Parasitology

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Infection with *Toxoplasma gondii* increases the risk of psychiatric disorders in Taiwan: a nationwide population-based cohort study

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Abstract

This study aimed to evaluate associations between toxoplasmosis and psychiatric disorders in Taiwan based on the National Health Insurance Research Database, Taiwan (1997–2013). Patients newly diagnosed with toxoplasmosis formed the case group ($n = 259$), and the control group included propensity-score matched patients without toxoplasmosis ($n = 1036$). The primary outcome was incidence of psychiatric disorders. Cox proportional hazards regression and stratified analyses were performed to examine risk of developing specific psychiatric disorders between patients with and without toxoplasmosis. Patients with toxoplasmosis had significantly higher incidence of psychiatric disorders than those without toxoplasmosis ($P = 0.016$). A significant difference was found in numbers of psychiatric disorders between the two groups during 14 years of follow-up (log-rank $P < 0.001$). Those with toxoplasmosis had significantly higher risk of bipolar disorder [adjusted hazard ratio (aHR = 3.60, 95% confidence interval (CI) = 2.07, 7.26), depression (aHR = 4.94, 95% CI = 2.15, 11.80) and anxiety (aHR = 5.36, 95% CI = 2.98, 25.88), but no significant between-group differences were found for schizophrenia and other psychiatric disorders. In conclusion, the present nationwide population-based analysis revealed that *Toxoplasma gondii* infection in Taiwan significantly increases the risk for developing bipolar disorder, depression and anxiety, but not for schizophrenia and other psychiatric disorders.

Introduction

Toxoplasma gondii is a zoonotic parasite that causes opportunistic infection globally. Although roughly one-third of the world's population is affected by *T. gondii* infection, seroprevalence of anti-*T gondii* immunoglobulin G (IgG) and IgM antibodies varies greatly by geographic regions and countries, with lower seroprevalence in European countries and the United States (Pappas *et al.*, 2009). Regional differences in seroprevalence can range from 10 to 80% (Robert-Gangneux and Darde, 2012), but the lack of systematic reporting of seropositivity makes it difficult to understand associated risk factors (Pappas *et al.*, 2009). Although *T. gondii* infection is found in many warm-blooded animals, domestic cats are the definitive host (Chiang *et al.*, 2014; Achaw *et al.*, 2019; Ybanez *et al.*, 2019). Numerous studies demonstrated that all cats in the world can shed *T. gondii* oocytes in feces, leading to environmental contamination and public health threats (Dabritz and Conrad, 2010; Berger-Schoch *et al.*, 2011; Lilly and Wortham, 2013; Zulpo *et al.*, 2018). Human are likely to be infected *via* ingestion of *T. gondii* oocyte-contaminated soil and water, and/or consumption of raw or undercooked meat containing *T. gondii* tissue cysts (Elmore *et al.*, 2010; Berger-Schoch *et al.*, 2011; Chiang *et al.*, 2014). Stray cats with increased exposure to pathogens are more likely to be infected by *T. gondii* than domestic cats (Hartmann *et al.*, 2013; Chalkowski *et al.*, 2019; Khodaverdi and Razmi, 2019; Palerme *et al.*, 2019). Domestic cats, however, can transmit *T. gondii* to their owners, so having a cat is an independent risk factor for *T. gondii* seropositivity in Ethiopia and Taiwan (Chiang *et al.*, 2014; Achaw *et al.*, 2019).

A survey revealed that among 1783 Taiwanese healthy blood donors, 161 (9.0%) donors were seropositive for anti-*T. gondii* IgG only and 5 (0.28%) donors were seropositive for both IgM and IgG, suggesting previous *T. gondii* infection (Chiang *et al.*, 2012). In healthy individuals, *T. gondii* infection is typically mild with flu-like symptoms and lymphadenopathy

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(Hill *et al.*, 2005), whereas central nervous system (CNS) disorders and ocular disease are also noted in congenital *T. gondii* infection (Chiang *et al.*, 2014). However, immunocompromised individuals such as those with HIV/AIDS (Hung *et al.*, 2005), those undergoing chemotherapy or transplant recipients (Dubey and Jones, 2008) and neonates (Hu *et al.*, 2006), may develop serious complications such as seizures, encephalitis or lung disease resembling tuberculosis. Notably, studies from around the world have reported associations between toxoplasma seropositivity and psychiatric disorders, such as psychosis, schizophrenia, bipolar disorder, major depression and anxiety (Lindgren *et al.*, 2018; Achaw *et al.*, 2019; Palerme *et al.*, 2019; Stepanova *et al.*, 2019; Ybanez *et al.*, 2019). However, inconsistent and even controversial results were reported.

A recent cross-sectional survey found significant associations between *T. gondii* seropositivity and psychotic-like symptoms, but not schizophrenia, in Finland (Lindgren *et al.*, 2018). Although, patients diagnosed with schizophrenia had a higher incidence of latent toxoplasmosis than healthy controls in Russia (Stepanova *et al.*, 2019). Results of a review and meta-analysis (Sutterland *et al.*, 2015) concluded higher odds of anti-toxoplasma IgG in patients with schizophrenia and bipolar disorder, but not in those with major depression. Clearly, there is still much to be learned about associations between *T. gondii* and specific mental disorders. We hypothesized that infection with *T. gondii* may increase the probability of developing psychiatric disorders. The comprehensive data from the National Health Insurance Research Database (NHIRD) of Taiwan may help to test our hypothesis. Therefore, the present nationwide population-based, longitudinal cohort study aimed to evaluate associations between infection with *T. gondii* and specific psychiatric disorders in a large population-based sample from the NHIRD.

Patients and methods

Data sources

In the present longitudinal cohort study, the data analysed were derived from the NHIRD of Taiwan, which covers 99.9% of the Taiwanese population (Wu *et al.*, 2010). The NHIRD includes all demographic and clinical information on outpatient and inpatient claims data. All clinical diagnoses and procedures are recorded based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM).

Ethical considerations

The present study protocol was approved by the Institutional Review Board (IRB) of Tri-Service General Hospital, Taiwan (TSGHIRB No.: B-109-23). Because all patient data were anonymized in the NHIRD, informed consent was waived.

Study population

The case group consisted of patients newly diagnosed with toxoplasmosis (*T gondii* infection), who were identified from the NHIRD (1997–2013) based on ICD-9-CM 130. The date when toxoplasmosis was diagnosed was defined as the index date, and patients diagnosed with psychiatric disorders before the index date were excluded to ensure the temporal order between *T. gondii* infection and psychiatric disorders. In addition, patients younger than 18 years were excluded. In addition, the non-toxoplasmosis control group was established by propensity score matching for age, gender and index year with a 4-fold ratio of the case group (ratio 4:1), thereby reducing selection bias.

