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ORIGINAL RESEARCH

Association Between Endometriosis and Mental Disorders Including Psychiatric Disorders, Suicide, and All-Cause Mortality -A Nationwide Population-Based Cohort Study in Taiwan

Tsan-Min Wang[1], Yi-Liang Lee[2,3], Chi-Hsiang Chung[1,4,5], Chien-An Sun[6,7], Chieh-Yi Kang[8], Gwo-Jang Wu[1,2,9], Wu-Chien Chien[1,4,5,10]

[1]Department of Medical Research, Tri-Service General Hospital, Taipei, 11490, Taiwan; [2]Department of Obstetrics and Gynecology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, Republic of China; [3]Department of Obstetrics and Gynecology, Kang Ning Hospital, Taipei, Taiwan, Republic of China; [4]School of Public Health, National Defense Medical Center, Taipei, 11490, Taiwan; [5]Taiwanese Injury Prevention and Safety Promotion Association (TIPSPA), Taipei, 11490, Taiwan; [6]Department of Public Health, College of Medicine, Fu-Jen Catholic University, New Taipei City, Taiwan, Republic of China; [7]Big Data Research Center, College of Medicine, Fu-Jen Catholic University, New Taipei City, Taiwan, Republic of China; [8]Department of Obstetrics & Gynecology, Chi Mei Medical Center Gynecologic Oncologist Division, Tainan City, Taiwan, Republic of China; [9]Graduate Institute of Medical Sciences, National Defense Medical Center, Taipei, 11490, Taiwan; [10]Graduate Institute of Life Sciences, National Defense Medical Center, Taipei, 11490,Taiwan

Correspondence: Wu-Chien Chien; Gwo-Jang Wu, Email chienwu@ndmctsgh.edu.tw; gwojang@yahoo.com

Objective: A multitude of previous studies has substantiated that endometriosis correlated highly with psychiatric health. This study aims to investigate the association between endometriosis and psychiatric health.

Methods: Utilizing the National Health Insurance Research Database of Taiwan, 100,770 enrolled participants, including 20,154 patients with endometriosis and 80,616 in the control group (1:4), matched for age, and index date from Taiwan's Longitudinal Health Insurance Database between January 1, 2000, and December 31, 2015. The Cox proportional regression model was used to compare the risk of mental disorders during the 16 years of follow-up after adjusting for confounding factors.

Results: Of the study patients, 4083 (20.26%) developed mental disorders; 9225 of the 80,616 controls (11.44%) developed mental disorders. The Cox regression demonstrated that, after adjusting for age, monthly income, urbanization level, etc., people with endometriosis are more likely to suffer from mental disorders compared to those without endometriosis (hazard ratio [HR]=2.131; 95% confidence interval [CI]= 1.531–2.788; p<0.001). The result illustrated that women over 40 years old had a more significant risk.

Conclusion: Compared to people without endometriosis, this study provides evidence that patients with endometriosis are at a 2.131-fold higher risk of developing mental disorders, especially in elder women. Regular psychiatric follow-up might be needed for those patients.

Keywords: endometriosis, mental disorders, national health insurance research database, cohort study, Taiwan, women

Introduction

Endometriosis is an estrogen-dependent common gynecological disease, characterized by the presence of endometrial tissue in sites other than the uterine cavity.[1,2] Estimates of prevalence are approximately 10% in the general population; for women with reduced fertility, the prevalence rate ranges from 25% to 40%.[3] Nevertheless, visitation of the disease is required for a diagnosis; for the reason that, these values are potentially underestimated. According to the classification of the American Society for Reproductive Medicine, there are four different stages of endometriosis; stages I and II represent initial stages, while stages III and IV are advanced stages.[4,5] The stage of endometriosis is based on the location, amount, depth, and size of the endometriotic foci.[4–6] Even though some patients may be asymptomatic, common clinical manifestations may encompass chronic pelvic pain, dysmenorrhea, dyspareunia, dysuria, subfertility, and infertility.[7–9]Due to the range of symptoms,

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endometriosis is often diagnosed later in the disease process, resulting in delayed treatment, which negatively affects the quality of patients' life.[7,10] The high risk of recurrence is a major challenge for females with endometriosis.[3,11] After treatment, the symptomatic recurrence rates of endometriosis have been reported to range from 21.5% at two years to 50% at five years.[1,12]

Psychiatric, or mental disorders, are defined as being 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.[13,14] Psychiatric disorders are associated with suicide and all-cause mortality.[15,16] In our study, mental disorders encompass psychiatric disorders, suicide, and all-cause mortality. In addition, we also analyzed some details covering anxiety, depression, bipolar, sleep disorders, etc.

Previous literature proved that people with endometriosis had an increased risk of anxiety, bipolar disorders, and suicide.[12,17,18] Under these circumstances, we hypothesized that endometriosis is associated with mental disorders which include psychiatric disorders, suicide, and all-cause mortality, conducted a nationwide, population-based, cohort study, and utilized the National Health Insurance Research Database (NHIRD). According to recent literature, endometriosis may have a negative impact on patients' low quality of life as well as psychiatric health, similar to that for chronic pelvic pain.[19,20] Simultaneously, pain in endometriosis serve as a risk factor for subsequent psychiatric disorders.[20] In the discussion part, we state the association between chronic pelvic pain and subsequent psychiatric disorders. However, there is a lack of study directly utilizing large databases to examine patients with endometriosis and the risk of mental disorders in Taiwan. Therefore, it is needed to verify the association between them.

