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Intestinal infectious diseases increase the risk of psychiatric disorders

A nationwide population-based cohort study

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Abstract

Intestinal infectious diseases (IIDs) are among the most common diseases and are prevalent worldwide. IIDs are also one of the major disease groups with the highest incidence worldwide, especially among children and older adults. We observed a higher probability of IIDs in patients from the psychiatric department of Tri-Service General Hospital. Therefore, our objective was to investigate if there is an association between IIDs and the risk of developing psychiatric disorders. This nationwide population-based study used the database of the National Health Insurance (NHI) program in Taiwan. The study included 150,995 patients from 2000 to 2015, comprising 30,199 patients with IIDs as the study group and 120,796 patients without IIDs as the control group. Cox proportional hazards regression analysis was performed to calculate the hazard ratio of psychiatric disorders during the 16-year follow-up. Of the patients with IIDs, 4022 (13.32%) developed psychiatric disorders compared to 8119 (6.72%) who did not ($P < .001$). The adjusted hazard ratio (aHR) for overall psychiatric disorders in the study group was 2.724 (95% confidence interval [CI]: 2.482–2.976; $P < .001$). More specifically, the study group had a higher risk of developing a psychiatric disorder, including sleep disorders, depression, anxiety, bipolar disorder, post-traumatic stress disorder (PTSD)/acute stress disorder (ASD), schizophrenia, mental retardation (MR), substance abuse, and other psychiatric disorders. Furthermore, refractory IIDs (seeking medical attention for IIDs 3 or more times) increased the risk (aHR: 3.918; 95% CI: 3.569–4.280; $P < .001$) of developing psychiatric disorders. There was an association between IIDs and the increased risk of developing psychiatric disorders. The novel role of etiological factors in the development of psychiatric disorders deserves more attention, and the control of pathogens that cause IIDs is of urgent public health importance.

Abbreviation: 95% CI = 95% confidence interval, aHR = adjusted hazard ratio, ASD = acute stress disorder, FGIDs = functional gastrointestinal disorders, GI = gastrointestinal, ICD-9-CM = international classification of diseases, ninth revision, clinical modification, IIDs = intestinal infectious diseases, IL = interleukin, MR = mental retardation, NHI = national health insurance, NHIRD = national health insurance research database, NT$ = new Taiwan dollars, PTSD = post-traumatic stress disorder.

Keywords: cohort study, intestinal infectious diseases (IIDs), psychiatric disorders

1. Introduction

Infectious intestinal diseases (IIDs) are among the most prevalent diseases worldwide. IIDs are one of the major diseases with the highest incidence globally, and they are especially prevalent among children and older adults.[1] These diseases place a significant health burden on individuals and communities, and their morbidity is high even in developed countries.[2] A study found that IIDs annually affect approximately 25% of the population of the United Kingdom, resulting in a burden of approximately

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All data generated or analyzed during this study are included in this published article [and its supplementary information files]

This study was conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). The Institutional Review Board of the Tri-Service General Hospital approved this study (TSGHIRB No. B-111-02).

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£1.5 billion each year on the economy, population, and National Health Service.[3] Additionally, IIDs are the leading cause of death in South Asian countries.[4]

IIDs are spread by fecal-oral transmission,[5] and they are caused by various pathogens, including *Salmonella*, *Shigella*, *Vibrio cholera*, and rotavirus.[6] IIDs can occur due to inadequate drinking water, sanitation, and hygiene. These are not only of great concern in developing countries but are also a problem in low-income populations and rural areas of developed countries.[7] Additionally, many studies have reported several causes of IIDs, including consumption of microbe-contaminated food, lack of clean water, and high poverty levels.[7–9] Ingestion of unsafe drinking water can lead to infection by diarrhea-causing pathogens and is one of the leading causes of death in children in low-income countries.[10] Sanitation levels are associated with sewage treatment and represent the national capacity for adequate waste management and the supply of safe drinking water.[11] In a report assessing the global environmental burden of disease, the World Health Organization estimated that the population attributable fraction of diarrheal disease, due to risk factors such as inadequate drinking water, sanitation, and hygiene, is > 25%.[12]

