85	1052	32.90	

Note: P: Chi-square/Fisher exact test on category variables and t-test on continue variables.

Abbreviations: MS, multiple sclerosis; NT\$, New Taiwan Dollars; AIDS/HIV, acquired immunodeficiency syndrome/human immunodeficiency virus infection.

(95% confidence interval = 4.448—5.870,  $p < 0.001$ ). The results suggested that patients in the MS group who had CCI scores of 2 to 4 and who received medical care from a regional hospital or medical center exhibited a higher risk of psychiatric disorders. Male patients exhibited a lower risk.

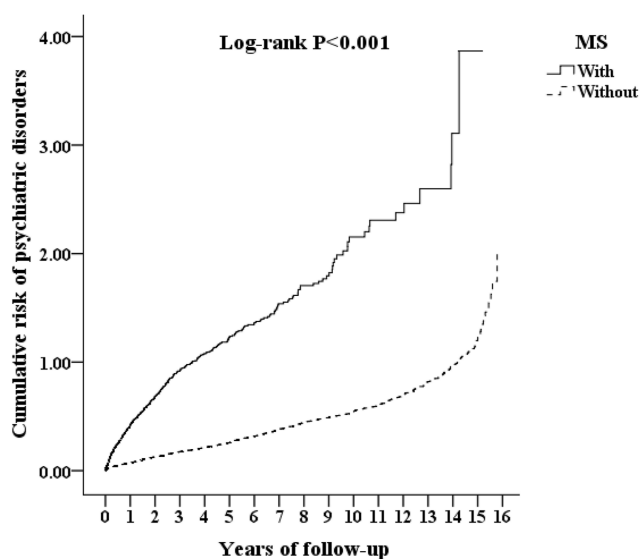


Figure 2 Kaplan-Meier for cumulative incidence of psychiatric disorders aged 20 and over stratified by multiple sclerosis (MS) with Log rank test.

### Sensitivity Analysis and Types of Psychiatric Disorders After MS Diagnosis

As presented in Table 3, the MS group had associations with psychiatric disorders such as depression, anxiety, bipolar disorder, sleep disorders, schizophrenia, schizophreniform disorder, and other psychotic disorder (adjusted HR: 12.464, 4.650, 6.987, 9.103, 2.552, 2.600, 2.441, and 2.574, respectively; all  $p < 0.001$ ) but not with substance-related disorders. The results of the sensitivity analysis of patients with MS (Table 3) also indicated their association with an increased risk of psychiatric disorders such as depression, anxiety, bipolar disorder, sleep disorders, schizophrenia, schizophreniform disorder, and other psychotic disorder, even after the exclusion of patients who had been diagnosed these psychiatric disorders during the first 1 year. However, after exclusion of patients with these psychiatric disorders during the first 5 years, MS was not associated with schizophrenia and schizophreniform disorder.

### Medications for MS and the Risk of Psychiatric Disorders

We also analyzed the association between medications, or DMDs, for MS (Figure 3), and the portion of days covered (PDC) was 1%–50% (Table 4). In general, the results

**Table 2** Factors of Psychiatric Disorders by Using Fine and Gray's Competing Risk Model

Variables	Competing Risk in the Model							
	Crude SHR	95% CI	95% CI	P	Adjusted SHR	95% CI	95% CI	P
<b>Multiple sclerosis</b> (reference: without)	4.407	3.918	5.087	<0.001	5.044	4.448	5.870	<0.001
<b>Psychiatric diagnoses with multiple sclerosis (531/1066, 4.622.86 per 10<sup>5</sup> person-years)</b>								
<b>Psychiatric diagnoses without multiple sclerosis (891/3198, 2.485.31 per 10<sup>5</sup> person-years)</b>								
Male (reference: female)	0.763	0.673	0.891	<0.001	0.875	0.767	0.995	0.045
Peripheral vascular disease (reference: without)	8.385	2.082	34.665	<0.001	5.359	1.309	22.518	<0.001
Cerebrovascular disease (reference: without)	1.650	1.338	2.089	<0.001	1.470	1.163	1.906	<0.001
Chronic pulmonary disease (reference: without)	1.808	1.433	2.341	<0.001	1.917	1.504	2.510	<0.001
Peptic ulcer disease (reference: without)	1.778	1.446	2.244	<0.001	1.604	1.294	2.040	<0.001
Diabetes mellitus (reference: without)	1.690	1.454	2.015	<0.001	1.555	1.321	1.879	<0.001
Renal disease (reference: without)	3.407	2.511	4.744	<0.001	3.513	2.562	4.944	<0.001
Liver disease (reference: without)	1.993	1.659	2.459	<0.001	2.138	1.763	2.661	<0.001
Hyperlipidemia (reference: without)	2.258	1.847	2.833	<0.001	1.751	1.404	2.242	<0.001
Coronary artery disease (reference: without)	1.947	1.647	2.361	<0.001	1.666	1.388	2.052	<0.001
Systemic lupus erythematosus (reference: without)	2.136	1.337	3.503	<0.001	1.818	1.130	3.003	<0.001
Rheumatoid arthritis (reference: without)	2.562	1.263	5.336	0.007	2.975	1.459	6.231	<0.001
Deficiency anemias (reference: without)	1.714	1.242	2.427	<0.001	2.389	1.721	3.406	<0.001
Fluid and electrolyte disorders (reference: without)	1.888	1.533	2.386	<0.001	1.540	1.237	1.967	<0.001
Urbanization Level I (reference: without)	0.783	0.814	1.027	0.068	0.833	0.690	1.032	0.073
Medical center (reference: without)	1.205	1.047	1.421	0.003	1.872	1.750	2.064	<0.001