Materials and Methods

Data Source

In 1995, the National Health Insurance (NHI) program was launched, and it has included contracts with 97% of medical providers with approximately a 23million beneficiaries, or more than 99% of the entire population, as of June 2009.[21,22] The NHIRD contains all claims data of the beneficiaries, using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes to record diagnoses.[23,24] The details of this program have been documented in a previous study.[22]

In this study, we used data from the NHIRD to investigate the association between subjects with endometriosis over a 16-year period.[25] As a subset of the NHIRD, the Longitudinal Health Insurance Database of a two million randomized sampled population in 2000–2015, was used to study the association between endometriosis and the risk of mental disorders, including psychiatric disorders, suicide, all-cause mortality.[26]

In this study, we used data from the NHIRD to investigate the association between patients with endometriosis (ICD-9-CM:617) and patients suffering from mental disorders, encompassing all-cause mortality (ICD-9-CM: 800–999), suicide (ICD-9-CM: E950-E959), and psychiatric disorders (ICD-9-CM: 290–319) over a 16-year period, from the total hospitalization Longitudinal Health Insurance Database in Taiwan (2000–2015).

All procedure concerning human participants in this study were carried out in accordance with the Declaration of Helsinki and institutional research council and similar relevant ethical standards. The study was approved by the Institution Review Board of Tri-Service General Hospital at the National Defense Medical Center in Taipei, Taiwan. (TSGH IRB No. B-111-19) Additionally, on account of the regulations in Taiwan, our ethics committee waived the need for informed consent.

Study Design and Sampled Participants

Figure 1 is the flowchart of this study, illustrating the case-screening process (inclusion and exclusion criteria) and the follow-up results, as well as the risk of mental disorders between patients with endometriosis and the reference cohort. After the exclusion criteria took effect, a total of 100,770 participants, encompassing 20,154 in the study group and 80,616 in the comparison group (1:4), were enrolled during the study period (2000–2015). The mental disorders incidence of the endometriosis group is 20.26%; nevertheless, the control group showed mental disorders incidence of 11.44%.

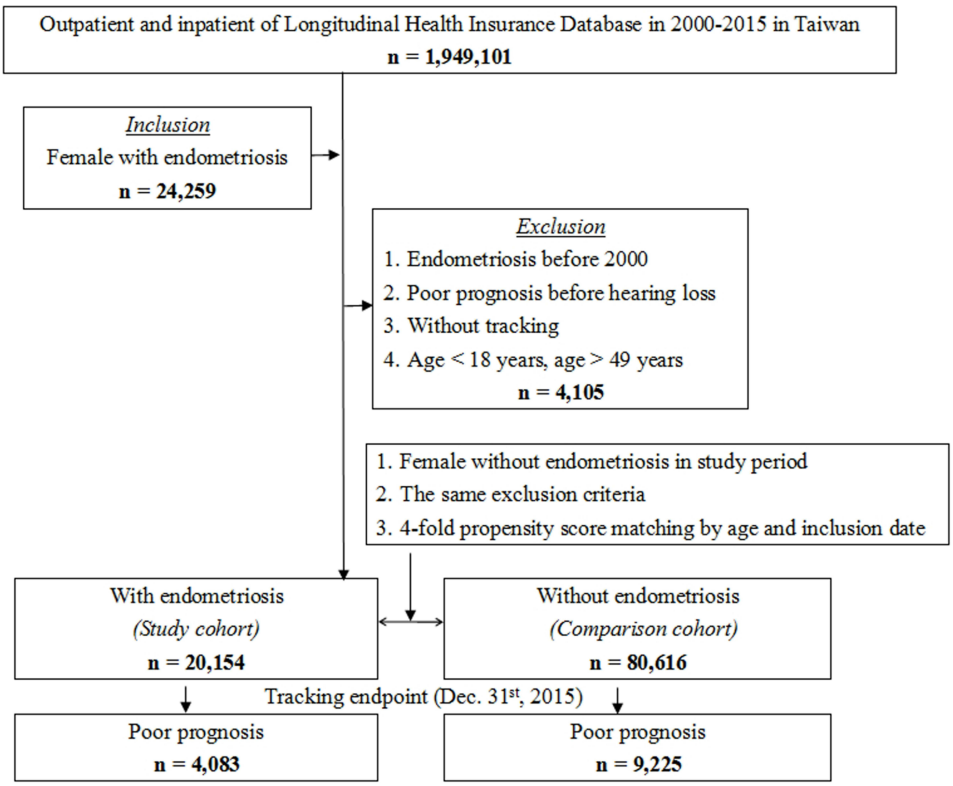

Figure 1 The flowchart of this study.

This study was of a population-based, matched-cohort design. Patients with newly diagnosed endometriosis were selected from the Longitudinal Health Insurance Database from January 1, 2000, to December 31, 2015. The patients with endometriosis before 2000 were excluded. This method could function as a way to make sure that these diseases were recent-onset with references from other studies for the association between endometriosis and mental disorders, utilizing the NHIRD.[27]

Additionally, the patients diagnosed with mental disorders (including anxiety, depression, bipolar, sleep disorders, posttraumatic stress disorder (PTSD)/ acute stress disorder (ASD), dementia, eating disorders, substance-related disorders (SRD), psychotic disorders, autism, and other mental disorders) suicide, all-caused mortality, sleep disorders, and psychotic disorders, before 2000, or before their first visit for endometriosis were also excluded.[28] A total of the patients who were enrolled, covering 20,154 participants in the study cohort and 80,616 controls without endometriosis, were matched for age and index date.[28,29] Each enrolled participant was required to have made at least three outpatient visits or one inpatient episode in the 1-year study period for endometriosis according to these ICD-9-CM codes.[29](Table S1)