A crowded environment is a risk factor for the spread of IIDs, as well as a higher risk factor for psychiatric disorders due to increased mental stress[13]; therefore, IIDs refers to a group of infections and are most commonly found in large families and institutions, such as orphanages, boarding schools, mental homes, and hospitals.[14] Psychiatric disorders, also called mental disorders, are defined as clinically significant behavioral or psychological syndromes with high individual distress, anxiety, and premature mortality.[15] In the USA, the regional disease burden attributable to mental, neurological, and substance use disorders and self-harm comprised 19% of the total disability-adjusted life-years and 34% of the total years lived with disability in 2015.[16] Mental health problems represent an important public health challenge worldwide. As such, there is growing interest in the role of microbes, such as viruses and protozoan parasites, in some psychiatric disorders.[17–19] For instance, several studies have shown a higher risk of morbidity among individuals with anxiety, depression, or sleep disorders who have been exposed to pinworm infections.[20] Additionally, it has been reported that the extensively studied protozoan parasite *Toxoplasma gondii* is associated with various psychiatric disorders, such as schizophrenia.[21,22] Due to its neurotropic nature and brain-damaging characteristics, *T gondii* is a potential causative agent of mental and behavioral disorders.[18]

Recently, we observed an unexpected trend in the Tri-Service General Hospital, Taiwan, in which patients with IIDs often presented with psychiatric disorders. This raised the question of a possible association between IIDs and psychiatric disorders. Therefore, we conducted a nationwide population-based cohort study to identify whether there is an association between IIDs and psychiatric disorders. Our findings show that IIDs could potentially increase the risk of developing psychiatric disorders, suggesting a clinically important role of IIDs.

2. Material and Methods

2.1. Data sources

National Health Insurance (NHI) program began in Taiwan in 1995, and it covers more than 99% of the Taiwanese population, with approximately 23 million beneficiaries.[23] Data for this study were collected from the NHI Research Database (NHIRD) of Taiwan. The NHRID uses the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes to record diagnoses.[24] A subset of the NHIRD, the Longitudinal Health Insurance Database, which recorded data from 2000 to 2015, was used to investigate the association between IIDs and psychiatric disorders. The Longitudinal Health Insurance Database was used to select 2 million individuals from the NHI enrollee population randomly. Patients with the ICD-9-CM codes of IID-related diagnoses were included in the study group, such as cholera (ICD-9-CM 001), typhoid and paratyphoid fever (ICD-9-CM 002), other salmonella infections (ICD-9-CM 003), shigellosis (ICD-9-CM 004), other food poisoning (bacterial) (ICD-9-CM 005), amebiasis (ICD-9-CM 006), other protozoal intestinal diseases (ICD-9-CM 007), intestinal infections due to other organisms (ICD-9-CM 008), and ill-defined intestinal infections (ICD-9-CM 009). Detailed information on the ICD-9-CM codes used in this study is provided in Supplemental Digital Content (Table S1, http://links.lww.com/MD/H516).

2.2. Study design and population

Patients newly diagnosed with IIDs were selected from January 1, 2000, to December 31, 2015. The following exclusion criteria were used: patients with IIDs before the index date, patients with psychiatric disorders before the start of tracking, patients without tracking, patients of unknown age, and patients of unknown sex. Therefore, 30,199 patients with IIDs were included in the study group. A non-IIDs control group (120,796 patients) was established by matching age and index year in a 4-fold ratio to the study group.

2.3. Covariates

We examined sociodemographic factors in the study and control groups, including age, monthly income, season, place of residence, urbanization level, and type of hospital. The patients were divided into 4 groups according to age: <20 years, 20–39 years, 40–64 years, and ≥65 years. Patients were divided based on their monthly income, in New Taiwan dollars (NT$), into 3 groups: <18,000, 18,000–34,999, and ≥ 35,000. In this study, the 4 seasons (spring, summer, autumn, and winter) were considered. Patients living in different areas of Taiwan, including northern, middle, southern, and eastern Taiwan, as well as the outlet islands, were compared. The patients were classified into 4 levels of urbanization, from highest (1) to lowest (4). Three types of hospitals where patients sought medical attention were considered: medical centers, regional hospitals, and local hospitals.

2.4. Main outcome measures

All study participants were followed from the index date until the onset of all recorded psychiatric disorders in the NHIRD. The incidence and risk of each psychiatric disorder, including sleep disorders, depression, anxiety, bipolar disorder, post-traumatic stress disorder (PTSD)/acute stress disorder (ASD), schizophrenia, substance abuse, MR, and other psychiatric disorders, were compared between the study and control groups.