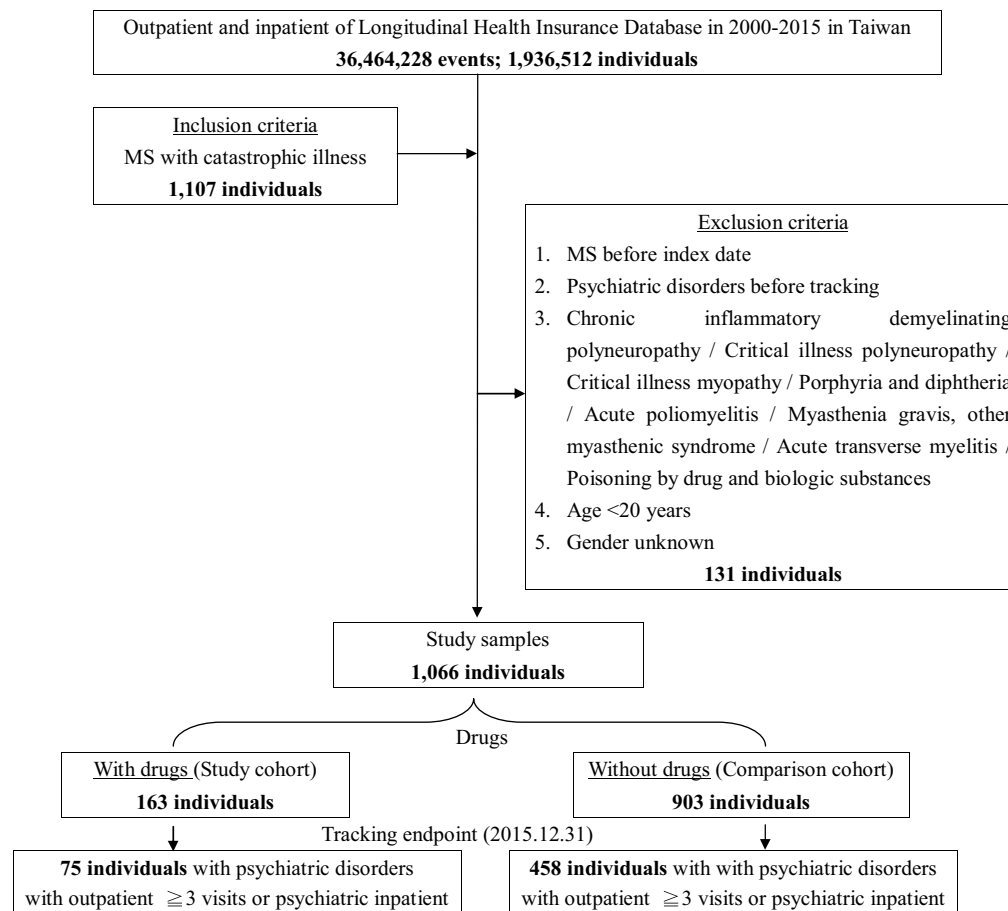
Abbreviations: SHR, subdistribution hazard ratio; CI, confidence interval; Adjusted HR, adjusted variables listed in the Table 1.