Primary outcome

In the case group, the patients with psychiatric disorders were tracked from the index date to the onset of all recorded psychiatric disorders, whereas the patients without psychiatric disorders were followed from the index date to the end of the study period. The primary outcome was the incidence of psychiatric disorders, consisting of schizophrenia (ICD-9-CM 295), bipolar disorder (ICD-9-CM 296.0, 296.4–296.8), depression (ICD-9-CM 296.2–296.3, 300.4, 311), anxiety (ICD-9-CM 300) and other psychiatric disorders (ICD-9-CM 295–312), while excluding overlapping codes. Eligible patients with the following other psychiatric disorders were identified in the present study, such as unspecified affective psychoses (296.90), other specified affective psychoses (296.99), unspecified psychosis (298.9), acute alcoholic intoxication, continuous (303.01), other and unspecified alcohol dependence (303.90), other and unspecified alcohol dependence, continuous (303.91), opioid type dependence, unspecified (304.00), alcohol abuse (305.0), alcohol abuse, unspecified (305.00), tobacco use disorder (305.1), psychogenic respiratory malfunction (306.1), tension headache (307.81), unspecified adjustment reaction (309.9) and postconcussion syndrome (310.2).

Covariates

The sociodemographic variables of the case and control groups, included age, insurance premium, season of diagnosis, place of residence, urbanization level and hospital level. The eligible patients were divided into three age groups: 18–44 years, 45–64 years and ⩾65 years. Insurance premiums in New Taiwan Dollars (NTD) were classified into three groups: <18 000, 18 000–34 999 and ⩾35 000. Regarding place of residence, Taiwan was divided into five regions, such as northern, middle, southern and eastern Taiwan, as well as outlying islands. Urbanization levels of residences were categorized into four levels: from the highest urbanization (level 1) to the lowest urbanization (level 4). The levels of hospital care were classified into three groups: local hospitals, regional hospitals and medical centres.

Statistical analysis

Categorical variables are expressed as counts and percentages; continuous variables are expressed as mean and standard deviation (mean ± S.D.). Differences in categorical variables between case and control groups were examined by χ^2 test or Fisher's exact test, whereas continuous variables were examined by *t*-test. Differences in the incidence of psychiatric disorders between the two groups were assessed by the Kaplan–Meier method with a log-rank test, and the result was presented as a survival curve. Univariate and multivariate Cox proportional hazards regression analyses were performed to examine the risk of developing psychiatric disorders. In addition, stratified analyses were performed based on the demographics and psychiatric disorders to explore the hazard ratios (HRs) between patients with and without toxoplasmosis. All *P* values were two-sided and $P < 0.05$ was considered statistically significant. All statistical analyses were conducted using the statistical software package SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

In the present longitudinal cohort study, 259 patients with toxoplasmosis were included in the case group, and 1036 patients without toxoplasmosis were included in the control group based on propensity score matching at a 1:4 ratio (Fig. 1). The demographic and clinical characteristics of the

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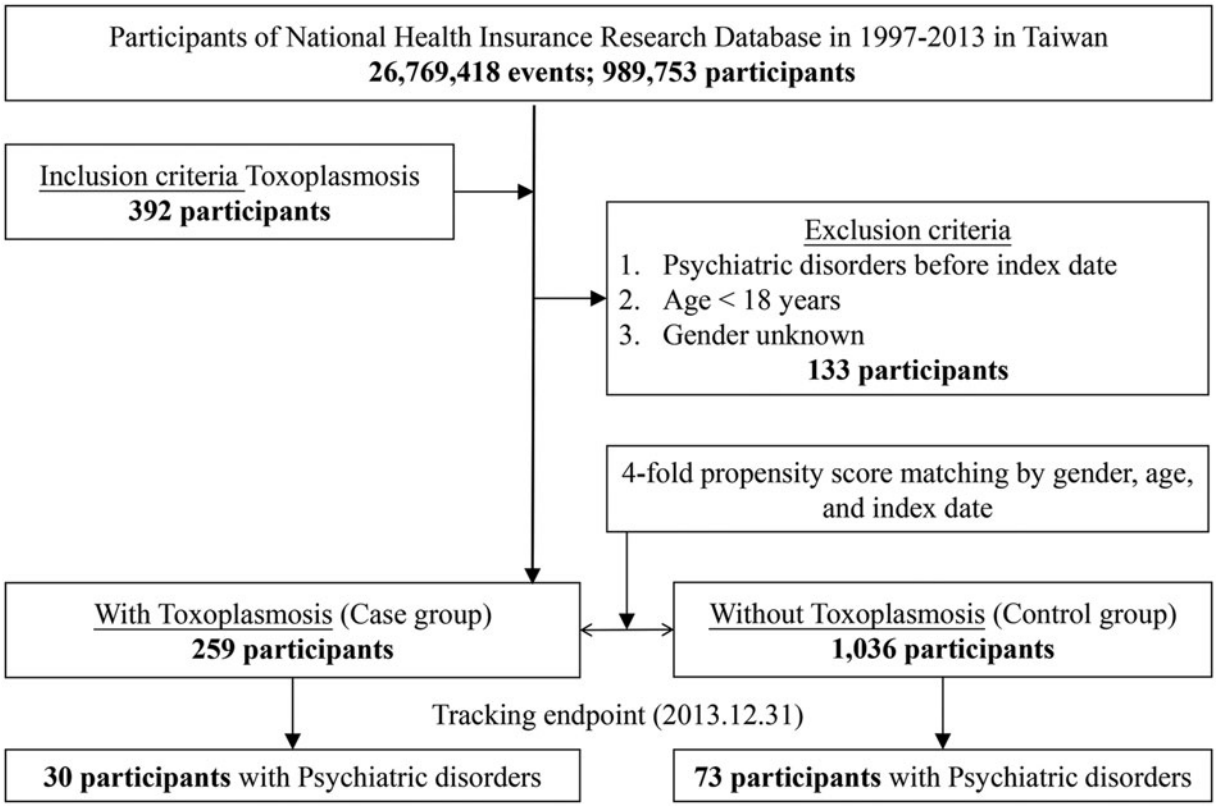

Fig. 1. Flowchart of patient selection.

total population, case group and control group are summarized in Table 1. No significant differences were found in age, age group, gender, insurance premium and season of diagnosis between the case and control groups. In contrast, level of hospital care, urbanization level and place of residence were significantly different between patients with and without toxoplasmosis (all $P < 0.001$). Furthermore, patients with toxoplasmosis had significantly higher Charlson comorbidity index (CCI) scores than those without toxoplasmosis ($P < 0.001$) (Table 1).