2.5. Statistical analysis

All statistical analysis was performed using SPSS software (version 22.0; SPSS, Chicago, IL). The chi-square test was used to analyze categorical variables. The t-test, which analyzes continuous variables, was used to evaluate differences between the study and control groups. Differences in the risk of psychiatric disorders in the study and control groups were evaluated using the Kaplan–Meier method with a log-rank test and were presented as cumulative risk. Cox proportional hazards regression analysis was used to determine the risk of psychiatric disorders, and data were expressed as an adjusted hazard ratio (aHR) with 95% confidence intervals (CI).

3. Results

3.1. Demographic characteristics of the study population at the baseline and the endpoint

Based on propensity score matching (the ratio of the study group to the control group was 1:4), there were 30,199 individuals with IIDs in the study group and 120,796 individuals without IIDs in the control group (Fig. 1). The demographic characteristics of the study and control groups at the beginning of the study are shown in Table 1. There were no significant differences in age between the control and study groups (21.45 ± 26.45 vs 21.52 ± 24.08). The percentage of individuals with a monthly income of less than NT$ 18,000 was significantly higher in the study group than in the control group (99.29% vs 99.12%; $P < .001$). Compared to the control group, the study group had more medical visits in the summer (25.41% vs 25.41%), and a higher proportion of patients lived in southern Taiwan (32.57% vs 24.13%; $P < .001$). Regarding the medical care system, more patients with IIDs sought medical help in regional hospitals than the control group (55.35% vs 33.6%; $P < .001$). The demographic characteristics of the study and control groups at the tracking endpoint are described in Supplemental Digital Content (Table S2, http://links.lww.com/MD/H517). Except for the difference in age (24.99 ± 27.15 vs 29.38 ± 25.65%; $P < .001$), age groups (< 20 years) (63.94% vs 49.68%; $P < .001$), and season (autumn) (26.44% vs 23.77%; $P < .001$) between the study and control groups, all the characteristics between patients with and without IIDs were similar to those observed at the baseline.

3.2. Association of IIDs with psychiatric disorders

The incidence of psychiatric disorders was higher in the study group (4022 patients, 13.32%) than in the control group (8119 patients, 6.72%) ($P < .001$) (Table 2). In addition, Kaplan–Meier analysis for the cumulative risk of psychiatric disorders during 16 years of follow-up showed a statistical difference in the study group compared to the control group (log-rank $P < .001$). This difference began in the first year of tracking (Fig. 2). The median duration from the diagnosis of IIDs to the onset of psychiatric disorders was 2.48 years (Supplemental Digital Content (Table S3, http://links.lww.com/MD/H518)). Furthermore, the incidence of some subgroups of psychiatric disorders were significantly higher in the study group than in the control group, including sleep disorders (2.87% vs 1.35%; $P < .001$), depression (1.97% vs 1.04%; $P < .001$), anxiety (2.04% vs 0.91%; $P < .001$), bipolar disorder (0.29% vs 0.18%; $P < .001$), PTSD/ASD (0.07% vs 0.03%; $P < .001$), schizophrenia (1.07% vs 0.45%; $P < .001$), substance abuse (0.96% vs 0.59%; $P < .001$), mental retardation (MR) (0.65% vs 0.26%; $P < .001$), and other psychiatric disorders (4.50% vs 2.40%; $P < .001$). The risk of psychiatric disorders in patients with IIDs was analyzed using Cox regression and presented as an aHR, with reference to the control group (Table 3). Patients