Covariates

The covariates included age groups (<=19, 20–44, 45–64, ≥65 years), geographical area of residence (north, center, south, and east of Taiwan), urbanization level of residence (levels 1 to 4), and monthly income (in New Taiwan Dollars [NT$]; < 18,000, 18,000–34,999, ≥35,000; approximately 30 New Taiwan Dollars to US dollar). The urbanization level of residence was defined according to the population and various indicators of the level of development.[30] Level 1 was defined as a population of > 1,250,000, and a specific designation as political, economic, cultural, and metropolitan development. Level 2 was defined as a population between 500,000 and 1,249,999, and as playing an important role in politics, economy, and culture. Urbanization levels 3 and 4 were defined as a population between 149,999 and 499,999, and <149,999, respectively.[31]

Major Outcome

All of the study participants were followed from the index date until the onset of, mental disorders (ICD-9-CM: 290–319) (including anxiety (ICD-9-CM: 300), depression (ICD-9-CM: 296.2–296.3, 300.4, 311), bipolar (ICD-9-CM: 296.0, 296.4–296.8), sleep disorders (ICD-9-CM: 307.4, 780.5), PTSD/ASD (ICD-9-CM: 308, 309.81), dementia (ICD-9-CM: 290.0–290.4, 290.8–290.9, 331.0), eating disorders (ICD-9-CM: 307.1, 307.5), SRD (ICD-9-CM: 291–292, 303.3, 303.9, 304–305), psychotic disorders (ICD-9-CM: 295, 297–298), autism (ICD-9-CM: 299.0), and other mental disorders (ICD-9-CM: 290–319 excluding listed above)), suicide (ICD-9-CM: E950-E959), all-cause mortality (ICD-9-CM: 800–999), withdrew from the NHI program, or the end of 2015. In addition, each psychiatric diagnosis was required to have made at least three outpatient visits within the 1-year study period for psychiatric disorders according to these ICD-9-CM codes.[27,32]

Statistical Analyses

All statistical analyses were performed using the SPSS for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). χ^2 and *t*-tests were used to evaluate the distributions of the categorical and continuous variables, respectively. The results were presented as hazard ratio (HR) with a 95% confidence interval (CI).[25] The differences in the risk of subsequent mental disorders between the endometriosis and non-endometriosis cohorts were estimated via the Kaplan-Meier method and Log rank tests. A two-tailed p-value < 0.05 was considered to indicate the statistical significance.[32,33]

Results

Of a total of 100,770 participants, Kaplan-Meier survival analysis revealed that there was a statistically significant difference in the development of mental disorders, including psychiatric disorders and suicide besides, at the 1st year of follow-up, the difference between the two groups became significant (long-rank, p<0.001) (Figure 2).

The average follow-up period for the diagnosis of endometriosis to mental disorders was 7.21±5.34 years, which is less than the comparison group (7.84±5.80 years). Besides, we also studied the incidence and prevalence of mental disorders among different cohorts (Tables 1 and S2).

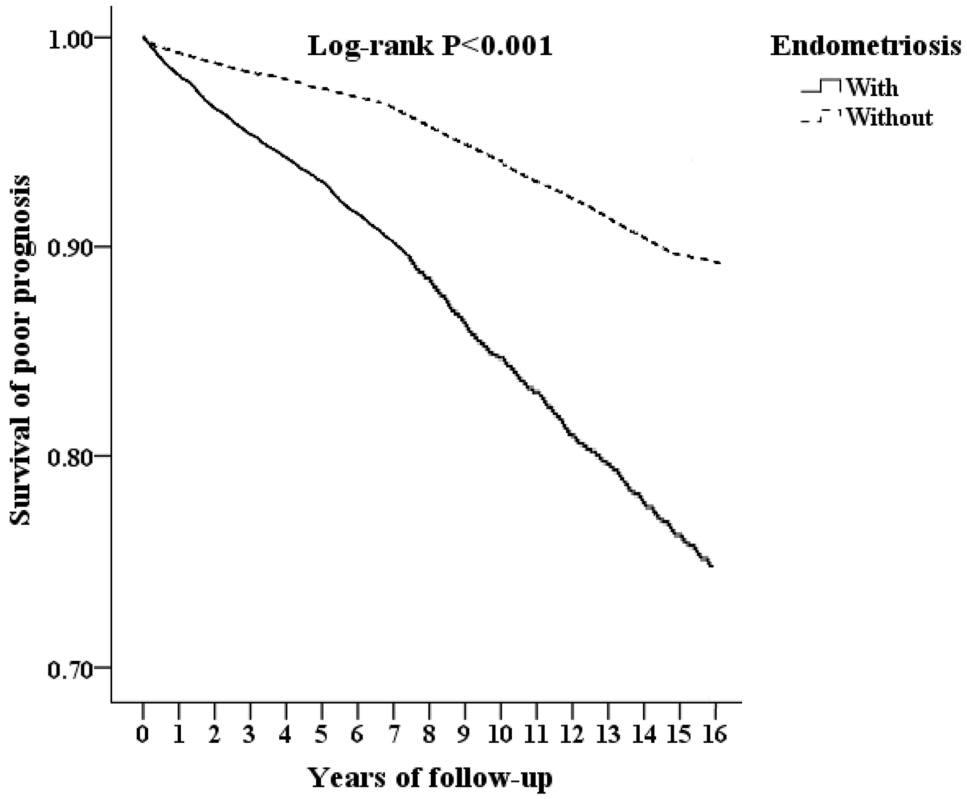

Figure 2 Kaplan-Meier for survival of mental disorders among aged 18–49 women stratified by endometriosis with Log rank test.

Table 1 Years to Mental Disorders

Endometriosis	Min	Median	Max	Mean ± SD
With	0.02	6.12	15.85	7.21 ± 5.34
Without	0.02	6.86	15.89	7.84 ± 5.80
Overall	0.02	6.67	15.89	7.71 ± 5.72

Note: Mean: average number.
Abbreviation: SD, standard deviation.