Patients with toxoplasmosis had a significantly higher incidence of psychiatric disorders than those without toxoplasmosis ($P = 0.016$). Thirty out of 259 (11.6%) patients in the case group were diagnosed with psychiatric disorders, and 73 out of 1036 (7.0%) patients in the control group were diagnosed with psychiatric disorders (Table 2). Particularly, the incidence of anxiety was significantly higher in patients with toxoplasmosis than in those without toxoplasmosis ($P = 0.002$) (Table 2). In addition, Kaplan–Meier analysis of the cumulative incidence of psychiatric disorders over 14 years of follow-up demonstrated a significant difference in incidence of psychiatric disorders between the case group and control group (log-rank $P < 0.001$), and a significant difference was observed as early as the first year of follow-up (Fig. 2).

The risk factors for psychiatric disorders in the total population were identified by univariate and multivariate Cox regression analyses (Table 3). After adjusting for age, gender, insurance premium, season of diagnosis, level of hospital care, urbanization level and CCI, multivariate Cox proportional hazards regression analyses revealed that in the total population, patients with toxoplasmosis had a significantly higher adjusted HR (aHR) for psychiatric disorders [aHR = 3.79, 95% confidence interval (CI) = 2.37, 6.07] compared to those without toxoplasmosis. Younger patients also had significantly higher HRs for psychiatric disorders (45–64 *vs* ⩾65: aHR = 2.23, 95% CI = 1.14, 4.36; 18–44 *vs* ⩾65: aHR = 5.50, 95% CI = 2.89, 10.44). Male patients had a significantly higher risk for psychiatric disorders than female patients (aHR = 2.44, 95% CI = 1.52, 3.89). Medical visits in the autumn were significantly associated with a lower risk for psychiatric disorders compared to medical visits in the spring (aHR = 0.47, 95% CI = 0.26, 0.86). Compared to seeking medical help in local hospitals, seeking medical assistance in regional hospitals and hospital centres were significantly associated with higher HRs for psychiatric disorders (regional hospital *vs* local hospital: aHR = 1.67, 95% CI = 1.37, 2.22; hospital centre *vs* local hospital: aHR = 1.82, 95% CI = 1.49, 2.37). Patients with more severe comorbidities had a significantly higher risk for psychiatric disorders (aHR = 1.08, 95% CI = 1.02, 1.15) (Table 3).

Table 4 summarizes the risk of developing psychiatric disorders in patients with or without toxoplasmosis stratified by demographic variables. After adjusting for significant variables identified in univariate Cox regression analyses shown in Table 3, multivariate Cox regression analyses revealed that the risk of developing psychiatric disorders was significantly higher in patients with toxoplasmosis than in those without toxoplasmosis, regardless of being stratified by almost all demographic and clinical variables. Although patients who had insurance premiums less than NTD18 000 were significantly associated with an elevated risk of psychiatric disorders (aHR = 3.78, 95% CI = 2.36, 6.10) (Table 4), only one event occurred in patients with an insurance premium higher than NTD18 000.

Furthermore, Cox proportional hazards regression model was applied to estimate the risk for developing each psychiatric disorder in patients with toxoplasmosis in relative to those without toxoplasmosis (Table 5). After adjusting for significant variables identified in univariate Cox regression analyses shown in Table 3, multivariate Cox regression analyses revealed that compared to the control group, the case group had significantly higher risk of bipolar disorder (aHR = 3.60, 95% CI = 2.07, 7.26), depression (aHR = 4.94, 95% CI = 2.15, 11.80) and anxiety (aHR = 5.36, 95% CI = 2.98, 25.88). In contrast, no significant differences in the HRs of developing schizophrenia and other psychiatric disorders between the two groups were observed (Table 5).

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Table 1. Demographic and clinical characteristics of the total population, case group and control group

Variables	Total population, *n* = 1295	With toxoplasmosis, *n* = 259 (case group)	Without toxoplasmosis, *n* = 1036 (control group)	*P*
Age (years)	44.36 ± 16.40	44.10 ± 16.21	44.43 ± 16.45	0.779
Age group (years)				0.999
≧65	165 (12.7)	33 (12.7)	132 (12.7)	
45–64	375 (29.0)	75 (29.0)	300 (29.0)	
18–44	375 (29.0)	151 (58.3)	604 (58.3)	
Gender				0.999
Female	500 (38.6)	100 (38.6)	400 (38.6)	
Male	795 (61.4)	159 (61.4)	636 (61.4)	
Insurance premium (NTD)				0.364
<18 000	1268 (97.9)	255 (98.5)	1013 (97.8)	
18 000–34 999	19 (1.5)	4 (1.5)	15 (1.4)	
≧35 000	8 (0.6)	0	8 (0.8)	
Season of diagnosis				0.415
Spring (March–May)	324 (25)	60 (23.2)	264 (25.5)	
Summer (June–August)	323 (24.9)	75 (29.0)	248 (23.9)	
Autumn (September–November)	321 (24.8)	62 (23.9)	259 (25.0)	
Winter (December–February)	327 (25.3)	62 (23.9)	265 (25.6)	
Level of hospital care				**<0.001**
Local hospital	370 (28.6)	11 (4.2)	359 (34.7)	
Regional hospital	396 (30.6)	63 (24.3)	333 (32.1)	
Hospital centre	529 (40.8)	185 (71.4)	344 (33.2)	
Urbanization level				**<0.001**
4 (lowest)	175 (13.5)	17 (6.6)	158 (15.3)	
3	106 (8.2)	8 (3.1)	98 (9.5)	
2	522 (40.3)	108 (41.7)	414 (40.0)	
1 (highest)	492 (38)	126 (48.6)	366 (35.3)	
Place of residence				**<0.001**
Northern Taiwan	557 (43.0)	146 (56.4)	411 (39.7)	
Middle Taiwan	351 (27.1)	48 (18.5)	303 (29.2)	
Southern Taiwan	295 (22.8)	44 (17.0)	251 (24.2)	
Eastern Taiwan	87 (6.7)	20 (7.7)	67 (6.5)	
Outlying islands	5 (0.4)	1 (0.4)	4 (0.4)	
CCI	1.16 ± 2.35	2.76 ± 3.36	0.75 ± 1.81	**<0.001**

Categorical variables are presented as counts (percentages); continuous variables are presented as mean ± S.D.
Significant *P* values are shown in bold.

