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Pinworm infections associated with risk of psychiatric disorders-A nationwide cohort study in Taiwan
Pinworm infections and psychiatric disorders

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ABSTRACT

Aim: This study aimed to investigate the association between males with pinworm infections and the risk of developing psychiatric disorders.
Method: A total of 2044 enrolled patients, with 511 pinworm subjects and 1533 unexposed subjects (1:3) matched for sex, age and index year, from Taiwan's Longitudinal Health Insurance Database (LHID) from 2000 to 2015, selected from the National Health Insurance Research Database (NHIRD). After adjusting for confounding factors, the Cox regression model was used to compare the risk of developing psychiatric disorders during the 15 years of follow-up.
Results: Of all the enrollees, 24 in the pinworm cohort and 18 in the unexposed cohort (343.10 vs 84.96 per 100,000 person-year) developed psychiatric disorders. The Cox regression model revealed that, after adjusting for sex, age, monthly income, urbanization level, geographic region, and comorbidities, the adjusted HR was 4.581 (95% CI: 2.214–9.480, $p < .001$, $p < .001$). Pinworm infections were associated with the increased risk in anxiety disorders, depressive disorders, and sleep disorders, respectively.
Conclusion: Patients who suffered from pinworm infections have a higher risk of developing psychiatric disorders, and this finding should be considered as a timely reminder for the clinicians to provide much more attention for these patients because of their mental health issues.

1. Introduction

Enterobiasis, also known as pinworm infection, is one of the most common human helminth infections worldwide, particularly in temperate climates [1]. Millions of people have been infected, especially children, which may well have attributed to environmental and personal hygiene [2]. Crowding is a risk factor for the spread of pinworm as well as psychiatric disorders by increasing mental stress [3], therefore, pinworm is known as a group infection and most commonly found in large families and in institutions including orphanages, boarding schools, mental homes, and hospitals [4].

Even though the majority of pinworm cases are symptomless, children with heavy pinworm infections often suffer from irritability and loss of appetite, nausea, insomnia, bed-wetting, nightmares, grinding of the teeth, diarrhea, pruritus ani, catarrhal inflammation, pruritus vulvae, recurrent cellulitis, and endometritis [5]. Moreover, biologic underpinnings as immunological abnormalities of the two disorders were similar. Previous studies have also correlated that infectious or inflammatory diseases were associated with psychiatric disorders, such as dementia [6–8], mood disorders [9–11], or even intellectual disability [12]. Therefore, we hypothesized that an association may exist between

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pinworm infections and the risk of psychiatric disorders. We have conducted this study to examine the risk of psychiatric disorder after pinworm infections.

2. Methods

2.1. Data sources

In this study, we used data from the National Health Insurance Research Database (NHIRD) to investigate the association between subjects with pinworm infections over a 15-year period. As a subset of the NHIRD, Longitudinal Health Insurance Database (LHID) of a two million randomized sampled population in 2000–2015, was used to study the association between allergic diseases and the risk of psychiatric disorders. The details of the program have been documented in previous studies [6–8,10,13–15].

The National Health Insurance (NHI) Program was launched in Taiwan in 1995, and as of June 2009, included contracts with 97% of the medical providers with approximately 23 million beneficiaries, or more than 99% of the entire population [16]. The NHIRD uses the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes to record diagnoses [17]. All diagnoses of pinworm infections were confirmed by pediatricians, general practitioners, or emergency medicine physicians according to the clinical findings, and the psychiatric disorders were made by board-certified psychiatrists, according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) and its Text-revised edition (DSM-IV-TR) [18,19]. Licensed medical records technicians also reviewed and verified the diagnostic coding before claiming the reimbursements in Taiwan's hospitals [20]. The NHI Administration randomly reviews the records of ambulatory care visits and inpatient claims periodically to verify the accuracy of the diagnoses [21]. Therefore, it is suitable using the NHIRD to study the association between pinworm infections and psychiatric disorder.

2.2. Study design and sampled participants

This study was a retrospective matched-cohort design. Patients with pinworm infections were selected from January 1 to December 31, 2000, according to the ICD-9-CM codes: 127.4. A total of 2044 enrolled patients including the 511 patients with pinworm infections, and 1533 in the age-, sex-, and index-year, (1:3) matched unexposed group without pinworm infections in this study (Fig. 1).

The covariates included sex, age group (0–11, 12–19, 20–49, ≥50 years), geographical area of residence (north, center, south, and east of Taiwan), urbanization level of residence (levels 1 to 4), levels of hospitals as medical centers, regional hospitals and local hospitals, and insurance premium (in New Taiwan Dollars [NT$]; <18,000, 18,000–34,999, ≥35,000). The urbanization level of residence was defined according to the population and various indicators of the level of development. 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 the political system, economy, and culture. Urbanization levels 3 and 4 were defined as a population between 149,999 and 499,999, and <149,999, respectively [22].