Table 2 shows age groups, monthly insured premiums, comorbidities, season of medical visits, geographical area of residence, urbanization, level of care, of the study subjects, and controls. The distribution of age, pneumonia, injury, tumor, and season of medical visits between these two groups was not a statistically significant difference. The majority of participants were above 40 (48.55%) for the endometriosis group and the control group. The patients suffering from endometriosis were more likely to live in northern and southern Taiwan and urbanization level 1 and 2, receiving medical care from the hospital centers and regional hospitals, paying the less insured premium. The endometriosis cohort tended to have more diabetes mellitus (DM), hypertension (HTN), renal disease, hyperlipidemia, thyrotoxicosis, chronic liver disease (CLD) than the non-endometriosis control cohort.

Table 3 demonstrated the result of Cox regression analysis of some factors associated with the risk to developmental disorders. The crude HR is 2.978 (95% CI= 2.237–3.865, p<0.001). After adjusting for age, monthly insured premium,

Table 2 Characteristics of Study in the Baseline

Endometriosis	Total		With		Without		*P*
Variables	**n**	**%**	**n**	**%**	**n**	**%**	
Total	100,770		20,154	20.00	80,616	80.00	
Age (years)	40.10 ± 18.26		40.08 ± 18.22		40.11 ± 18.27		0.835
Age groups (yrs)							0.999
≦19	1020	1.01	204	1.01	816	1.01	
20–29	14,875	14.76	2975	14.76	11,900	14.76	
30–39	35,950	35.68	7190	35.68	28,760	35.68	
≧40	48,925	48.55	9785	48.55	39,140	48.55	
Insured premium (NT$)							<0.001
<18,000	82,104	81.48	16,452	81.63	65,652	81.44	
18,000–34,999	10,444	10.36	2331	11.57	8113	10.06	
≧35,000	8222	8.16	1371	6.80	6851	8.50	
DM							<0.001
Without	88,161	87.49	17,257	85.63	70,904	87.95	
With	12,609	12.51	2897	14.37	9712	12.05	
HTN							<0.001
Without	87,391	86.72	16,753	83.12	70,638	87.62	
With	13,379	13.28	3401	16.88	9978	12.38	

(*Continued*)

Table 2 (Continued).

Endometriosis	Total		With		Without		*P*
Variables	**n**	**%**	**n**	**%**	**n**	**%**	
Renal disease							<0.001
Without	89,216	88.53	17,634	87.50	71,582	88.79	
With	11,554	11.47	2520	12.50	9034	11.21	
Hyperlipidemia							0.009
Without	93,705	92.99	18,656	92.57	75,049	93.09	
With	7065	7.01	1498	7.43	5567	6.91	
Thyrotoxicosis							<0.001
Without	98,870	98.11	19,668	97.59	79,202	98.25	
With	1900	1.89	486	2.41	1414	1.75	
Pneumonia							0.064
Without	89,964	89.28	17,920	88.92	72,044	89.37	
With	10,806	10.72	2234	11.08	8572	10.63	
CLD							0.003
Without	92,436	91.73	18,382	91.21	74,054	91.86	
With	8334	8.27	1772	8.79	6562	8.14	
Injury							0.247
Without	85,449	84.80	17,037	84.53	68,412	84.86	
With	15,321	15.20	3117	15.47	12,204	15.14	
Tumor							0.632
Without	97,618	96.87	19,513	96.82	78,105	96.89	
With	3152	3.13	641	3.18	2511	3.11	
Season of medical visit							0.999
Spring (Mar-May)	25,250	25.06	5050	25.06	20,200	25.06	
Summer (Jun-Aug)	25,560	25.36	5112	25.36	20,448	25.36	
Autumn (Sep-Nov)	25,375	25.18	5075	25.18	20,300	25.18	
Winter (Dec-Feb)	24,585	24.40	4917	24.40	19,668	24.40	
Location							<0.001
Northern Taiwan	34,377	34.11	6275	31.14	28,102	34.86	
Central Taiwan	26,395	26.19	5145	25.53	21,250	26.36	
Southern Taiwan	25,308	25.11	5523	27.40	19,785	24.54	
Eastern Taiwan	12,082	11.99	2991	14.84	9091	11.28	
Outlying islands	2608	2.59	220	1.09	2388	2.96	

(*Continued*)

Table 2 (Continued).

Endometriosis	Total		With		Without		*P*
Variables	**n**	**%**	**n**	**%**	**n**	**%**	
Urbanization level							<0.001
1 (The highest)	32,716	32.47	6173	30.63	26,543	32.93	
2	36,769	36.49	6972	34.59	29,797	36.96	
3	14,360	14.25	3125	15.51	11,235	13.94	
4 (The lowest)	16,925	16.80	3884	19.27	13,041	16.18	
Level of care							<0.001
Hospital center	27,413	27.20	7652	37.97	19,761	24.51	
Regional hospital	38,903	38.61	6862	34.05	32,041	39.75	
Local hospital	34,454	34.19	5640	27.98	28,814	35.74	

Notes: *P*: Chi-square/Fisher exact test on category variables and *t*-test on continue variables; the pink boxes demonstrate the statistical significance. (p-value<0.05).