**Table 3** Factors of Psychiatric Disorders Subgroup and Sensitivity Analysis by Using Fine and Gray's Competing Risk Model

Sensitivity Analysis	MS (with vs without)		(N in the MS Patients)	No Competing Risk in the Model			Competing Risk in the Model			
	Psychiatric Diagnoses			Adjusted HR	95% CI	95% CI	P	Adjusted SHR	95% CI	P
<b>Overall</b>	<b>Overall</b>	531	5.063	4.447	5.870	<0.001	5.044	4.448	5.870	<0.001
	Depression	55	12.512	11.027	14.082	<0.001	12.464	11.030	14.082	<0.001
	Anxiety	447	4.668	4.114	5.254	<0.001	4.650	4.115	5.254	<0.001
	Bipolar	5	7.014	6.182	7.894	<0.001	6.987	6.184	7.894	<0.001
	Sleep disorders	38	9.139	8.054	10.285	<0.001	9.103	8.056	10.285	<0.001
	Psychotic disorders	7	2.562	2.258	2.883	<0.001	2.552	2.258	2.883	<0.001
	Schizophrenia	1	2.605	2.321	3.031	<0.001	2.600	2.309	3.021	<0.001
	Schizophreniform disorder	2	2.520	2.175	2.881	<0.001	2.441	2.196	2.914	<0.001
	Other psychotic disorders	4	2.588	2.285	3.008	<0.001	2.574	2.270	3.003	<0.001
	Substance-related disorders	2	0.580	0.331	1.676	0.278	0.578	0.365	1.679	0.306
	Alcohol use disorders	2	0.841	0.522	1.050	0.124	0.838	0.625	1.030	0.062
	Other drug use disorders	0	0	-	-	0.902	0	-	-	0.978
<b>First year diagnoses excluded</b>	<b>Overall</b>	269	3.334	2.927	3.865	<0.001	3.320	2.928	3.865	<0.001
	Depression	28	7.908	6.969	8.899	<0.001	7.877	6.971	8.899	<0.001
	Anxiety	228	3.099	2.730	3.487	<0.001	3.086	2.731	3.487	<0.001
	Bipolar	4	9.037	7.965	10.171	<0.001	9.002	7.966	10.171	<0.001
	Sleep disorders	17	4.955	4.367	5.578	<0.001	4.936	4.368	5.578	<0.001
	Psychotic disorders	5	2.259	1.991	2.542	<0.001	2.250	1.991	2.542	<0.001
	Schizophrenia	1	2.404	2.022	2.798	<0.001	2.363	2.015	2.743	<0.001
	Schizophreniform disorder	1	0	-	-	0.971	0	-	-	0.986
	Other psychotic disorders	3	2.259	1.993	2.619	<0.001	2.234	1.970	2.588	<0.001
	Substance-related disorders	2	0.822	0.614	1.036	0.226	0.818	0.704	1.028	0.217
	Alcohol use disorders	2	1.130	0.995	1.272	0.238	1.125	0.996	1.273	0.279
	Other drug use disorders	0	0	-	-	0.897	0	-	-	0.942
<b>First 5 years diagnoses excluded</b>	<b>Overall</b>	62	2.792	2.451	3.236	<0.001	2.780	2.452	3.236	<0.001
	Depression	5	4.407	3.884	4.959	<0.001	4.389	3.885	4.959	<0.001
	Anxiety	50	2.442	2.152	2.748	<0.001	2.432	2.153	2.748	<0.001
	Bipolar	1	6.463	5.696	7.274	<0.001	6.438	5.697	7.274	<0.001
	Sleep disorders	6	5.288	4.660	5.951	<0.001	5.268	4.661	5.951	<0.001
	Psychotic disorders	1	1.763	1.553	1.983	<0.001	1.756	1.554	1.983	<0.001
	Schizophrenia	0	0	-	-	0.972	0	-	-	0.983
	Schizophreniform disorder	0	0	-	-	0.986	0	-	-	0.989
	Other psychotic disorders	1	1.756	1.505	2.062	<0.001	1.727	1.435	2.000	<0.001
	Substance-related disorders	0	0	-	-	0.796	0	-	-	0.763
	Alcohol use disorders	0	0	-	-	0.837	0	-	-	0.892
	Other drug use disorders	0	0	-	-	0.955	0	-	-	0.978

**Abbreviations:** PYs, person-years; SRD, substance-related disorders; HR, hazard ratio; SHR, subdistribution hazard ratio; adjusted for the variables listed in Table 1; CI, confidence interval.