Table 2. Incidence of psychiatric disorders in the total population, case group and control group

Variables	Total population, *n* = 1295	With toxoplasmosis, *n* = 259 (case group)	Without toxoplasmosis, *n* = 1036 (control group)	*P*
Psychiatric disorders	103 (8.0)	30 (11.6)	73 (7.0)	**0.016**
Schizophrenia	12 (0.9)	2 (0.8)	10 (1.0)	0.772
Bipolar disorder	8 (0.6)	2 (0.8)	6 (0.6)	0.664
Depression	27 (2.1)	9 (3.5)	18 (1.7)	0.072
Anxiety	26 (2.0)	12 (4.6)	14 (1.4)	**0.002**
Other psychiatric disorders	30 (2.3)	5 (1.9)	25 (2.4)	0.664

Values are presented as counts (percentage).
Significant *P* values are shown in bold.

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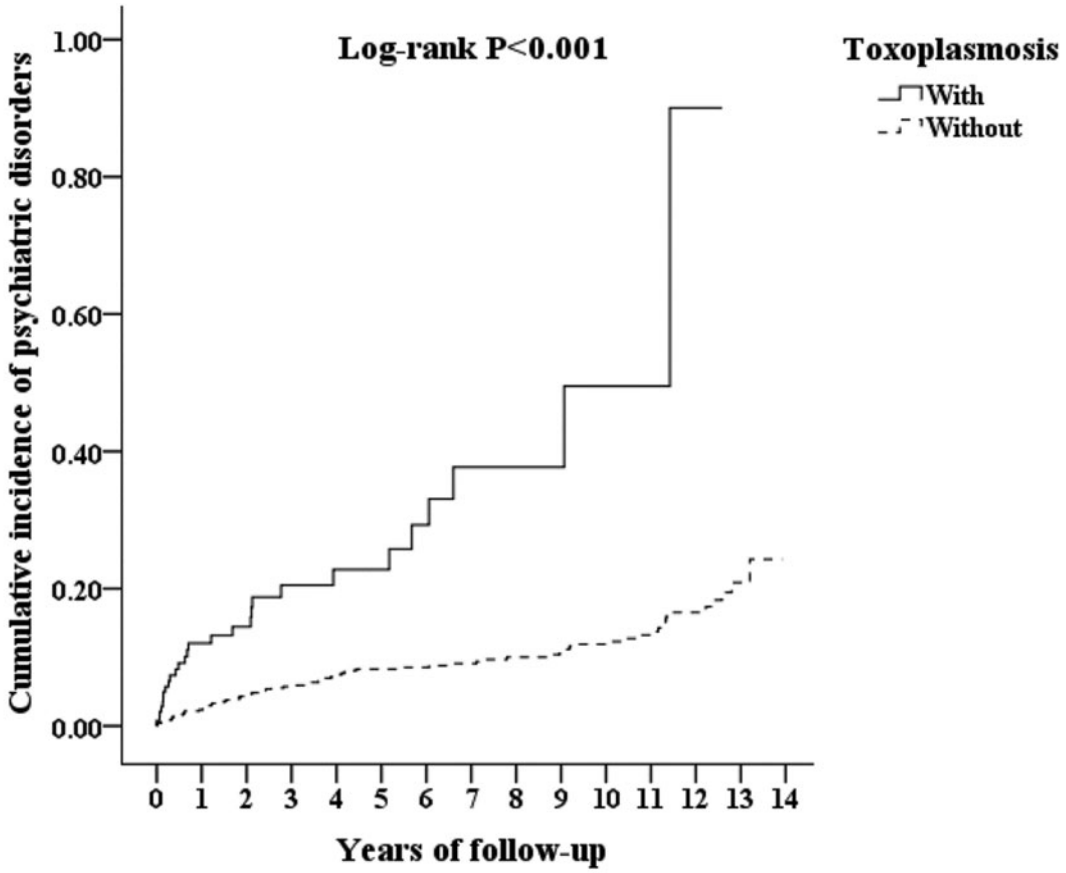

Year of follow-up	Numbers of patients with psychiatric disorders		*p*
	With Toxoplasmosis (n = 259)	Without Toxoplasmosis (n = 1,036)	
1	16	16	**0.049**
2	18	29	**0.033**
3	22	36	**0.019**
4	23	44	**0.033**
5	23	48	**0.026**
6	25	49	**0.008**
7	27	51	**0.001**
8	27	54	**0.001**
9	27	56	**<0.001**
10	28	60	**<0.001**
11	28	62	**<0.001**
12	29	68	**<0.001**
13	29	72	**<0.001**
14	30	73	**<0.001**

Fig. 2. Kaplan–Meier for cumulative incidence of psychiatric disorders stratified by *Toxoplasmosis* using log-rank test.

Discussion

In the present Taiwanese population-based cohort study, patients with toxoplasmosis had a significantly higher risk for psychiatric disorders than the non-toxoplasmosis control population, demonstrated by consistently higher aHR, regardless of stratification by demographic variables. In particular, compared to patients without toxoplasmosis, those with confirmed toxoplasmosis had significantly higher risk of bipolar disorder, depression and anxiety. However, no significant differences were found in the risk of schizophrenia and other psychiatric disorders between the patients with and without toxoplasmosis.

To our best knowledge, the present study is the first to explore associations between toxoplasmosis and several psychiatric

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Table 3. Risks of psychiatric disorders in the total population evaluated by Cox regression analyses

	Univariate		Multivariate	
Variables	HR (95% CI)	*P*	aHR (95% CI)	*P*
Toxoplasmosis	3.98 (2.56, 6.20)	**<0.001**	3.79 (2.37, 6.07)	**<0.001**
Age group (years)				
⩾65	Reference		Reference	
45–64	2.35 (1.21, 4.56)	**0.012**	2.23 (1.14, 4.36)	**0.019**
18–44	4.68 (2.5, 8.74)	**<0.001**	5.50 (2.89, 10.44)	**<0.001**
Gender				
Female	Reference		Reference	
Male	1.72 (1.11, 2.66)	**0.016**	2.44 (1.52, 3.89)	**<0.001**
Insurance premium (NTD)				
<18 000	Reference		Reference	
18 000–34 999	0.83 (0.16, 5.93)	0.85	0.73 (0.1, 5.32)	0.752
⩾35 000	NA		NA	
Season of diagnosis				
Spring	Reference		Reference	
Summer	0.88 (0.52, 1.47)	0.611	0.79 (0.47, 1.34)	0.38
Autumn	0.5 (0.27, 0.9)	**0.021**	0.47 (0.26, 0.86)	**0.015**
Winter	0.84 (0.49, 1.42)	0.504	0.83 (0.48, 1.43)	0.501
Level of hospital care				
Local hospital	Reference		Reference	
Regional hospital	1 (0.64, 1.57)	0.228	1.67 (1.37, 2.22)	**0.002**
Hospital centre	1.08 (0.65, 1.8)	0.262	1.82 (1.49, 2.37)	**0.005**
Urbanization level				
4 (lowest)	Reference		Reference	
3	0.92 (0.5, 1.71)	0.797	0.99 (0.58, 2.38)	0.852
2	0.89 (0.38, 2.1)	0.788	0.81 (0.45, 2.24)	0.546
1 (highest)	1 (0.56, 1.79)	0.993	1.17 (0.65, 2.6)	0.66
Place of residence				
Northern Taiwan	Reference			
Middle Taiwan	0.81 (0.49, 1.35)	0.413		
Southern Taiwan	1.02 (0.62, 1.68)	0.935		
Eastern Taiwan	1.59 (0.86, 2.97)	0.143		
Outlying islands	NA			
CCI	1.06 (1.01, 1.12)	**0.047**	1.08 (1.02, 1.15)	**0.014**