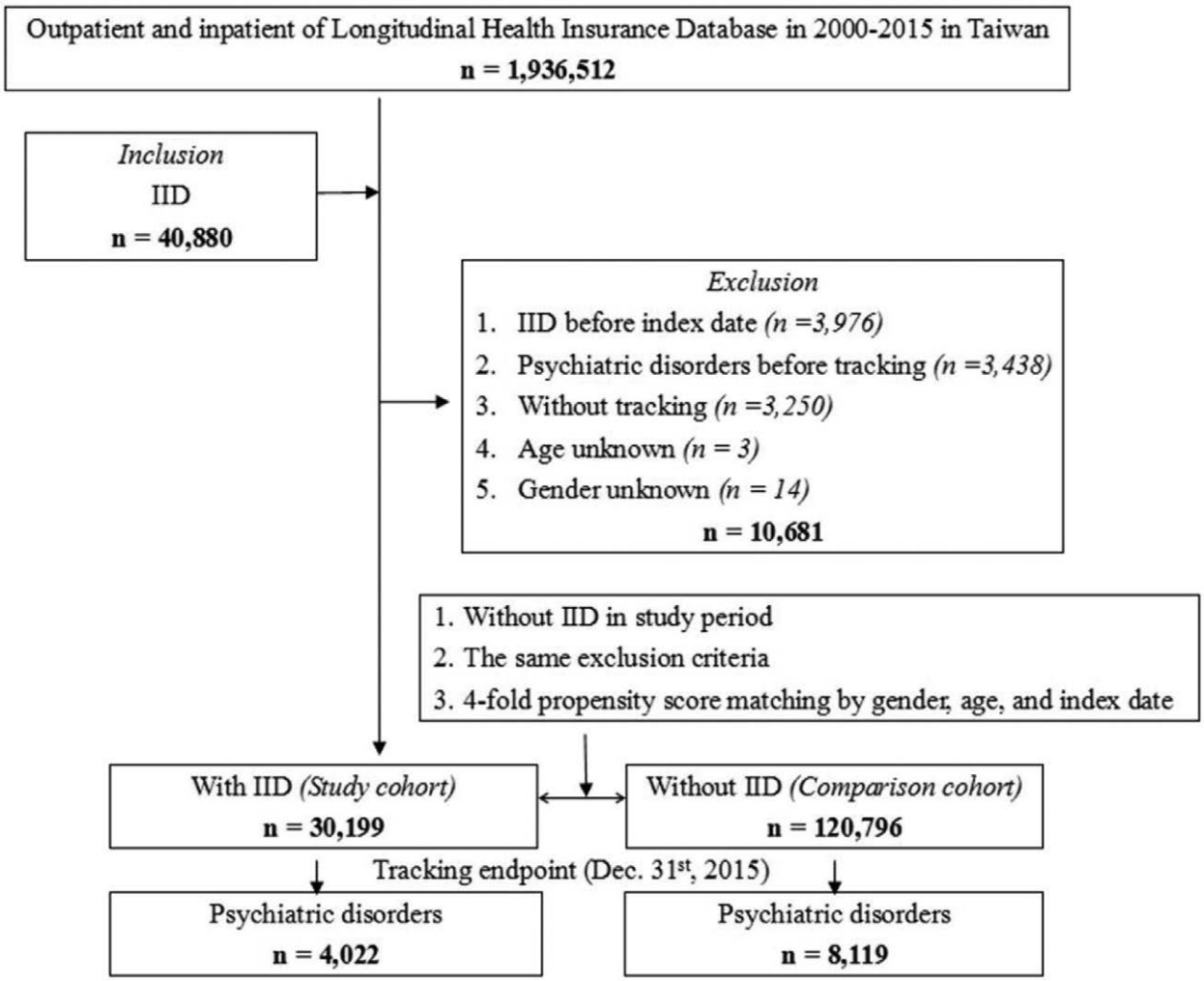

Figure 1. Flowchart of the study sample selection.

Table 1

Demographic characteristics of the study and control populations at the baseline.

Characteristic	Total		With		Without		*P* value*
	n	%	*n*	%	*n*	%	
Total	150,995		30,199	20.00	120,796	80.00	
Age (yrs)	21.51 ± 24.53		21.45 ± 26.25		21.52 ± 24.08		.657
Age group (yrs)							.999
<20	101,580	67.27	20,316	67.27	81,264	67.27	
20-39	11,835	7.84	2367	7.84	9468	7.84	
40-64	19,330	12.80	3866	12.80	15,464	12.80	
≥ 65	18,250	12.09	3650	12.09	14,600	12.09	
Insured premium (NT$)							.009
<18,000	149,724	99.16	29,986	99.29	119,738	99.12	
18,000–34,999	991	0.66	172	0.57	819	0.68	
≥35,000	280	0.19	41	0.14	239	0.20	
Season							.999
Spring (March-May)	37,605	24.90	7521	24.90	30,084	24.90	
Summer (June-August)	38,370	25.41	7674	25.41	30,696	25.41	
Autumn (September-November)	37,900	25.10	7580	25.10	30,320	25.10	
Winter (December-February)	37,120	24.58	7424	24.58	29,696	24.58	
Location							<.001
Northern Taiwan	56,774	37.60	8674	28.72	48,100	39.82	
Middle Taiwan	45,226	29.95	9445	31.28	35,781	29.62	
Southern Taiwan	38,979	25.81	9835	32.57	29,144	24.13	
Eastern Taiwan	9011	5.97	2141	7.09	6870	5.69	
Outlets islands	1005	0.67	104	0.34	901	0.75	
Urbanization level							<.001
1 (The highest)	49,294	32.65	7103	23.52	42,191	34.93	
2	64,969	43.03	14,637	48.47	50,332	41.67	
3	11,944	7.91	2081	6.89	9863	8.17	
4 (The lowest)	24,788	16.42	6378	21.12	18,410	15.24	
Level of care							<.001
Hospital center	44,583	29.53	7409	24.53	37,174	30.77	
Regional hospital	57,299	37.95	16,716	55.35	40,583	33.60	
Local hospital	49,113	32.53	6074	20.11	43,039	35.63	

NT$ = New Taiwan dollars.