**Figure 3** The flowchart of study sample selection from National Health Insurance Research Database in Taiwan.

revealed no association between the use of these medications and the overall risk of psychiatric disorders (Figure 4 and Table 5). However, in the present study, the use of glatiramer acetate, interferon- $\beta$ -1a, interferon- $\beta$ -1b, natalizumab, teriflunomide was determined to exhibit an association with a reduction in the anxiety risk. The use of glatiramer acetate, interferon- $\beta$ -1a, interferon- $\beta$ -1b, teriflunomide was also noted to exhibit an association with a reduction in the risk of depression.

## Discussion

### Association Between MS, DMDs, and the Risk of Psychiatric Disorders

Our derived results suggest that MS is associated with an elevated risk of psychiatric disorders among adults. We also noted that after covariates were adjusted for, the risk of psychiatric disorders is nearly five-fold greater among adults with MS relative to those without MS. The results of Kaplan–Meier analysis indicated that the patients with MS in this study had a significantly higher rate of survival

for 15 years without psychiatric disorders than did adults without MS.

In addition, we found that the DMD compliance among patients with MS was lower than 50% because the PDC was 1%–50%. Although some studies conducted in other countries have addressed this matter, the present study is also the first to report findings regarding DMD adherence or compliance in Taiwan.<sup>61,62</sup> Furthermore, the use of such DMDs was noted to exhibit an association with a reduction in the anxiety and depression risks.

### Comparison of This Study with Previous Literature

A previously executed systematic review ranked psychiatric disorders as follows with respect to their prevalence: depression (23.7%), anxiety (21.9%), alcohol abuse (14.8%), bipolar disorder (5.83%), psychosis (4.3%), and substance abuse (2.5%).<sup>20</sup> Compared with the population-based studies on individual disorders, such as anxiety disorders,<sup>21,63,64</sup> depression,<sup>64,65</sup> and psychosis,<sup>24</sup> identified

**Table 4** Distribution of Disease-Modifying Medications for Multiple Sclerosis

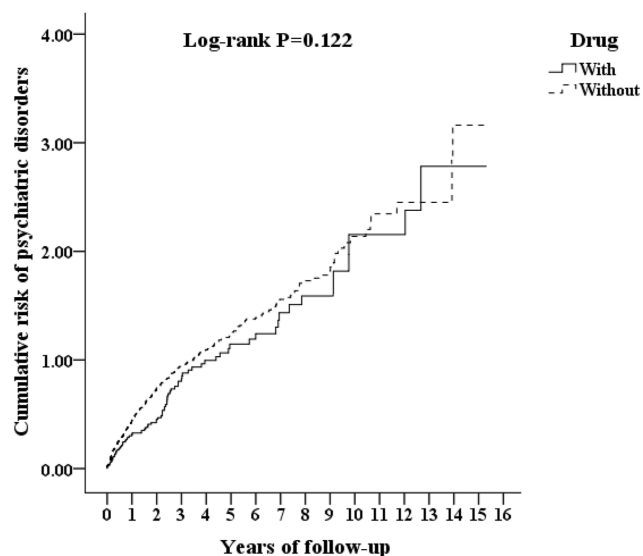
Variables	n	%	Events	Events %	PYs	Rate (per 10 <sup>5</sup> PYs)
<b>Total</b>	1066		531	49.81	11,483.42	4624.06
<b>Drugs</b>						
Without	882	82.74	456	51.70	9075.13	5024.72
With	184	17.26	75	40.76	2408.29	3114.24
<b>Fingolimod</b>						
Without	931	87.34	471	50.59	9739.24	4836.11
PDC 1–50%	135	12.66	60	44.44	1744.18	3440.01
PDC 51–100%	0	0	0	-	0	-
MPR 1–50%	89	8.35	55	61.80	1216.99	4519.35
MPR 51–100%	46	4.32	5	10.87	527.19	948.42
<b>Glatiramer acetate</b>						
Without	929	87.15	474	51.02	9745.85	4863.61
PDC 1–50%	137	12.85	57	41.61	1737.57	3280.44
PDC 51–100%	0	0	0	-	0	-
MPR 1–50%	97	9.10	51	52.58	1301.82	3917.59
MPR 51–100%	40	3.75	6	15.00	435.75	1376.92
<b>Interferon-β-1a</b>						
Without	910	85.37	484	53.19	9645.12	5018.08
PDC 1–50%	151	14.17	45	29.80	1533.25	2934.94
PDC 51–100%	5	0.47	2	40.00	305.05	655.63
MPR 1–50%	102	9.57	44	43.14	1425.25	3087.18
MPR 51–100%	54	5.07	3	5.56	413.05	726.30
<b>Interferon-β-1b</b>						
Without	918	86.12	501	54.58	9575.98	5231.84
PDC 1–50%	142	13.32	29	20.42	1513.12	1916.57
PDC 51–100%	6	0.56	1	16.67	394.32	253.60
MPR 1–50%	101	9.47	28	27.72	1499.76	1866.97
MPR 51–100%	47	4.41	2	4.26	407.68	490.58
<b>Natalizumab</b>						
Without	924	86.68	510	55.19	9480.25	5379.60
PDC 1–50%	131	12.29	20	15.27	1813.12	1103.07
PDC 51–100%	11	1.03	1	9.09	190.05	526.18
MPR 1–50%	94	8.82	20	21.28	1806.27	1107.25
MPR 51–100%	48	4.50	1	2.08	196.90	507.87
<b>Teriflunomide</b>						
Without	928	87.05	498	53.66	9698.25	5134.95
PDC 1–50%	130	12.20	33	25.38	1327.42	2486.03
PDC 51–100%	8	0.75	0	0	457.75	0
MPR 1–50%	107	10.04	29	27.10	1301.56	2228.10
MPR 51–100%	31	2.91	4	12.90	483.61	827.11