The following intestinal or parasitic diseases were excluded: irritable bowel syndrome (ICD-9-CM 564.1), other and unspecified noninfectious gastroenteritis and colitis (ICD-9-CM 558.9), ulcerative colitis (ICD-9-CM 556.9), regional enteritis of unspecified site (ICD-9-CM 555.9), colorectal cancer (ICD-9-CM 153.0–153.3, 153.6–153.9, 154.0–154.3, 154.8, 159.0), protozoa intestinal infections (ICD-9-CM 006–007), helminthiases (ICD-9-CM 120–126, 127.1–127.3127.5–127.9, 128–129), other infestations (ICD-9-CM 130–135), other parasitic diseases (ICD-9-CM 136.2–136.9, 139), and other intestinal infections (ICD-9-CM 001–005, 008–009). Subjects with history of psychiatric disorder before tracing were also excluded.

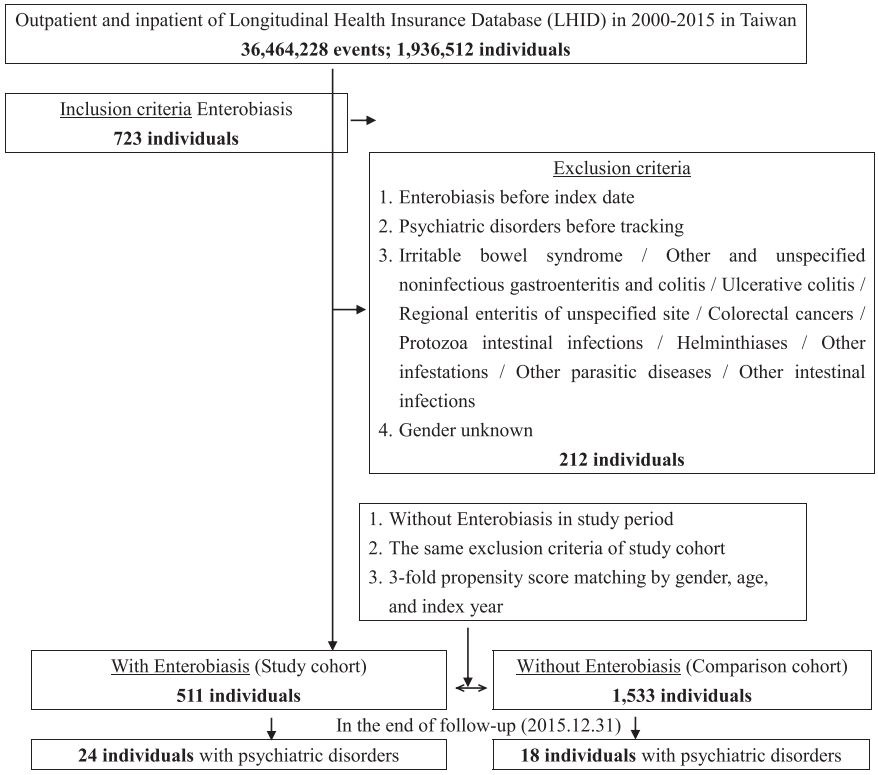

Fig. 1. The flowchart of study sample selection from National Health Insurance Research Database in Taiwan.

2.3. Outcome measures

Previous studies found that anxiety, depressive, bipolar, and sleep disorders were associated with inflammatory or infectious disorders in children and adolescents [23–29], from Taiwan's NHIRD. Therefore, we included these psychiatric disorders in the present study. All the study participants were followed from the index date until the onset of psychiatric disorder including anxiety (ICD-9-CM 300), depression (ICD-9-CM 296.2–296.3, 300.4, 311), bipolar disorders (ICD-9-CM 296.0, 296.4–296.8), and sleep disorders (ICD-9-CM 307.4, 780.5), withdrawal from the NHI program, or the end of 2015.

2.4. Statistical analysis

All analyses were performed using the SPSS software version 22 (SPSS Inc., Chicago, Illinois, USA). χ^2 and *t*-tests were used to evaluate the distributions of the categorical and continuous variables, respectively. The Fisher exact test for categorical variables was used to statistically examine the differences between the two cohorts. The multivariate Cox proportional hazards regression analysis was used to determine the risk of psychiatric disorder, and the results were presented as a hazard ratio (HR) with a 95% confidence interval (CI). The difference in the risk of psychiatric disorder, between the study and unexposed groups, was estimated using the Kaplan-Meier method with the log-rank test. A 2-tailed *p* value <.05 was considered to indicate statistical significance.