*Chi-square/Fisher's exact test on categorical variables and t-test on continuous variables.

with IIDs showed a higher risk of psychiatric disorders and an aHR of 2.724 (95% CI: 2.482–2.976; $P < .001$).

3.3. Risk of psychiatric disorders in the IIDs group stratified by covariates

The risk of psychiatric disorders in the IID groups, stratified by previously described variables, was further evaluated (Table 3). All the patients with IIDs had a higher risk of developing psychiatric disorders, irrespective of being stratified by independent variables. Specifically, patients with IIDs stratified by different age groups revealed that patients aged ≥ 65 years had the highest risk (aHR = 3.858; $P < .001$) compared to the control group. Study subjects which Male participants with the highest risk (aHR = 2.878; $P < .001$) were associated with a higher risk of psychiatric disorders. Additionally, there was an association between a monthly income of less than NT$ 18,000 (aHR = 2.736; $P < .001$) and a higher risk of psychiatric disorders. The season (autumn) (aHR = 2.913; $P < .001$) and high level of urbanization (level 1) (aHR = 3.437; $P < .001$) were associated with a higher risk of psychiatric disorders. Furthermore, patients who sought medical attention at a medical center (aHR = 3.338; $P < .001$) had a markedly increased risk of psychiatric disorders.

3.4. Risk of the subgroups of psychiatric disorders in patients with IIDs

The main subgroups of psychiatric disorders were also examined in the patients with IIDs (Table 4). Compared to the control group, patients with IIDs had a higher risk of sleep disorders (aHR = 2.913; 95% CI: 2.654-3.182; $P < .001$), depression (aHR = 2.598; 95% CI: 2.368–2.839; $P < .001$), anxiety (aHR = 3.069; 95% CI: 2.796–3.353; $P < .001$), bipolar disorder (aHR = 2.215; 95% CI: 2.018–2.420; $P < .001$), PTSD/ASD (aHR = 2.951; 95% CI: 2.688–3.224; $P < .001$), schizophrenia (aHR = 3.299; 95% CI: 3.006–3.604; $P < .001$), substance abuse (aHR = 2.224; 95% CI: 2.026–2.430; $P < .001$), MR (aHR = 3.450; 95% CI: 3.143–3.769; $P < .001$), and other psychiatric disorders (aHR = 2.581; 95% CI: 2.352–2.820; $P < .001$).

3.5. Increased risk of psychiatric disorders in patients with refractory IIDs

We evaluated the risk of psychiatric disorders in patients with IIDs who sought medical help more than once (Table 5). Compared to the control group, the risk of overall psychiatric disorders in the study group was proportional to the number of medical visits. Of these patients, those who sought medical attention 3 or more times for IIDs had a higher risk of overall psychiatric disorders (aHR = 3.918; 95% CI: 3.569–4.280; $P < .001$) than those who sought medical help only once or twice (aHR = 2. 162; 95% CI: 1.964–2.362; $P < .001$).

4. Discussion

In this study, patients with IIDs had a higher risk of overall psychiatric disorders, with an aHR of 2.724, compared to patients without IIDs. This means that patients with IIDs have a 2.724-fold increased risk of developing psychiatric disorders.

Table 2

Incidence of psychiatric disorders in the patients with intestinal infectious diseases compared with the control group.