**Abbreviations:** PYs, Person-year; PDC, portion of days covered; MPR, medication possession ratio.

during our systematic review, our study is the first to use a large and nationwide administrative data set for several major psychiatric disorders.

Furthermore, the treatment prevalence rates of the psychiatric disorders among the patients in our study were

83.9% for anxiety disorders, 10.3% for depression, and 7.1% for sleep disorders; by contrast, the prevalence rates of psychotic disorders, bipolar disorder, and substance-related disorders were lower than 2% in the reviewed studies.<sup>14</sup> We speculate that this difference may be related



**Figure 4** Kaplan–Meier for cumulative risk of psychiatric disorders among MS patients aged 20 and over stratified by treatment with Log rank test.

to the different follow-up period and different enrollment criteria for psychiatric disorders in this study. This study enrolled only patients who had made three visits in a year for treating their diagnosed psychiatric disorder. Furthermore, our study involved a longer follow-up duration for the psychiatric disorders in the patients with MS following their hospital stay; this longer duration constitutes a strength of the study. However, the reasons for this difference require further investigation.

Confavreux and Compston reported that the prognosis for men with MS is typically worse than that for women, and disability appears to have more of an impact on the quality of life in men.<sup>66</sup> Another study also found that the very early stages of MS are accompanied by disturbances in psychological well-being and mild cognitive dysfunction, particularly in male patients.<sup>67</sup> However, in the present study, male patients with MS were determined to have a lower risk of psychiatric disorders (adjusted HR = 0.792 [95% CI = 0.651–0.953,  $p = 0.006$ ]). One possible explanation for this finding is that the psychological support provided by the health professionals might be insufficient for men,<sup>68</sup> thus reducing the rates of early detection and early referrals and consequently lowering the psychiatric diagnostic rates in the NHIRD. Furthermore, previous studies have found that the male patients generally tended to be reluctant to seek help from psychiatric services.<sup>69–71</sup> This might also contribute to the apparently lower risk of psychiatric disorders in the male patients with MS. In addition, we determined higher insurance premiums to

have an association with a higher MS risk. The reasons underlying this association are not known. We speculate that subjects with higher insurance premiums, suggesting that they have higher income, might have higher accessibility to health care systems. Nonetheless, the reasons for this lower risk are still unknown and need to be researched further with more detail.

In contrast to other studies, although this study found an association between MS and an increased risk of anxiety, depression, psychotic disorders, sleep disorders, and bipolar disorder, no association was noted between MS and substance-related disorders.<sup>72,73</sup> Low baseline rates of alcohol or drug use disorders in Taiwan might be one explanation for this discrepancy.<sup>74</sup>

In this claims data set–based study, we identified patients with MS on the basis of a discharge diagnosis of MS, as confirmed by CIC approval. The number of patients with MS who did not have CICs was difficult to estimate because all studies on the prevalence of MS in Taiwan have analyzed data from the NHIRD.<sup>15–17,75</sup> However, we speculate that most of the patients with MS were issued CICs because NHI regulations exempt them from copayment for MS-related medical care. Furthermore, most researchers using data from the NHIRD have used CIC status to confirm MS diagnosis.<sup>24,25,46,56,76–81</sup> Nonetheless, a community-based study in Taiwan is necessary to determine the proportion of patients with MS who do not have CICs. In addition, NHI regulations mandate that a period of three to seven days elapse after confirmation of diagnosis by a physician before CICs can be issued so that medical charts can be reviewed by NHIA-appointed specialists to verify the validity of certificates issued for CIC-qualifiable diseases, including MS.<sup>82</sup> However, determining the mean number of days between diagnosis of MS and CIC registration remains difficult.