2.5. Ethics approvals

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 (IRB No. 2-107-05-026).

Table 1
Characteristics of study in the baseline.

Enterobiasis	With		Without		*P*
Variables	n	%	n	%	
Total	511	25.00	1533	75.00	
Gender					0.999
Male	255	49.90	765	49.90	
Female	256	50.10	768	50.10	
Age (years)	10.80 ± 17.64		10.85 ± 17.39		0.960
Age group (years)					0.999
0–11	437	81.23	1311	81.23	
12–19	12	2.23	36	2.23	
20–49	27	5.02	81	5.02	
≧50	62	11.52	186	11.52	
Insured premium (NT$)					0.367
<18,000	511	100.00	1527	99.61	
18,000–34,999	0	0.00	5	0.33	
≧35,000	0	0.00	1	0.07	
CCI	0.20 ± 0.71		0.18 ± 0.62		0.579
Location					<0.001
Northern Taiwan	138	27.01	675	44.03	
Middle Taiwan	163	31.90	397	25.90	
Southern Taiwan	149	29.16	349	22.77	
Eastern Taiwan	59	11.55	93	6.07	
Outlets islands	2	0.39	19	1.24	
Urbanization level					<0.001
1 (The highest)	150	29.35	624	40.70	
2	228	44.62	635	41.42	
3	31	6.07	86	5.61	
4 (The lowest)	102	19.96	188	12.26	
Level of care					<0.001
Medical center	142	27.79	545	35.55	
Regional hospital	272	53.23	542	35.36	
Local hospital	97	18.98	446	29.09	

P: Chi-square/Fisher exact test on category variables and *t*-test on continue variables.
CCI: Charlson comorbidity index; NT$: New Taiwan dollars.

3. Results

3.1. Sample characteristics

Table 1 shows the sex, age, urbanization, and area of residence, level of care, and the insurance premium of the subjects with or without pinworm infections. The residence of subjects with pinworm infections is higher in Middle, Southern and Eastern Taiwan, in the lower urbanization (Levels 2–4) than the unexposed without pinworm infections. The subjects with pinworm infections are higher in insured premium <18,000 and in reginal hospital care than the unexposed.

3.2. Kaplan-Meier model for the cumulative risk of psychiatric disorders

Of the pinworm infections patients, 24 (343.10 per 10^5 person-years) developed psychiatric disorders when compared to 18 (84.96 per 10^5 person-years) in the unexposed group, and the difference was statistically significant (log-rank, $p < .001$, Fig. 2). In this study, the risk of psychiatric disorders in the pinworm infections subjects is higher than the unexposed group as per the adjusted HR 4.581 (95% CI: 2.214–9.480, $p < .001$, Table 2).

3.3. The risk of psychiatric disorders in patients with pinworm infections

We have included anxiety disorder, depression, bipolar disorder, and sleep disorder in the analysis. Anxiety disorder, depression, and sleep disorder were higher in the pinworm infections group ($p < .001$) than the unexposed group. We further separated the pinworm infections by the number of times of hospital visits. There were 498 subjects (97.46%) that visited a hospital once and 13 subjects (2.54%) twice for pinworm infections treatment. The risk of psychiatric disorder rises to 221.960-fold ($p < .001$) if there were two visits for pinworm infections as were 2.592-fold ($p = .034$) in the one visit group (Table 2). No bipolar disorder patient was traced in the non-pinworm infections unexposed group (Table 3).

4. Discussion

4.1. Association between pinworm infections and the risk of psychiatric disorders

Pinworm infection occurs worldwide, whose effects are particularly common in children, with a prevalence rate in this group ranging from

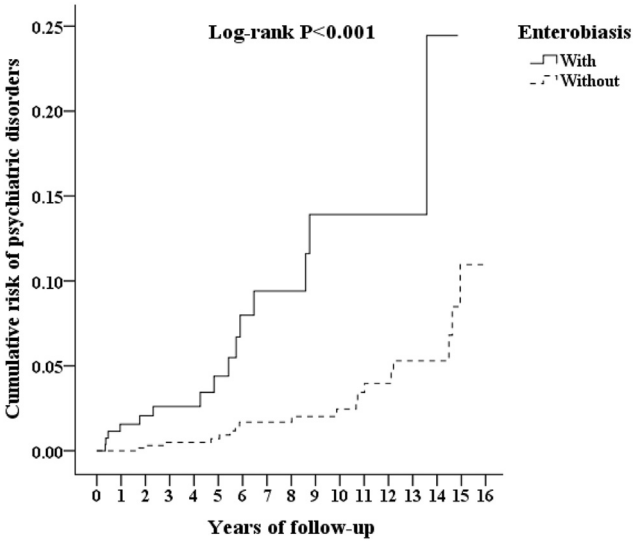

Fig. 2. Kaplan-Meier for cumulative risk of psychiatric disorders stratified by enterobiasis with log-rank test.