aHR, adjusted hazard ratio; CI, confidence interval; NA, not applicable.
Significant *P* values are shown in bold.

disorders using a national population sample in Taiwan. Notably, we found no significant differences in the risk of schizophrenia between patients with and without *T. gondii* infection. In consistent with our findings, no significant association between *T. gondii* seropositivity and risk of schizophrenia was reported by two population-based studies conducted in Finland and New Zealand (Sugden *et al.*, 2016; Lindgren *et al.*, 2018) and a case-control study carried out in the Netherlands (de Witte *et al.*, 2015).

Nevertheless, overwhelming evidence suggests otherwise. A recent large internet-based cohort study revealed that toxoplasmosis was significantly associated with schizophrenia in Czechia (Flegr and Horáček, 2020), and such association has been previously documented *via* systemic review and meta-analysis (Torrey *et al.*, 2012; Sutterland *et al.*, 2015). Latent toxoplasmosis incidence, evidenced by anti-*T. gondii* IgM and IgG concentrations, was significantly higher in patients with schizophrenia than healthy controls in Russia (Stepanova *et al.*, 2019). Comparably, elevated serum levels of anti-*T. gondii* IgG and IgM in patients with schizophrenia in relative to those of controls were found in China (Chen *et al.*, 2019). Furthermore, an analysis of the Danish Blood Donor Study suggested that *T. gondii* infection was a possible causative factor for schizophrenia due to the temporality of pathogen exposure (Burgdorf *et al.*, 2019).

Regarding the discrepancies among previous studies examining the relationship between *T. gondii* infection and

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Table 4. Multivariate Cox regression analysis for psychiatric disorders in patients with or without toxoplasmosis stratified by demographics

	With toxoplasmosis		Without toxoplasmosis		With *vs* without	
Stratified variables	Events	Person-years	Events	Person-years	aHR (95% CI)	*P*
Gender						
Female	12	1427.04	23	4346.23	3.35 (2.09, 5.30)	**<0.001**
Male	18	1351.98	50	7804.81	4.38 (2.75, 7.02)	**<0.001**
Age group (years)						
⩾65	2	573.66	11	3897.94	2.58 (1.23, 4.01)	**0.001**
45–64	8	937.68	24	4428.95	3.20 (1.99, 5.12)	**<0.001**
18–44	20	1267.68	38	3824.15	3.36 (2.10, 5.40)	**<0.001**
Insurance premium (NTD)						
<18 000	30	2764.89	72	11 878.48	3.78 (2.36, 6.10)	**<0.001**
18 000–34 999	0		1	159.36	NA	NA
⩾35 000	0		0		NA	NA
Season of diagnosis						
Spring	9	486.38	22	2701.64	4.80 (3.00, 7.44)	**<0.001**
Summer	8	724.05	24	3285.96	3.20 (1.94, 5.10)	**<0.001**
Autumn	3	768.16	11	3271.45	2.44 (1.50, 3.98)	**<0.001**
Winter	10	800.43	16	2891.99	4.63 (2.87, 6.99)	**<0.001**
Urbanization level						
4 (lowest)	4	180.06	15	1748.74	5.27 (3.17, 8.78)	**<0.001**
3	2	223.41	6	1010.50	3.12 (1.90, 5.12)	**<0.001**
2	11	1172.46	38	5709.56	2.77 (1.45, 4.64)	**<0.001**
1 (highest)	13	1203.08	14	3682.24	5.79 (3.65, 9.54)	**<0.001**
Level of hospital care						
Local hospital	5	457.46	20	2763.70	3.12 (1.89, 5.25)	**<0.001**
Regional hospital	11	912.35	33	5355.89	4.04 (2.12, 6.03)	**<0.001**
Hospital centre	14	1409.20	20	4031.46	4.30 (2.64, 6.79)	**<0.001**

aHR, adjusted hazard ratio; CI, confidence interval; NA, not applicable.
Significant *P* values are shown in bold.

Table 5. The risk for specific psychiatric disorders between the case and control groups evaluated by Cox regression analyses

	Case group *vs* control group (reference)		
Psychiatric disorders	aHR	95% CI	*P*
Schizophrenia	1.14	0.20, 6.59	0.897
Bipolar disorder	3.60	2.07, 7.26	**0.001**
Depression	4.94	2.15, 11.80	**<0.001**
Anxiety	5.36	2.98, 25.88	**<0.001**
Other psychiatric disorders	1.36	0.49, 3.79	0.560

aHR, adjusted hazard ratio; CI, confidence interval.
Significant *P* values are shown in bold.

schizophrenia, Yolken *et al.* (2017) hypothesized that the timing of patient evaluation might be one of possible explanations in a nested case-control study. They found that patients, who were diagnosed with recent onset psychosis and took a serologic test soon after psychosis manifested, had elevated odds of seropositivity for IgG antibodies against *T. gondii*; however, patients with established schizophrenia did not have significantly higher odds of *T. gondii* IgG seropositivity (Yolken *et al.*, 2017). Several schizophrenia medications were demonstrated to possess anti-*T. gondii* activity in cell culture (Jones-Brando *et al.*, 2003), which may partially explain non-reactivity of anti-*T. gondii* IgG antibodies in established schizophrenia. In addition, serum levels of anti-*T. gondii* antibodies were suggested to decline in the absence of persistent exposure to *T. gondii* (Rougier *et al.*, 2017). In the present population-based study, toxoplasmosis was defined based on ICD diagnostic code without serological evidence. The ICD-9-CM coding system does not contain a specific code for recent onset psychosis. Hence, additional prospective longitudinal cohort studies are required to further investigate *T. gondii* infection in schizophrenia patients relying on antibody titres and *T. gondii* exposure history.