## Potential Mechanisms Underlying the Elevated Risk of Psychiatric Disorders Among Patients with MS

Studies have reported associations of multiple factors, such as brain pathology, genetics, immunological changes, psychosocial influences, and dysregulation of the hypothalamic–pituitary–adrenal axis, with anxiety disorders and depression.<sup>83</sup> One study reported that MS, depressive disorder, bipolar disorder, and schizophrenia may share the mechanism of downregulating oligodendrocyte genes.<sup>84</sup> However, the mechanisms that underlie the MS–psychiatric disorder risk association require further investigation.

**Table 5** Factors of Subgroup in Different Disease-Modifying Drugs Among Multiple Sclerosis Patients by Using Cox Regression and Fine and Gray's Competing Risk Model

Drugs (Reference: without)	Model	No Competing Risk in the Model						Competing Risk in the Model						
		Adjusted HR	95% CI	95% CI	P	Adjusted SHR	95% CI	95% CI	P					
<b>Overall</b>	<b>Dementia Subgroup</b>													
	<b>Overall</b>	0.666	0.423	1.075	0.401	0.670	0.418	1.086	0.375					
	Depression	0.572	0.222	1.267	0.133	0.522	0.223	1.210	0.134					
	Anxiety	0.731	0.512	0.963	0.023	0.744	0.572	0.969	0.029					
	Bipolar	0	-	-	0.866	0	-	-	0.945					
	Sleep disorders	0.501	0.178	1.413	0.203	0.586	0.284	1.563	0.242					
	Psychotic disorders	1.563	0.303	7.986	0.672	1.489	0.301	7.761	0.668					
	Schizophrenia	1.298	0.212	7.425	0.663	1.283	0.205	7.413	0.651					
	Schizophreniform disorder	1.387	0.298	7.774	0.670	1.375	0.287	7.758	0.665					
	Other psychotic disorders	1.675	0.426	8.030	0.684	1.652	0.411	7.992	0.681					
	Substance-related disorders	0	-	-	0.632	0	-	-	0.671					
	Alcohol use disorders	0	-	-	0.611	0	-	-	0.662					
	Other substance use disorders	0	-	-	0.995	0	-	-	0.998					
	<b>Fingolimod</b>	<b>Overall</b>	0.741	0.568	1.176	0.355	0.743	0.569	1.182	0.377				
Depression		0.588	0.235	1.478	0.267	0.592	0.236	1.487	0.273					
Anxiety		0.768	0.574	1.026	0.089	0.789	0.575	1.027	0.091					
Bipolar		0	-	-	0.517	0	-	-	0.565					
Sleep disorders		0.689	0.244	1.945	0.491	0.694	0.246	1.958	0.498					
Psychotic disorders		2.188	0.422	11.346	0.339	2.219	0.428	11.504	0.331					
Schizophrenia		2.065	0.386	9.865	0.277	2.097	0.397	10.120	0.284					
Schizophreniform disorder		2.131	0.403	10.331	0.320	2.178	0.421	10.867	0.328					
Other psychotic disorders		2.244	0.482	11.429	0.384	2.299	0.503	11.682	0.396					
Substance-related disorders		0	-	-	0.693	0	-	-	0.761					
Alcohol use disorders		0	-	-	0.692	0	-	-	0.760					
Other substance use disorders		0	-	-	0.976	0	-	-	0.978					
<b>Glatiramer acetate</b>		<b>Overall</b>	0.629	0.457	1.172	0.138	0.695	0.317	1.584	0.380				
		Depression	0.470	0.170	1.301	0.151	0.473	0.171	1.310	0.155				
	Anxiety	0.784	0.586	0.969	0.038	0.785	0.587	0.973	0.041					
	Bipolar	0	-	-	0.351	0	-	-	0.367					
	Sleep disorders	0.518	0.159	1.689	0.281	0.522	0.161	1.702	0.287					
	Psychotic disorders	2.405	0.466	12.421	0.284	2.441	0.473	12.610	0.276					
	Schizophrenia	2.321	0.401	11.785	0.226	2.386	0.431	11.976	0.204					
	Schizophreniform disorder	2.385	0.457	12.011	0.271	2.404	0.462	12.448	0.258					
	Other psychotic disorders	2.434	0.513	12.986	0.375	2.473	0.589	13.375	0.317					
	Substance-related disorders	0	-	-	0.842	0	-	-	0.853					
	Alcohol use disorders	0	-	-	0.838	0	-	-	0.849					