Table 2
Factors of enterobiasis and psychiatric disorders by using Cox regression.

Variables	Crude HR	95% CI	95% CI	*P*	Adjusted HR	95% CI	95% CI	*P*
Enterobiasis (reference: without)	4.947	2.459	9.952	<0.001	4.581	2.214	9.480	<0.001
Number (s) of visit: 1 (N = 498, 97.46%)	2.409	1.028	5.643	0.043	2.592	1.075	6.250	0.034
Number (s) of visit: ≥2 (N = 13, 2.54%)	36.759	15.391	87.789	<0.001	221.960	55.818	882.625	<0.001
Male (reference: female)	1.385	0.699	2.745	0.351	1.265	0.633	2.532	0.506
Age of 12–19 (reference: 0–11)	0.265	0.080	0.875	0.029	0.265	0.078	0.899	0.033
Age of 20–49 (reference: 0–11)	0.763	0.269	2.167	0.611	0.568	0.183	1.763	0.328
Age ≥50 (reference: 0–11)	1.416	0.595	3.367	0.432	1.224	0.465	3.224	0.685

HR = hazard ratio, CI = confidence interval, Adjusted HR: Adjusted variables listed in Table 1.

29% to 61% in different countries [30]. In Taiwan, the unexposed of pinworm infection among school children should be considered as being successful [31]. To our knowledge, this was the first study aiming to discuss the association between pinworm infections and the risk of psychiatric disorders. In this study, the risk to the subjects is higher than the unexposed group as 4.581-fold ($p < .001$). Anxiety disorder, depression, and sleep disorder were higher in the pinworm infections group, when compared to the unexposed group. Mean onset of psychiatric disorder in the pinworm infections group were 5.34 ± 4.58 years.

4.2. Comparison of this study to previous literatures

Parasitic diseases present with psychiatric symptoms, such as Echinococcosis, have been reported [32] with direct brain invasions [33]. Previous studies have also revealed associations between parasitic diseases and (neuro)psychiatric disorders, for example, toxoplasmosis, malaria, and *Angiostrongylus cantonensis* [34–36]. However, enterobiasis has no access to enter the brain. Scabies, as an ectoparasitic disease, was associated with the increased risks of bipolar disorder and intellectual disability [9,12]. Moreover, for the social factors such as a lower socioeconomic status and a crowded community, the immune-mediated inflammatory processes with an elevated interleukin level may also play a role in the pathophysiology of pinworm infection and the psychiatric disorders [9,12,37,38].

In this study, there were 723 pinworm infection patients among 1,936,512 individuals during 2000–2015, with prevalence rate of 0.037%. The prevalence rate was lower than expected. In Taiwan, the prevalence of pinworm infection was reduced from 19.9% in 1986 to 2.5% in 2001 after a 15-year population-based survey in Taipei, Taiwan [31]. Another study found that the rates of pinworm infections significantly reduced from 4.3% in 1990 to 0.40% in 2007, among pre-school children in Taipei [39]. Therefore, such a low prevalence in the present study might reflect the trends in the decrease of pinworm infections in Taiwan with the improvement of public health. However, one third of the pinworm infections are asymptomatic [30], and those patients who never search for help would not be recorded in the NHIRD.

As aforementioned, crowding is a risk factor for the spread of pinworm [3], nonetheless, in our study, the residence of subjects with pinworm infections is higher in the lower urbanization (Levels 2–4) than the unexposed without pinworm infections. We speculate that this could be related to the lack of resources in the prevention of pinworms infections in these areas.

4.3. Possible mechanisms for the increased risk of psychiatric disorders in patients with pinworms infections

Recurrent pinworm infections were associated with the extremely high risk of psychiatric disorders, but the reasons remained unknown in this study. This might be due to the fact that pinworm infections were associated with disadvantageous socio-economic levels [40–42]. Recurrent infections of pinworm might also increase the levels of proinflammatory responses, which are linked with the development of psychiatric disorders, as aforementioned. Reports have shown that cytokines such as interleukin (IL)-6, tumor necrosis factor-alpha (TNF-α), IL-10, and monocyte chemoattractant protein-1/CCL2 might be well associated with depressive, bipolar, or anxiety disorders [43]. Further studies are warranted to investigate the association and test this hypothesis.