Table 3 Factors of Mental Disorders by Using Cox Regression

Variables	Crude HR	95% CI	95% CI	*P*	Adjusted HR	95% CI	95% CI	*P*
Endometriosis								
Without	Reference				Reference			
With	2.978	2.237	3.865	<0.001	2.131	1.531	2.788	<0.001
Age groups (yrs)								
≦19	Reference				Reference			
20–29	1.897	1.234	2.701	<0.001	1.435	1.134	1.798	<0.001
30–39	2.765	1.883	3.342	<0.001	1.862	1.370	2.131	<0.001
≧40	3.004	2.245	3.798	<0.001	2.251	1.883	2.842	<0.001
Insured premium (NT$)								
<18,000	Reference				Reference			
18,000–34,999	0.782	0.286	1.567	0.725	0.883	0.372	1.771	0.682
≧35,000	0.645	0.201	1.268	0.789	0.725	0.295	1.482	0.735
DM								
Without	Reference				Reference			
With	2.250	1.860	2.776	<0.001	2.025	1.672	2.553	<0.001
HTN								
Without	Reference				Reference			
With	2.786	2.035	3.672	<0.001	2.421	1.896	3.112	<0.001

(*Continued*)

Table 3 (Continued).

Variables	Crude HR	95% CI	95% CI	*P*	Adjusted HR	95% CI	95% CI	*P*
Renal disease								
Without	Reference				Reference			
With	2.120	1.455	2.679	<0.001	2.018	1.431	2.621	<0.001
Hyperlipidemia								
Without	Reference				Reference			
With	1.562	1.134	1.972	<0.001	1.403	1.048	1.886	0.002
Thyrotoxicosis								
Without	Reference				Reference			
With	1.322	1.065	1.664	<0.001	1.276	1.001	1.596	0.050
Pneumonia								
Without	Reference				Reference			
With	1.786	1.256	2.576	<0.001	1.603	1.189	2.431	<0.001
CLD								
Without	Reference				Reference			
With	2.235	1.465	2.767	<0.001	2.111	1.352	2.577	<0.001
Injury								
Without	Reference				Reference			
With	2.330	1.425	3.239	<0.001	2.065	1.207	2.844	<0.001
Tumor								
Without	Reference				Reference			
With	2.706	1.756	3.875	<0.001	2.129	1.573	3.091	<0.001
Season of medical visit								
Spring	Reference				Reference			
Summer	0.925	0.620	1.372	0.446	0.844	0.531	1.221	0.511
Autumn	1.031	0.743	1.452	0.358	0.986	0.682	1.324	0.425
Winter	0.972	0.688	1.398	0.412	0.912	0.586	1.298	0.498
Location					Multicollinearity with urbanization level			
Northern Taiwan	Reference				Multicollinearity with urbanization level			
Central Taiwan	0.986	0.771	1.352	0.347	Multicollinearity with urbanization level			
Southern Taiwan	1.265	0.835	1.850	0.262	Multicollinearity with urbanization level			
Eastern Taiwan	0.771	0.465	1.221	0.564	Multicollinearity with urbanization level			
Outlying islands	0.523	0.121	2.894	0.899	Multicollinearity with urbanization level			

(*Continued*)

Table 3 (Continued).

Variables	Crude HR	95% CI	95% CI	*P*	Adjusted HR	95% CI	95% CI	*P*
Urbanization level								
1 (The highest)	2.354	1.476	3.398	<0.001	1.996	1.267	2.789	<0.001
2	1.986	1.255	2.737	<0.001	1.789	1.044	2.420	0.007
3	1.531	1.003	2.030	0.048	1.235	0.842	2.060	0.159
4 (The lowest)	Reference				Reference			
Level of care								
Hospital center	2.989	1.689	3.311	<0.001	2.603	1.581	2.989	<0.001
Regional hospital	2.065	1.452	2.689	<0.001	1.751	1.303	2.446	<0.001
Local hospital	Reference				Reference			

Notes: Adjusted HR: Adjusted variables listed in the table; Multicollinearity: correlated with other independent variables; the pink boxes demonstrate the statistical significance. (p-value<0.05).
Abbreviation: HR, hazard ratio; CI, confidence interval.

comorbidities, season of medical visits, geographical area of residence, and urbanization level of the residence, the adjusted HR is 2.131 (95% CI= 1.531–2.788, p<0.001). For the subgroup aged≥40 of the endometriosis group, the risk of developing mental disorders is 2.251 times higher than the participants aged≤19.

In Table 4, by stratification with age, monthly insured premiums, comorbidities, season of medical visits, urbanization levels, levels of care from medical visits, etc., the risk to develop mental disorders in the endometriosis cohort is higher than the control group. In different urbanization levels, geographic areas of residence, monthly income, levels of care,

Table 4 Factors of Mental Disorders Stratified by Variables Listed in the Table by Using Cox Regression

Endometriosis	With			With vs Without (Reference)			
Stratified	**Events**	**PYs**	**Rate (Per 10^5 PYs)**	**Adjusted HR**	**95% CI**	**95% CI**	***P***
Total	4083	188,033.75	2171.42	2.131	1.531	2.788	<0.001
Age groups (yrs)							
≦19	32	1847.30	1732.26	1.671	1.200	2.186	<0.001
20–29	583	27,392.41	2128.33	2.090	1.502	2.735	<0.001
30–39	1435	65,971.35	2175.19	2.136	1.534	2.794	<0.001
≧40	2033	92,822.69	2190.20	2.149	1.544	2.811	<0.001
Insured premium (NT$)							
<18,000	3310	152,369.22	2172.35	2.164	1.555	2.831	<0.001
18,000–34,999	572	23,931.20	2390.19	2.132	1.532	2.789	<0.001
≧35,000	201	11,733.33	1713.07	1.640	1.178	2.145	<0.001
DM							
Without	3438	160,268.64	2145.15	2.105	1.512	2.753	<0.001
With	645	27,765.11	2323.06	2.285	1.642	2.990	<0.001

(*Continued*)

Table 4 (Continued).