	Other substance use disorders	0	0.229	1.321	0.959	0	0.251	1.980	0.975	
<b>Interferon-β-1a</b>	<b>Overall</b>	0.683	0.229	1.321	0.258	0.688	0.251	1.980	0.975	
	Depression	0.611	0.353	0.978	0.027	0.603	0.270	0.907	0.204	
	Anxiety	0.562	0.305	0.921	0.003	0.552	0.286	0.911	0.001	
	Bipolar	0	-	-	0.898	0	-	-	0.912	
	Sleep disorders	0.702	0.465	1.986	0.702	0.729	0.503	2.234	0.698	
	Psychotic disorders	1.025	0.331	1.865	0.612	1.123	0.465	2.131	0.603	
	Schizophrenia	0.986	0.246	1.683	0.505	0.994	0.371	1.705	0.503	
	Schizophreniform disorder	1.011	0.287	1.774	0.572	1.086	0.442	1.972	0.555	
	Other psychotic disorders	1.027	0.352	1.895	0.638	1.197	0.586	2.186	0.611	
	Substance-related disorders	0	-	-	0.862	0	-	-	0.912	
	Alcohol use disorders	0	-	-	0.976	0	-	-	0.986	
	Other substance use disorders	0	-	-	0.933	0	-	-	0.975	
	<b>Interferon-β-1b</b>	<b>Overall</b>	0.785	0.422	1.256	0.223	0.794	0.483	1.367	0.254
		Depression	0.533	0.372	0.986	0.039	0.552	0.384	0.952	0.022
Anxiety		0.482	0.306	0.925	0.010	0.497	0.311	0.914	0.004	
Bipolar		0	-	-	0.897	0	-	-	0.903	
Sleep disorders		0.862	0.562	1.287	0.796	0.972	0.672	1.597	0.711	
Psychotic disorders		0.994	0.765	1.306	0.535	1.204	0.886	2.013	0.672	
Schizophrenia		0.952	0.542	1.184	0.502	0.996	0.556	1.487	0.611	
Schizophreniform disorder		1.097	0.688	1.211	0.530	1.125	0.701	1.706	0.653	
Other psychotic disorders		1.246	0.803	1.562	0.569	1.284	0.897	2.025	0.684	
Substance-related disorders		0	-	-	0.896	0	-	-	0.903	
Alcohol use disorders		0	-	-	0.883	0	-	-	0.903	
Other substance use disorders		0	-	-	0.964	0	-	-	0.972	
<b>Natalizumab</b>		<b>Overall</b>	0.714	0.553	1.066	0.424	0.728	0.569	1.078	0.463
		Depression	0.884	0.672	1.030	0.089	0.897	0.688	1.124	0.131
	Anxiety	0.702	0.511	0.962	0.024	0.713	0.534	0.986	0.033	
	Bipolar	0	-	-	0.712	0	-	-	0.865	
	Sleep disorders	0.803	0.598	1.724	0.386	0.834	0.661	2.561	0.399	
	Psychotic disorders	1.030	0.666	1.802	0.295	1.135	0.689	2.978	0.304	
	Schizophrenia	0.892	0.601	1.713	0.276	0.972	0.638	2.886	0.285	
	Schizophreniform disorder	1.045	0.782	2.035	0.308	1.206	0.833	3.015	0.311	
	Other psychotic disorders	0.997	0.643	1.786	0.281	1.085	0.672	2.956	0.297	
	Substance-related disorders	0	-	-	0.974	0	-	-	0.985	
	Alcohol use disorders	0	-	-	0.986	0	-	-	0.977	

(Continued)

Table 5 (Continued).