In the present study, patients with confirmed toxoplasmosis had significantly higher risk of bipolar disorder, and other recent studies have also reported associations between *T. gondii* infection and bipolar disorder (Wu *et al.*, 2010; Sutterland *et al.*, 2015). In addition, Del Grande *et al.* (2017) demonstrated the link between *T. gondii* and bipolar disorder, emphasizing the human immune response, the presence of latent toxoplasmosis and an increased risk of bipolar disorder and suicidal/aggressive behaviour. Findings of this report suggest that re-exposure to the parasite

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could modify the individual's immune response and reactivate latent toxoplasmosis (Del Grande *et al.*, 2017), as has been suggested for schizophrenia (Sutterland *et al.*, 2015). Furthermore, the potential of latent toxoplasmosis to provoke the development of bipolar disorder has been suggested (Afifi *et al.*, 2018).

The present study showed that both depression and anxiety were more likely to occur in patients with toxoplasmosis than in those without, whereas varying results have been found in the literature. The elevated levels of *T. gondii* IgG antibodies were correlated with depression and anxiety in pregnant women (Groër *et al.*, 2011), but another study reported no association between *T. gondii* seropositivity and prenatal depression (Alvarado-Esquivel *et al.*, 2017). A community-based study found that *T. gondii* seropositivity was associated with anxiety, but not depression (Markovitz *et al.*, 2015), and a cohort study indicated that toxoplasmosis was associated with anxiety (Flegr and Horáček, 2020). Two meta-analyses concluded that *T. gondii* infection was not associated with depression (Wang *et al.*, 2014; Nayeri Chegeni *et al.*, 2019). Notably, a Danish study found that *T. gondii* seropositivity was associated with moderate–severe depression, but not mild–severe (Bay-Richter *et al.*, 2019*a*; Nayeri Chegeni *et al.*, 2019); therefore, severity of depression may be one possible reason for conflicting relationships between *T. gondii* infection and depression reported in the literature.

Vector-borne parasitic diseases have been noted previously for associations with mental disorders. Our previous nationwide population-based cohort study (Lin *et al.*, 2019), demonstrated a higher risk for psychiatric disorders among women with *Trichomonas vaginalis* infection, specifically a higher likelihood of trichomoniasis in psychiatric patients. Although cats act as a reservoir for *T. gondii* infections (Lilly and Wortham, 2013; Zulop *et al.*, 2018), the vectors only pose a risk in the initial cystic stage when cats shed oocytes (Hartmann *et al.*, 2013). If sheep, cattle and pigs ingest *T. gondii* oocyte-contaminated soil and water, tissue cysts will develop, and humans are likely to be infected if they consume undercooked meat (Berger-Schoch *et al.*, 2011). Actual clinical disease does not occur often in *T. gondii* positive cats, manifesting mainly in immunosuppressed cats that may display CNS effects if disease symptoms finally do appear (Hartmann *et al.*, 2013). This pattern may present clues about the mental effects of *T. gondii* infection in humans.

Toxoplasma gondii has a tropism for muscle and brain tissue, where it may establish chronic infection through cyst formation (Weiss and Dubey, 2009). The intracellular parasite *T. gondii* can alter dopamine metabolism within neurons; such metabolic fluctuation may cause behavioural changes in the host (Parlog *et al.*, 2015). In a mouse model of *T. gondii* infection, degenerating neurons shown upregulated complement proteins and were surrounded by activated microglia, which are both signs of neurodegeneration typical of psychiatric disorders (Li *et al.*, 2019). Changes in neuronal connectivity and synaptic plasticity also have been suggested as part of the mechanism responsible for psychiatric disorders upon *T. gondii* infection (Parlog *et al.*, 2015).

Genetic background is also suggested to be an important influence on the response to latent toxoplasmosis (Bay-Richter *et al.*, 2019*b*; Torrey and Yolken, 2019). Supportive of the role of gene-mediated immune response to *T. gondii*, Wang *et al.* (2019) identified two schizophrenia-related genes with significant toxoplasmosis-associated variants. Kano *et al.* (2018) found that the specific mental health-relate gene (disrupted in schizophrenia, or DISC1) activated transcription factors against *T. gondii* infection, and that the genotype DISC1 Phe/Phe was associated with higher titres of *T. gondii* antibodies in sera. Furthermore, *via* a comprehensive system analysis of *T. gondii*-infected human brains, Ngô *et al.* (2017) identified several susceptibility genes for congenital toxoplasmosis and suggested that *T. gondii* modulates critical signalling pathways, which contributes to the development of epilepsy, neurodegeneration and cancer.

Strengths and limitations

One of the main strengths of the present study is the utilization of the NHIRD, which contains nationwide longitudinal data of 99.9% of Taiwan's population, and minimizes discrepancies and biases. Hence, the NHIRD is an excellent data source for population-level analysis. However, because only data from Taiwanese patients are used, the current findings may not be generalizable to other populations or other countries. The use of secondary retrospective data does not support inferences of causation and only indicates associations. The NHIRD does not provide data of individual patients' lifestyle, family history, the date when *T. gondii* infection occurred, and serological data, which limits the analysis of potential influencing factors. The diagnoses of toxoplasmosis and psychiatric disorders were identified in the present study based on ICD-9 codes from the NHIRD database, and it is possible that coding errors and misclassification may exist, as noted in a previous study (Kern *et al.*, 2006). Although one-third of the world population was estimated to be infected by *T. gondii* (Montoya and Liesenfeld, 2004), latent *T. gondii* infection was not indicated in the NHIRD.

Conclusions

The present nationwide population-based analysis revealed that *T. gondii* infection in Taiwan significantly increases risk for developing bipolar disorder, depression and anxiety, but not schizophrenia or other psychiatric disorders. The epidemiologic role of *T. gondii* in the development of psychiatric disorders is an urgent public health issue that may benefit from increasing the awareness of this association and its prominent risk factors among the general public, healthcare professionals and public health agencies.

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Conflict of interest. None.

Ethical standards. The current study protocol was reviewed and approved by the Institutional Review Board of Tri-Service General Hospital, Taiwan. Because all patient data were deidentified in the National Health Insurance Research Database (NHIRD) of Taiwan, informed consent was waived.

References

Achaw B, Tesfa H, Zeleke AJ, Worku L, Addisu A, Yigzaw N and Tegegne Y (2019) Sero-prevalence of *Toxoplasma gondii* and associated risk factors among psychiatric outpatients attending University of Gondar Hospital, Northwest Ethiopia. *BMC Infectious Diseases* **19**, 581.