Endometriosis	With			With vs Without (Reference)			
Stratified	**Events**	**PYs**	**Rate (Per 10^5 PYs)**	**Adjusted HR**	**95% CI**	**95% CI**	***P***
HTN							
Without	3348	154,801.69	2162.77	2.124	1.526	2.778	<0.001
With	735	33,232.06	2211.72	2.163	1.554	2.830	<0.001
Renal disease							
Without	3550	163,912.67	2165.79	2.124	1.526	2.779	<0.001
With	533	24,121.08	2209.69	2.182	1.568	2.854	<0.001
Hyperlipidemia							
Without	3761	173,710.50	2165.10	2.125	1.527	2.780	<0.001
With	322	14,323.25	2248.09	2.201	1.582	2.880	<0.001
Thyrotoxicosis							
Without	3982	183,435.30	2170.79	2.129	1.530	2.786	<0.001
With	101	4598.45	2196.39	2.206	1.585	2.886	<0.001
Pneumonia							
Without	3600	165,922.60	2169.69	2.131	1.531	2.788	<0.001
With	483	22,111.15	2184.42	2.132	1.531	2.789	<0.001
CLD							
Without	3705	170,962.79	2167.14	2.127	1.528	2.783	<0.001
With	378	17,070.96	2214.29	2.168	1.557	2.836	<0.001
Injury							
Without	3420	158,308.87	2160.33	2.120	1.523	2.774	<0.001
With	663	29,724.88	2230.45	2.187	1.571	2.861	<0.001
Tumor							
Without	3940	181,615.53	2169.42	2.130	1.530	2.786	<0.001
With	143	6418.22	2228.03	2.161	1.553	2.828	<0.001
Season of medical visit							
Spring	995	46,764.70	2127.67	2.202	1.582	2.881	<0.001
Summer	1013	47,927.65	2113.60	2.074	1.490	2.713	<0.001
Autumn	1065	47,388.22	2247.39	2.159	1.551	2.824	<0.001
Winter	1010	45,953.18	2197.89	2.089	1.501	2.733	<0.001
Urbanization level							
1 (The highest)	1305	56,949.38	2291.51	2.249	1.616	2.942	<0.001
2	1404	65,038.72	2158.71	2.111	1.517	2.762	<0.001

(*Continued*)

Table 4 (Continued).

Endometriosis	With			With vs Without (Reference)			
Stratified	**Events**	**PYs**	**Rate (Per 10^5 PYs)**	**Adjusted HR**	**95% CI**	**95% CI**	***P***
3	625	29864.11	2092.81	2.071	1.488	2.710	<0.001
4 (The lowest)	749	36,181.54	2070.12	2.032	1.460	2.659	<0.001
Level of care							
Hospital center	1789	71,814.44	2491.14	2.556	1.836	3.344	<0.001
Regional hospital	1231	62,696.85	1963.42	2.044	1.469	2.674	<0.001
Local hospital	1063	53,522.46	1986.08	1.779	1.278	2.327	<0.001

Notes: Adjusted HR = Adjusted Hazard ratio: Adjusted for the variables listed in Table 3.; CI = confidence interval; the pink boxes demonstrate the statistical significance. (p-value<0.05).
Abbreviations: PYs, Person-years.

seasons of visit, the subjects were associated with an increased risk of mental disorders, encompassing psychiatric disorders, suicide, and all-cause mortality.

Table 5 revealed the adjusted HR of suicide with adjusted HR: 1.447, p=0.009, all-cause mortality with adjusted HR: 2.315, p<0.001, psychiatric disorders with adjusted HR: 2.125, p<0.001, depression with adjusted HR: 2.773, p<0.001, anxiety with adjusted HR: 2.494, p<0.001, sleep disorders with adjusted HR: 2.295, p<0.001 in the study cohort, in

Table 5 Factors of Mental Disorders Subgroups by Using Cox Regression

		Endometriosis		With vs Without (Reference)	
Sensitivity Test	**Mental Disorders Subgroups**	**Adjusted HR**	**95% CI**	**95% CI**	***P***
Overall	Overall	2.131	1.531	2.788	<0.001
	Mental disorders	2.125	1.527	2.781	<0.001
	Anxiety	2.494	1.791	3.262	<0.001
	Depression	2.773	1.992	3.628	<0.001
	Bipolar	1.367	0.982	1.788	0.072
	Sleep disorders	2.295	1.649	3.002	<0.001
	PTSD / ASD	2.194	1.576	2.870	<0.001
	Dementia	1.128	0.811	1.476	0.186
	Eating disorders	1.971	1.416	2.579	<0.001
	SRD	2.080	1.494	2.721	<0.001
	Psychotic disorders	1.794	1.289	2.348	<0.001
	Autism	1.126	0.809	1.473	0.197
	Other mental disorders	1.061	0.763	1.389	0.245
	Suicide	1.447	1.040	1.893	0.009
	All-caused mortality	2.315	1.663	3.029	<0.001

(*Continued*)

Table 5 (Continued).