	Total		With		Without		
Variable	**n**	**%**	**n**	**%**	**n**	**%**	***P* value[a]**
Total	150,955		30,199	20.00	120,796	80.00	
Psychiatric disorders							<.001
Without	138,854	91.96	26,177	86.68	112,677	93.28	
With	12,141	8.04	4022	13.32	8119	6.72	
Sleep disorders							<.001
Without	148,494	98.34	29,333	97.13	119,161	98.65	
With	2501	1.66	866	2.87	1635	1.35	
Depression							<.001
Without	149,144	98.77	29,605	98.03	119,539	98.96	
With	1851	1.23	594	1.97	1257	1.04	
Anxiety							<.001
Without	149,278	98.86	29,584	97.96	119,694	99.09	
With	1717	1.14	615	2.04	1102	0.91	
Bipolar disorders							<.001
Without	150,692	99.80	30,112	99.71	120,580	99.82	
With	303	0.20	87	0.29	216	0.18	
PTSD/ASD							.007
Without	150,932	99.96	30,177	99.71	120,755	99.97	
With	63	0.04	87	0.29	41	0.03	
Schizophrenia							<.001
Without	150,131	99.43	29,875	98.93	120,256	99.55	
With	864	0.57	324	1.07	540	0.45	
Substance abuse							<.001
Without	149,988	99.33	29,909	99.04	120,079	99.41	
With	1007	0.67	290	0.96	717	0.59	
Mental retardation							<.001
Without	150,484	99.66	30,002	99.35	120,482	99.74	
With	511	0.34	197	0.65	314	0.26	
Other psychiatric disorders							<.001
Without	146,738	97.18	28,839	95.50	117,899	97.60	
With	4257	2.828	1360	4.50	2897	2.40	

ASD = acute stress disorder, PTSD = post-traumatic stress disorder.

aChi-square/Fisher's exact test on categorical variables and *t* test on continuous variables.

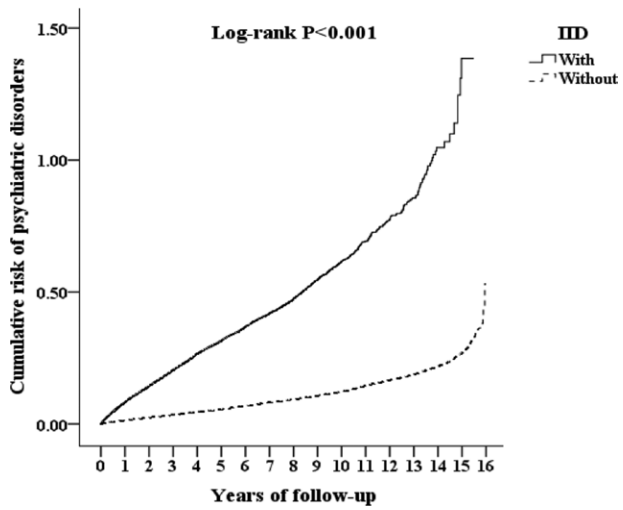

Figure 2. Kaplan–Meier for cumulative risk of psychiatric disorders stratified by IID with log-rank test. IID = intestinal infectious diseases.

Kaplan–Meier analysis also supported the cumulative risk of psychiatric disorders in patients with IIDs during the 16-year follow-up (log-rank $P < .001$). Specifically, patients with IIDs had a significantly increased risk of developing sleep disorders, depression, anxiety, bipolar disorder, PTSD/ASD, schizophrenia, substance abuse, MR, and other psychiatric disorders. These results highlight the novel role of pathogens in IIDs in causing psychiatric disorders and that clinician should pay more attention to the possible risk resulting from this neglected tropical disease.

Previous studies have reported that some psychiatric disorders are associated with inflammatory diseases such as periodontitis,[25] psoriasis,[26] and allergic diseases.[27] A possible mechanism for this association could be the release of pro-inflammatory cytokines, such as interleukin (IL)-6, IL-10, tumor necrosis factor-alpha, and monocyte chemoattractant protein-1, which are involved in the development of depression, anxiety, and bipolar disorder. Several types of bacteria, including *Campylobacter*, *Salmonella*, *Shigella*, and *Escherichia coli*; viruses, such as *rotavirus*, *Norwalk virus*, *cytomegalovirus*, and *herpes simplex virus*; and parasites, including *Giardia lamblia*, *Entamoeba histolytica*, and *Cryptosporidium*, can cause diarrhea. Different pathogens such as enterotoxins invade the host and cause infectious diarrhea.[28] *Salmonella* spp. are a leading cause of gastrointestinal (GI) diseases worldwide. Ma et al[29] reported that tumor necrosis factor-alpha modulates the expression of *Salmonella typhimurium* effector proteins and enhances IL-8 secretions in intestinal epithelial cells. Other studies have shown that IL-6 may play an important role in triggering a systemic immune response against *Salmonella*.[30,31] *Campylobacter jejuni* infection, which induces the release of several cytokines and chemokines, including IL-8 and IL-10,[32] is a common cause of human acute bacterial gastroenteritis. Further investigation is needed to clarify whether intestinal infection-induced immune responses play a role in the development of psychiatric disorders.