Afifi MA, Jiman-Fatani AA, Al-Rabia MW, Al-Hussainy NH, El Saadany S and Mayah W (2018) More than an association: latent toxoplasmosis might provoke a local oxidative stress that triggers the development of bipolar disorder. *Journal of Microscopy and Ultrastructure* **6**, 139–144.

Alvarado-Esquivel C, Martínez-Martínez AL, Sánchez-Anguiano LF, Hernández-Tinoco J, Castillo-Orona JM, Salas-Martínez C, Sifuentes-Álvarez A, Sandoval-Carrillo AA, Salas-Pacheco JM, Liesenfeld O and Antuna-Salcido EI (2017) Lack of association between *Toxoplasma gondii*

exposure and depression in pregnant women: a case-control study. *BMC Infectious Diseases* **17**, 190.

Bay-Richter C, Buttenschøn HN, Mors O, Eskelund A, Budac D, Kærlev L and Wegener G (2019a) Latent toxoplasmosis and psychiatric symptoms – a role of tryptophan metabolism? *Journal of Psychiatric Research* **110**, 45–50.

Bay-Richter C, Petersen E, Liebenberg N, Elfving B and Wegener G (2019b) Latent toxoplasmosis aggravates anxiety- and depressive-like behaviour and suggest a role of gene–environment interactions in the behavioural response to the parasite. *Behavioural Brain Research* **364**, 133–139.

Berger-Schoch AE, Herrmann DC, Schares G, Müller N, Bernet D, Gottstein B and Frey CF (2011) Prevalence and genotypes of *Toxoplasma gondii* in feline faeces (oocysts) and meat from sheep, cattle and pigs in Switzerland. *Veterinary Parasitology* **177**, 290–297.

Burgdorf KS, Trabjerg BB, Pedersen MG, Nissen J, Banasik K, Pedersen OB, Sorensen E, Nielsen KR, Larsen MH, Erikstrup C, Bruun-Rasmussen P, Westergaard D, Thorner LW, Hjalgrim H, Paarup HM, Brunak S, Pedersen CB, Torrey EF, Werge T, Mortensen PB, Yolken RH and Ullum H (2019) Large-scale study of *Toxoplasma* and cytomegalovirus shows an association between infection and serious psychiatric disorders. *Brain, Behavior, and Immunity* **79**, 152–158.

Chalkowski K, Wilson AE, Lepczyk CA and Zohdy S (2019) Who let the cats out? A global meta-analysis on risk of parasitic infection in indoor *versus* outdoor domestic cats (*Felis catus*). *Biology Letters* **15**, 20180840.

Chen X, Chen B, Hou X, Zheng C, Yang X, Ke J, Hu X and Tan F (2019) Association between Toxoplasma gondii infection and psychiatric disorders in Zhejiang, Southeastern China. *Acta Tropica* **192**, 82–86.

Chiang TY, Hsieh HH, Kuo MC, Chiu KT, Lin WC, Fan CK, Fang CT and Ji DD (2012) Seroepidemiology of *Toxoplasma gondii* infection among healthy blood donors in Taiwan. *PLoS One* **7**, e48139.

Chiang TY, Kuo MC, Chen CH, Yang JY, Kao CF, Ji DD and Fang CT (2014) Risk factors for acute *Toxoplasma gondii* diseases in Taiwan: a population-based case-control study. *PLoS One* **9**, e90880.

Dabritz HA and Conrad PA (2010) Cats and *Toxoplasma*: implications for public health. *Zoonoses and Public Health* **57**, 34–52.

Del Grande C, Galli L, Schiavi E, Dell'Osso L and Bruschi F (2017) Is *Toxoplasma gondii* a trigger of bipolar disorder? *Pathogens* **6**, 3.

de Witte LD, van Mierlo HC, Litjens M, Klein HC, Bahn S and Osterhaus AD (2015) The association between antibodies to neurotropic pathogens and schizophrenia: a case-control study. *NPJ Schizophrenia* **1**, 15041.

Dubey JP and Jones JL (2008) *Toxoplasma gondii* infection in humans and animals in the United States. *International Journal for Parasitology* **38**, 1257–1278.

Elmore SA, Jones JL, Conrad PA, Patton S, Lindsay DS and Dubey JP (2010) *Toxoplasma gondii*: epidemiology, feline clinical aspects, and prevention. *Trends in Parasitology* **26**, 190–196.

Flegr J and Horáček J (2020) Negative effects of latent toxoplasmosis on mental health. *Frontiers in Psychiatry* **10**, 1012.

Groër MW, Yolken RH, Xiao JC, Beckstead JW, Fuchs D, Mohapatra SS, Seyfang A and Postolache TT (2011) Prenatal depression and anxiety in *Toxoplasma gondii*-positive women. *American Journal of Obstetrics and Gynecology* **204**, 433.e431–437.

Hartmann K, Addie D, Belak S, Boucraut-Baralon C, Egberink H, Frymus T, Gruffydd-Jones T, Hosie MJ, Lloret A, Lutz H, Marsilio F, Mostl K, Pennisi MG, Radford AD, Thiry E, Truyen U and Horzinek MC (2013) *Toxoplasma gondii* infection in cats: ABCD guidelines on prevention and management. *Journal of Feline Medicine and Surgery* **15**, 631–637.

Hill DE, Chirukandoth S and Dubey JP (2005) Biology and epidemiology of *Toxoplasma gondii* in man and animals. *Animal Health Research Reviews* **6**, 41–61.

Hu IJ, Chen PC, Su FC, Hsieh CJ, Jeng SF, Liao HF, Su YN, Lin SJ and Hsieh WS (2006) Perinatal toxoplasmosis, northern Taiwan. *Emerging Infectious Diseases* **12**, 1460–1461.

Hung CC, Chen MY, Hsieh SM, Hsiao CF, Sheng WH and Chang SC (2005) Prevalence of *Toxoplasma gondii* infection and incidence of toxoplasma encephalitis in non-haemophiliac HIV-1-infected adults in Taiwan. *International Journal of STD & AIDS* **16**, 302–306.

Jones-Brando L, Torrey EF and Yolken R (2003) Drugs used in the treatment of schizophrenia and bipolar disorder inhibit the replication of *Toxoplasma gondii*. *Schizophrenia Research* **62**, 237–244.

Kano SI, Hodgkinson CA, Jones-Brando L, Eastwood S, Ishizuka K, Niwa M, Choi EY, Chang DJ, Chen Y, Velivela SD, Leister F, Wood J, Chowdari K, Ducci F, Caycedo DA, Heinz E, Newman ER, Cascella N, Mortensen PB, Zandi PP, Dickerson F, Nimgaonkar V, Goldman D, Harrison PJ, Yolken RH and Sawa A (2018) Host–parasite interaction associated with major mental illness. *Molecular Psychiatry* **25**, 194–205.