Drugs (Reference: without)	Model	No Competing Risk in the Model				Competing Risk in the Model			
		Adjusted HR	95% CI	95% CI	P	Adjusted SHR	95% CI	95% CI	P
Teriflunomide	Dementia Subgroup								
	Other substance use disorders	0	-	-	0.913	0	-	-	0.973
	Overall	0.825	0.398	2.896	0.483	0.899	0.412	3.011	0.499
	Depression	0.664	0.402	0.936	0.011	0.688	0.435	0.972	0.028
	Anxiety	0.502	0.345	0.892	<0.001	0.598	0.387	0.902	<0.001
	Bipolar	0	-	-	0.901	0	-	-	0.925
	Sleep disorders	0.975	0.251	4.980	0.702	1.007	0.356	5.131	0.687
	Psychotic disorders	1.137	0.336	5.582	0.684	1.397	0.403	6.254	0.703
	Schizophrenia	1.206	0.453	5.986	0.633	1.452	0.657	6.842	0.650
	Schizophreniform disorder	1.085	0.303	5.010	0.695	1.186	0.338	5.687	0.717
	Other psychotic disorders	1.114	0.324	5.443	0.672	1.370	0.392	6.011	0.684
	Substance-related disorders	0	-	-	0.868	0	-	-	0.918
	Alcohol use disorders	0	-	-	0.899	0	-	-	0.903
	Other substance use disorders	0	-	-	0.951	0	-	-	0.942

Abbreviations: PYs, person-years; SHR, subdistribution Hazard ratio; adjusted for the variables listed in Table 1; CI, confidence interval.

### Study Strengths

This research has certain strengths. First, we employed Taiwan’s NHIRD, a very important resource covering a nationwide population. Second, other studies have verified the diagnostic validity of several neuropsychiatric disorders included in the NHIRD, including Tourette syndrome,<sup>85</sup> stroke,<sup>86–89</sup> sleep apnea,<sup>90</sup> and major depressive disorder.<sup>91</sup> Moreover, as mentioned, in-hospital licensed medical record technicians and NHI administrators would have verified the diagnoses in the claims data set.<sup>27,44</sup> Third, the consistency between the NHIRD and Taiwan’s National Health Survey with respect to various diagnoses,<sup>92</sup> medication usages,<sup>92</sup> and health system utilizations<sup>92,93</sup> has been verified by research. Fourth, a benefit of the Fine and Gray model is that it includes real mortality data for investigating how MS influences the risk of psychiatric disorders.<sup>94,95</sup> Therefore, this study was conducted using a large, nationwide, and reliable database to determine the association between MS and psychiatric morbidities in an Asian country.

### Limitations of This Study

This research has a few limitations that should be considered. First, because not all pieces of data are recorded in the NHIRD, we could not evaluate the influence of family history, neurological severity, types, laboratory parameters, findings from additional examinations (eg, neuroimaging), or use of rehabilitation services.<sup>80</sup> Therefore, the lack of data regarding the clinical and radiological course and treatment of the disease is a limitation of this nationwide study with a large sample size, similar to the case for other studies that have used the NHIRD to investigate MS.<sup>24,56,76,77</sup> Second, data regarding certain factors, such as those related to environmental conditions, psychosocial characteristics, and genetics, were not part of the data set. Because the data we applied in our study spanned 15 years and encompassed the entirety of the hospitals in Taiwan and more than 99% of Taiwan’s population, they are likely to be representative and valid.

### Conclusions

The present study provides evidence demonstrating that MS is associated with an increase in the risk of psychiatric disorders, such as anxiety disorders, depression, and bipolar disorder. This finding can remind clinicians regarding the importance of considering the risk of psychiatric disorders subsequently arising among patients with MS. For example, clinicians could

use the mental health screening instruments to identify the patients at risk early on. Additional studies are warranted to explore the association of MS with depression and anxiety disorders in a larger community sample by setting a longer follow-up duration and considering lifestyle, family history, psychosocial stressors, and MS severity.

## Data Sharing Statement

Data are available from the NHIRD published by the Taiwan NHI administration. Because of legal restrictions imposed by the government of Taiwan concerning the “Personal Information Protection Act,” data cannot be made publicly available. Requests for data can be sent as a formal proposal to the NHIRD ([http://www.mohw.gov.tw/cht/DOS/DMI.aspx?f\\_list\\_no=812](http://www.mohw.gov.tw/cht/DOS/DMI.aspx?f_list_no=812)).

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## Author Contributions

All authors made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; have approved of the final version of the manuscript for publication; and agree to be accountable for all aspects of the work.

## Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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