Another possibility is that a behavioral pathway may link IIDs with the risk of psychiatric disorders. For instance, patients with

Table 3

Risk of psychiatric disorders in the subjects with intestinal infectious diseases stratified by variables using Cox regression.

	With vs without IIDs		
Stratified	**Adjusted HR**	**95% CI**	***P* value**
Total	2.724	2.482-2.976	<.001
Gender			
Male	2.878	2.622-3.144	<.001
Female	2.546	2.320-2.782	<.001
Age group (yrs)			
<20	2.672	1.017–1.312	<.001
20-39	3.139	2.860-3.429	<.001
40-64	3.214	2.929-3.511	<.001
≥ 65	3.858	3.516-4.215	<.001
Insured premium (NT$)			
<18,000	2.736	2.493-2.989	<.001
18,000–34,999	2.317	2.111-2.532	<.001
≥35,000	0.933	0.851-1.020	.189
Season			
Spring	2.638	2.404-2.883	<.001
Summer	2.824	2.573-3.085	<.001
Autumn	2.913	2.654-3.183	<.001
Winter	2.546	2.319-2.781	<.001
Urbanization level			
1 (the highest)	3.437	3.132-3.755	<.001
2	2.562	2.335-2.799	<.001
3	2.482	2.261-2.712	<.001
4 (the lowest)	2.363	2.153-2.582	<.001
Level of care			
Hospital center	3.338	3.042-3.647	<0001
Regional hospital	2.538	2.313-2.773	<.001
Local hospital	2.432	2.216-2.657	<.001

IIDs = intestinal infectious diseases, NT$ = New Taiwan dollars.

Table 4

Risk of psychiatric disorders subgroup in the patients with intestinal infectious diseases identified by using Cox regression.

		Competing risk in the model				
Psychiatric disorder subgroup	**IIDs and non-IIDs**	**Population**	**Event**	**Adjusted HR**	**95% CI**	***P* value**
Overall	Without IIDs	120,796	8119	Ref.		
	With IIDs	30,199	4022	2.724	2.482-2.976	<.001
Sleep disorders	Without IIDs	120,796	1635	Ref.		
	With IIDs	30,199	866	2.913	2.654-3.182	<.001
Depression	Without IIDs	120,796	1257	Ref.		
	With IIDs	30,199	594	2.598	2.368-2.839	<.001
Anxiety	Without IIDs	120,796	1102	Ref.		
	With IIDs	30,199	615	3.069	2.796-3.353	<.001
Bipolar disorder	Without IIDs	120,796	216	Ref.		
	With IIDs	30,199	87	2.215	2.018-2.420	<.001
PTSD/ASD	Without IIDs	120,796	41	Ref.		
	With IIDs	30,199	22	2.951	2.688-3.224	<.001
Schizophrenia	Without IIDs	120,796	540	Ref.		
	With IIDs	30,199	324	3.299	3.006-3.604	<.001
Substance abuse	Without IIDs	120,796	717	Ref.		
	With IIDs	30,199	290	2.224	2.026-2.430	<.001
Mental Retardation	Without IIDs	120,796	314	Ref.		
	With IIDs	30,199	197	3.450	3.143-3.769	<.001
Other psychiatric disorders	Without IIDs	120,796	2897	Ref.		
	With IIDs	30,199	1360	2.581	2.352-2.820	<.001

95% CI = 95% confidence interval, ASD = acute stress disorder, HR = hazard ratio, IIDs: intestinal infectious diseases, PTSD = post-traumatic stress disorder.

IIDs may present with several GI symptoms, such as vomiting and diarrhea, which may affect patients' regular daily routine and social relationships. Their relatives and friends may be annoyed by diagnoses that can complicate their normal relationships. Therefore, difficulties associated with recovery may increase anxiety and other common mental disorders. Additionally, it has been reported that GI side effects (e.g., nausea/vomiting, diarrhea, constipation, and abdominal pain) are frequently observed in patients with major depressive disorder while taking antidepressants; this may lead to discontinuation of treatment.[33] There is an association between high-risk "taking antidepressants" and GI side effects in patients with psychiatric disorders. Thus, increased IIDs in psychiatric patients may result from the high-risk "taking antidepressants" behaviors of patients during the prodromal stage.

Table 5

Risk of psychiatric disorders subgroup among study population and trichomoniasis cohort identified by using Cox regression.