		Endometriosis		With vs Without (Reference)	
Sensitivity Test	**Mental Disorders Subgroups**	**Adjusted HR**	**95% CI**	**95% CI**	***P***
In the first year excluded	Overall	2.132	1.532	2.789	<0.001
	Mental disorders	2.123	1.525	2.777	<0.001
	Anxiety	2.491	1.790	3.259	<0.001
	Depression	2.755	1.979	3.604	<0.001
	Bipolar	1.363	0.979	1.783	0.083
	Sleep disorders	2.295	1.649	3.002	<0.001
	PTSD / ASD	2.696	1.937	3.528	<0.001
	Dementia	1.146	0.824	1.500	0.172
	Eating disorders	1.946	1.398	2.546	<0.001
	SRD	2.075	1.491	2.715	<0.001
	Psychotic disorders	1.761	1.265	2.304	<0.001
	Autism	0.963	0.692	1.260	0.305
	Other mental disorders	1.130	0.812	1.479	0.199
	Suicide	1.455	1.045	1.903	0.003
	All-caused mortality	2.331	1.674	3.049	<0.001
In the first 5 years excluded	Overall	2.141	1.538	2.802	<0.001
	Mental disorders	2.123	1.525	2.778	<0.001
	Anxiety	2.545	1.828	3.329	<0.001
	Depression	2.839	2.040	3.714	<0.001
	Bipolar	1.380	0.992	1.806	0.060
	Sleep disorders	2.328	1.672	3.045	<0.001
	PTSD / ASD	1.076	0.773	1.408	0.270
	Dementia	1.101	0.791	1.440	0.209
	Eating disorders	1.928	1.385	2.522	<0.001
	SRD	1.926	1.384	2.520	<0.001
	Psychotic disorders	1.812	1.302	2.371	<0.001
	Autism	1.020	0.733	1.334	0.278
	Other mental disorders	1.016	0.730	1.330	0.264
	Suicide	1.389	0.998	1.818	0.053
	All-caused mortality	2.417	1.736	3.162	<0.001

Notes: Adjusted HR = Adjusted Hazard ratio: Adjusted for the variables listed in Table 3.; CI = confidence interval; the pink boxes demonstrate the statistical significance. (p-value<0.05).

comparison with participants without endometriosis. Besides, we found a surprising thing that PTSD/ASD was statistically significant on the whole. When the first year was excluded, PTSD/ASD was statistically significant as well. Nevertheless, there is no statistically significant when the first five years were excluded.

Discussions

In our study, by using two million NHIRD with the advantage of a large dataset, we investigated the association between endometriosis and mental disorders covering psychiatric disorders, suicide, and all-cause mortality. In our study, we have excluded the patients and controls with psychiatric disorders before the follow-up period. After adjusting for comorbidities and other covariates, the overall adjusted HR was 2.131 (95% CI =1.531–2.788, p<0.001) when compared to the comparison cohort. To put it differently, patients with endometriosis had a 2.1-fold risk of developing mental disorders. Participants with endometriosis are associated with an increased risk of mental disorders, especially in depression and anxiety in this group. As a consequence, a regular psychiatric follow-up might be important for the patients who received endometriosis. The Kaplan–Meier analysis demonstrated that the study group had a significantly higher 16-year mental disorders-free survival rate than the controls.

In our study, mental disorders encompassing psychiatric disorders,[34,35] suicide,[36,37] and all-cause mortality are associated with endometriosis. Menghan (2020) carried out a cohort study in Sweden, which showed that for those with endometriosis, the adjusted HR of depressive disorders was 1.89, the adjusted HR of anxiety and stress-related disorders was 1.82, and the adjusted HR of bipolar and other affective psychotic disorders was 1.62.[38] Another cross-section study in the United States demonstrated that anxiety disorders predominated at 45% in patients with endometriosis, and this was followed by depressive disorders (31.3%).[1] By conducting a retrospective matched cohort study in the United States, comparing patients with documented endometriosis to those without, the adjusted HR of anxiety, depression, and self-directed violence were 1.38, 1.48, and 2.03, respectively.[12] In the same vein, after adjusting for other factors, the adjusted HR of depression was 2.494, the adjusted HR of anxiety was 2.773 in our study, similar to a previous study, utilizing the NHIRD as well.[39] Besides, Chen (2020) claimed that patients with endometriosis were more likely to suffer from bipolar disorders.[17] However, further studies are needed to clarify the underlying mechanism. Psychiatric disorders have an association with suicide and all-cause mortality.[15,40,41] Previous studies demonstrated the association between endometriosis and suicide. Endometriosis may be a risk factor to increase patients' suicide ideation.[36,42,43] Our study is the first general population-based cohort study to investigate the associations between endometriosis and suicide. In our study, after adjusting for covariates and comorbidities, the adjusted HR of suicide was 1.447. Conversely, Saavalainen (2019) argues that the association between all-cause mortality and endometriosis remains uncertain and is needed to carry out further studies to identify the association.[44] Nevertheless, in our study, patients with endometriosis have a 2.315-fold risk for developing all-cause mortality. It is needed to conduct further studies to clarify the underlying mechanisms.

Endometriosis is a risk factor for affecting patients' psychiatric health.[45,46] Mental disorders covering psychiatric disorders, suicide, all-cause mortality were most common in women of reproductive age and from low socioeconomic.[5] Due to the repetitive and consistent menstrual cycle, the menstrual cycle could maximize the endometriosis symptoms for reproductive age of women.[47] The underlying pathopsychological mechanism of the increased risk of mental disorders in people with endometriosis remains unclarified. The relationship between endometriosis and mental disorders is based on the symptoms of endometriosis.[10] Chronic pelvic pain, dysmenorrhea, dyspareunia, dysuria, subfertility, and infertility are features of endometriosis.[48–50] When estimating the association between endometriosis and psychiatric health, chronic pelvic pain is a critical variable needed to be taken into account, defined as a nonmalignant pain perceived in pelvic areas that is constant or recurs over 6 months.[51–53] Psychological factors should be involved, serving as an important factor to affect pain experience in people with endometriosis.[35,54] Chronic pain is a well-known mediator of sleep disorders, anxiety, and depression.[55,56] Chronic pain also function as a risk factor for suicide and all-cause mortality.[18,57] The previous study suggested that psychopathological diseases amplify pain symptoms in patients with endometriosis.[54] In this way, patients with psychiatric diseases may influence the severity of chronic pelvic pain, and chronic pelvic pain contributes to worsen psychiatric disorders, which created a vicious circle. The association between dysmenorrhea and stress is bidirectional.[58] Experiencing monthly repeated menstrual pain might increase the risk of experiencing psychiatric disorders especially depression and anxiety, or stress and vice versa.[58–60] Having these psychiatric disorders may exacerbate the severity of