4.4. Limitations

The present study has several limitations that warrant consideration. First, similar to previous studies using the NHIRD on infectious, parasitic, or inflammatory diseases [7–10,44], not all the data were recorded in

Table 3
Factors of psychiatric disorders subgroup stratified by pinworm infections subgroup by using Cox regression.

Enterobiasis		With			Without			With vs. Without				
Visits	Psychiatric disorders	Events		Rate (per 10^5 PYs)	Event	PYs	Rate (per 10^5 PYs)	Ratio	Adjusted HR	95% CI	95% CI	*P*
Overall	Overall	24	6995.05	343.10	18	21,187.23	84.96	4.039	4.581	2.214	9.480	<0.001
	Anxiety	5	6995.05	71.48	4	21,187.23	18.88	3.786	6.724	1.390	32.532	0.018
	Depression	8	6995.05	114.37	5	21,187.23	23.60	4.846	6.979	2.045	23.822	0.002
	Bipolar disorders	1	6995.05	14.30	0	21,187.23	0.00	–	–	–	–	–
	Sleep disorders	10	6995.05	142.96	9	21,187.23	42.48	3.365	6.284	2.340	16.878	<0.001
1	Overall	8	6719.41	119.06	18	21,187.23	84.96	1.401	2.592	1.075	6.250	0.034
	Anxiety	0	6719.41	0.00	4	21,187.23	18.88	0.000	0.000	–	–	0.969
	Depression	2	6719.41	29.76	5	21,187.23	23.60	1.261	3.153	0.511	19.445	0.216
	Bipolar disorders	0	6719.41	0.00	0	21,187.23	0.00	–	–	–	–	–
	Sleep disorders	6	6719.41	89.29	9	21,187.23	42.48	2.102	4.216	1.387	12.814	0.011
2	Overall	16	275.64	5804.74	18	21,187.23	84.96	68.326	221.960	55.818	882.625	<0.001
	Anxiety	5	275.64	1813.98	4	21,187.23	18.88	96.083	373.032	34.133	976.723	<0.001
	Depression	6	275.64	2176.78	5	21,187.23	23.60	92.240	814.549	50.549	1873.315	<0.001
	Bipolar disorders	1	275.64	362.80	0	21,187.23	0.00	–	–	–	–	–
	Sleep disorders	4	275.64	1451.19	9	21,187.23	42.48	34.163	501.295	57.534	967.805	<0.001

PYs = Person-years; Adjusted HR = Adjusted Hazard ratio: Adjusted for the variables listed in Table 3; CI = confidence interval.

the NHIRD, and we were unable to evaluate the severity, laboratory parameters, or images in these patients. Second, other factors, such as genetic, psychosocial, and environmental factors, were not included in the dataset. Third, for some patients who have to pay for their own over-the-counter drugs for the pinworm infections, their self-medications would not have been included in the NHIRD. However, due to the high coverage of medical providers (97%) and beneficiaries (>99%) of the NHI system, most of the people would ask for help from the NHI-contracted hospitals or clinics for their pinworm infections. Fourth, ascertainment bias is possible if people who were treated for pinworm were more medically attentive so that they also sought treatment for psychiatric conditions. Fifth, the risk of psychiatric disorder rises to 221.960-fold ($p < .001$) if there were two visits for pinworm infections as were 2.592-fold ($p = .034$) in the one visit group. This could be an effect of small numbers of cases since the CI's are very wide.

4.5. Strength of this study

One of the primary strengths of this study is the set of ICD-9 codes, and a number of studies have demonstrated the accuracy and validity of several major diagnoses in the NHIRD, including DM [45,46], cancer [47–49], myocardial infarction [45,50,51], and the central nervous system diseases, such as Tourette syndrome [52] and stroke [45,53–55]. Other studies also validated the accuracy of infectious or inflammation-related diagnoses recorded in the NHIRD, such as pneumonia [56], tuberculosis contact [57], tuberculosis [58], asthma [59], and COPD [59].

Correspondingly, the long-term observation period from 2000 to 2015 allowed for more credibility, when compared with other similar studies, to propose physical mechanisms and plausible hypotheses. Finally, and most importantly, we have tried to explain the mutual biological and psychological mechanism between the pinworm infections and the psychiatric disorders.

5. Conclusion

Patients with pinworm infections may have a 4-fold increased risk of developing psychiatric disorders. These findings might well be a clear signal to the clinicians caring for patients with pinworm infections. Further research is necessary to explore the underlying mechanism(s) of this association.

Acknowledgment

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Competing interest

None.

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