		Study population				
Psychiatric disorders subgroup	**IIDs visits**	**Population**	**Event**	**Adjusted HR**	**95% CI**	***P* value**
Overall	without IIDs	120,796	8119	Ref.		
	with IIDs	30,199	4022	2.724	2.482-2.976	<.001
	IIDs 1-2 visit	20,530	2171	2.162	1.964-2.362	<.001
	IIDs ≥ 3 visits	9669	1851	3.918	3.569-4.280	<.001

95% CI = 95% confidence interval, HR = hazard ratio, IIDs: intestinal infectious diseases.

We found that patients with IIDs aged ≥ 65 or 40–64 years had a higher risk of psychiatric disorders than those aged 20 to 39 years. Since the maximal follow-up time was 16 years, we propose that a certain portion of the trichomoniasis population aged 20 to 39 years may not have reached the age of onset for most major psychiatric disorders.[34] Another possible reason for this observation may be autism spectrum disorder (ASD), which is a heterogeneous neurodevelopmental disorder characterized by the presence of functionally impairing social communication challenges and restrictive, repetitive patterns of behavior that present early in life. Typically, ASD begins before the age of 3 years and can last throughout a person's life.[35] However, previous studies have shown that co-occurring GI symptoms are associated with increased self-injurious behaviors, restricted stereotypical behaviors, aggressive behaviors, sleep problems, and attention problems in children with ASD. In patients with ASD, a higher number of GI symptoms are associated with an increase in self-injurious behaviors, somatic complaints, reduced sleep duration, and increased parasomnias,[36] thus increasing the risk in patients with IIDs.

Mental disorders contribute to 7% of the global burden of disease worldwide, as estimated by the disability-adjusted life years; this is rising, especially in low- and middle-income countries.[37] Low income has been directly linked to psychiatric disorders.[38] Likewise, this study found an association between an increased risk of psychiatric disorders in patients with IIDs and a monthly income of less than NT$ 18,000.

Functional GI disorders (FGIDs) are a highly prevalent group of disorders diagnosed solely by symptomatology; due to a lack of understanding of their underlying structural or chemical abnormalities.[39] Common FGIDs include gastroesophageal reflux disease, functional dysphagia, functional dyspepsia, gastroparesis, irritable bowel syndrome, functional constipation, diarrhea, and fecal incontinence.[39] However, chronic GI dysfunctions (i.e., FGIDs) have been reported to develop from bacterial infections (e.g., acute gastroenteritis), viral infections, organic changes in epithelial cell structure, immunocompetent cells, and inflammatory cytokines.[40] Another study reported that functional gastroenteritis disorders correlated with the intestinal microbiota.[41] It has been well established that patients with FGIDs, along with symptoms related to the GI tract, have coexisting psychosocial symptoms such as stress, anxiety, and depression; therefore, a biopsychosocial model (i.e., gut-microbiota-brain axis) has been proposed for FGIDs.[39] Further investigation is needed to identify the etiologic factors of IIDs on the microbiota and their role in the development of psychiatric disorders.

A major strength of this study was its large-scale, population-based, nationwide design. Additionally, long-term monitoring from 2000 to 2015 increased the validity of the analysis. However, this study has several limitations. First, the diagnoses were made using ICD-9 codes recorded in the NHIRD; however, this database does not contain all types of data, such as laboratory parameters and genetic factors, which may help to postulate the mechanisms mediating the development of psychiatric disorders in patients with IIDs. Second, IIDs are largely neglected because of ineffective screening protocols and a lack of public health attention. The exact number of patients with IIDs might be higher than that of those seeking medical attention; therefore, the incidence of psychiatric disorders resulting from IIDs could be underestimated.

5. Conclusions

To our knowledge, this is the first study to provide evidence of an association between IIDs and the risk of overall psychiatric disorders. The potential role of IIDs in the development of psychiatric disorders highlights their clinical importance and impact on public health. Clinicians should pay more attention to IIDs and the pathogens that cause them; these infections not only cause IIDS symptoms but could also increase the risk of developing psychiatric disorders, especially in patients with refractory IIDs.

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Authors' contributions

J.-M.H., C.-H.T., C.-A.S., W.-C.C. and C.-P.Y.: conception and design, analysis and interpretation of the data, critical review, and approval of the final version submitted for publication. Y.-C.H., I.-J.L., C.-H.C. and C.-P.Y.: statistical analysis, critical review, and approval of the final version submitted for publication. J.-M.H., C.-H.T., C.-A.S., W.-C.C. and C.-P.Y.: drafting of the paper, critical review, and approval of the final version submitted for publication. All authors have read and agreed to the published version of the manuscript.

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