menstrual pain.[59,61] Tayyeb (2022) points out that dyspareunia, painful sexual intercourse, affecting approximately 10 to 28% of the population in a lifetime is a common female health problem.[62] The previous studies suggested that dyspareunia and dysuria have a significant effect on physical as well as mental health, contributing to depression, anxiety, etc.[62–65] Infertility is a common medical condition, leading to mental, psychological, physical detriments to the patients.[66,67] According to statistics, up to 30–40% of women who have endometriosis also have a problem with fertility.[68] Infertility and associated diagnoses have overall health implications.[69] It has been considered as a social stigma, treated as a physically, mentally, socially damaging experience.[8,66]

Sexuality is a fundamental dimension of human life with critical implications for psychiatry health and global quality of life.[70,71] Nevertheless, female sexuality can be influenced by chronic gynecological diseases such as endometriosis.[70–72] As demonstrated by several previous studies, women with endometriosis tend to have a more significant risk of deep dyspareunia; additionally, endometriosis is also associated with an increased risk of mental and psychosexual disorders.[73–75] Chronic pelvic pain is one of the clinical manifestations of endometriosis which might contribute to the decreasing number of sexual relations.[72] Montanari argues that endometriosis-related dyspareunia may lead to less sexual satisfaction and an inability to reach orgasm during intercourse.[76] The high prevalence of sexual dysfunctions in women with endometriosis, including potential and ovarian endometriosis and deep infiltrating endometriosis, is alarming. (About two-thirds of women with endometriosis)[73,75] Dyspareunia may negatively affect the mental health and psychical health of women.[75] Besides, a meta-analysis suggests a bidirectional association between depression and sexual dysfunction.[77] However, we do not take sexual dysfunction into consideration in our study.

There are several clinical implications for the knowledge from the knowledge in this study. In the beginning, in this endometriosis group of women, conversation respecting psychiatric disorders, suicide, mortality should be included into the daily care. Providing a platform is necessary for those women who worsens the psychological disorder owing to pain perception. Additionally, for those with endometriosis, routine and active screening for psychiatric disorders could facilitate in diagnosis and manage the potential underlying psychological illness processes which could influence the quality of health, life, and social. Furthermore, both physical symptoms and emotion regulation difficulties should be incorporated into the therapy alternatives. In comparison with women without endometriosis, the significant presence of psychiatric disorders in women with endometriosis reveals that the association between endometriosis and mental disorders should be emphasized rather than consider subsequent psychiatric disorders as a common occurrence.

The strengths of this study encompass the following reasons. First of all, one of the primary strengths is the use of a database with a large, nationwide cohort of insured individuals. Besides, we have the ability to adjust for lots of potential confounders, and the implementations of multiple sensitive analyses contributing to increase the confidence in the results. Furthermore, for the first time, utilizing the large, nationwide database, we conducted a cohort study to examine the association between endometriosis and mental disorders including psychiatric disorders, suicide, all-cause mortality.

There are several limitations to this study. In the beginning, patients with endometriosis could be identified by the NHIRD; however, data on severity and impact were not available. Second, the previous study demonstrated that women with higher education levels were more likely to understand endometriosis and have recourse to a specialist for their endometriosis.[67,78] Although we took other socioeconomic such as urbanization levels, geographic areas of residence, and monthly insured premium into consideration, potential selection bias could exist due to the difference in education levels. Third, other confounding factors, such as genetic, environmental, diet factors are also not encompassed in the NHIRD. Fourth, as there are no images or other laboratory data recorded in the NHIRD, we could only base on the professional diagnosis for mental disorders covering psychiatric disorders, suicide, and all-cause mortality. Fifth, endometriosis is often diagnosed later; hence, it is possible that mental disorders occurred before people with endometriosis were diagnosed.[10,79] Nevertheless, in our study, that cases would be removed, which may contribute to potential bias. Sixth, the NHI program started in 1995; nonetheless, in our study, the data we used contained only a database of 16 years. Seventh, because of the use of NHIRD, there is a lack of stratified analysis to investigate the association between the different treatment of endometriosis and mental disorders. Eighth, although sexual dysfunction may negatively impact on subsequent psychiatric disorders, this factor is not taken into account in this study. Finally, this result is only limited to Taiwan, not necessarily representing other nations or regions.

Conclusions

In conclusion, the present study was designed to determine the association between endometriosis and mental disorders, including psychiatric disorders and suicide, especially in elder females. These experiments confirmed that endometriosis may be a risk factor for mental disorders by multiple regression analysis. Women with endometriosis were nearly twofold inclined to develop mental disorders. This project is the first comprehensive investigation to examine the association between endometriosis and mental disorders; nevertheless, the study was limited by the absence of the data from other nations and regions. We recommend that Health Promotion Administration complete of scales, advocate, and form the medical policies for the physical and mental health of women.

Data Sharing Statement

Data are available from the National Health Insurance Research Database (NHIRD) published by the Taiwan National Health Insurance (NHI) Administration; nevertheless, data cannot be made publicly available due to legal restrictions imposed by the government of Taiwan under the "Personal Information Protection Act". Requests for data can be sent as a formal proposal to the NHIRD (http://www.mohw.gov.tw).

Institutional Review Board Statement

The study was carried out in accordance with the Declaration of Helsinki's and was approved by the Institution Review Board of Tri-Service General Hospital at the National Defense Medical Center in Taipei, Taiwan. (TSGH IRB No. B-111-19).

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Disclosure

The authors report no conflicts of interest in this work.

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