Kern EF, Maney M, Miller DR, Tseng CL, Tiwari A, Rajan M, Aron D and Pogach L (2006) Failure of ICD-9-CM codes to identify patients with comorbid chronic kidney disease in diabetes. *Health Services Research* **41**, 564–580.

Khodaverdi M and Razmi G (2019) A serological and parasitological study of *Toxoplasma gondii* infection in stray cats of Mashhad, Khorasan Razavi province, Iran. *Veterinary Research Forum* **10**, 119–123.

Li Y, Severance EG, Viscidi RP, Yolken RH and Xiao J (2019) Persistent toxoplasma infection of the brain induced neurodegeneration associated with activation of complement and microglia. *Infection and Immunity* **87**, 8.e00139-19.

Lilly EL and Wortham CD (2013) High prevalence of *Toxoplasma gondii* oocyst shedding in stray and pet cats (*Felis catus*) in Virginia, United States. *Parasites & Vectors* **6**, 266.

Lin HC, Huang KY, Chung CH, Lin HA, Chen RM, Tsao CH, Chien WC and Chiueh TS (2019) Infection with *Trichomonas vaginalis* increases the risk of psychiatric disorders in women: a nationwide population-based cohort study. *Parasites & Vectors* **12**, 88.

Lindgren M, Torniainen-Holm M, Harkanen T, Dickerson F, Yolken RH and Suvisaari J (2018) The association between toxoplasma and the psychosis continuum in a general population setting. *Schizophrenia Research* **193**, 329–335.

Markovitz AA, Simanek AM, Yolken RH, Galea S, Koenen KC, Chen S and Aiello AE (2015) *Toxoplasma gondii* and anxiety disorders in a community-based sample. *Brain, Behavior, and Immunity* **43**, 192–197.

Montoya JG and Liesenfeld O (2004) Toxoplasmosis. *Lancet* **363**, 1965–1976.

Nayeri Chegeni T, Sharif M, Sarvi S, Moosazadeh M, Montazeri M, Aghayan SA, Balalami NJ, Gholami S, Hosseininejad Z, Saberi R, Anvari D, Gohardehi S and Daryani A (2019) Is there any association between *Toxoplasma gondii* infection and depression? A systematic review and meta-analysis. *PLoS One* **14**, e0218524.

Ngô HM, Zhou Y, Lorenzi H, Wang K, Kim TK, Zhou Y, El Bissati K, Mui E, Fraczek L, Rajagopala SV, Roberts CW, Henriquez FL, Montpetit A, Blackwell JM, Jamieson SE, Wheeler K, Begeman IJ, Naranjo-Galvis C, Alliey-Rodriguez N, Davis RG, Soroceanu L, Cobbs C, Steindler DA, Boyer K, Noble AG, Swisher CN, Heydemann PT, Rabiah P, Withers S, Soteropoulos P, Hood L and McLeod R (2017) Toxoplasma modulates signature pathways of human epilepsy, neurodegeneration & cancer. *Scientific Reports* **7**, 11496.

Palerme JS, Lamperelli E, Gagne J, Cazlan C, Zhang M and Olds JE (2019) Seroprevalence of *Leptospira* spp., *Toxoplasma gondii*, and *Dirofilaria immitis* in free-roaming cats in Iowa. *Vector-Borne and Zoonotic Diseases* **19**, 193–198.

Pappas G, Roussos N and Falagas ME (2009) Toxoplasmosis snapshots: global status of *Toxoplasma gondii* seroprevalence and implications for pregnancy and congenital toxoplasmosis. *International Journal for Parasitology* **39**, 1385–1394.

Parlog A, Schluter D and Dunay IR (2015) *Toxoplasma gondii*-induced neuronal alterations. *Parasite Immunology* **37**, 159–170.

Robert-Gangneux F and Darde ML (2012) Epidemiology of and diagnostic strategies for toxoplasmosis. *Clinical Microbiology Reviews* **25**, 264–296.

Rougier S, Montoya JG and Peyron F (2017) Lifelong persistence of toxoplasma cysts: a questionable dogma? (*Trends in Parasitology* 33, 93–101; 2017). *Trends in Parasitology* **33**, 414.

Stepanova EV, Kondrashin AV, Sergiev VP, Morozova LF, Turbabina NA, Maksimova MS, Romanov DV, Kinkulkina MA, Lazareva AV and Morozov EN (2019) Toxoplasmosis and mental disorders in the Russian Federation (with special reference to schizophrenia). *PLoS One* **14**, e0219454.

Sugden K, Moffitt TE, Pinto L, Poulton R, Williams BS and Caspi A (2016) Is *Toxoplasma gondii* infection related to brain and behavior impairments in humans? Evidence from a population-representative birth cohort. *PLoS One* **11**, e0148435.

Sutterland AL, Fond G, Kuin A, Koeter MW, Lutter R, van Gool T, Yolken R, Szoke A, Leboyer M and de Haan L (2015) Beyond the association. *Toxoplasma gondii* in schizophrenia, bipolar disorder, and addiction: systematic review and meta-analysis. *Acta Psychiatrica Scandinavica* **132**, 161–179.

https://doi.org/10.1017/S0031182020001183 Published online by Cambridge University Press

Torrey EF and Yolken RH (2019) Schizophrenia as a pseudogenetic disease: a call for more gene-environmental studies. *Psychiatry Research* **278**, 146–150.

Torrey EF, Bartko JJ and Yolken RH (2012) *Toxoplasma gondii* and other risk factors for schizophrenia: an update. *Schizophrenia Bulletin* **38**, 642–647.

Wang X, Zhang L, Lei Y, Liu X, Zhou X, Liu Y, Wang M, Yang L, Zhang L, Fan S and Xie P (2014) Meta-analysis of infectious agents and depression. *Scientific Reports* **4**, 4530.

Wang AW, Avramopoulos D, Lori A, Mulle J, Conneely K, Powers A, Duncan E, Almli L, Massa N, McGrath J, Schwartz AC, Goes FS, Weng L, Wang R, Yolken R, Ruczinski I, Gillespie CF, Jovanovic T, Ressler K, Pulver AE and Pearce BD (2019) Genome-wide association study in two populations to determine genetic variants associated with *Toxoplasma gondii* infection and relationship to schizophrenia risk. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* **92**, 133–147.

Weiss LM and Dubey JP (2009) Toxoplasmosis: a history of clinical observations. *International Journal for Parasitology* **39**, 895–901.

Wu TY, Majeed A and Kuo KN (2010) An overview of the healthcare system in Taiwan. *London Journal of Primary Care (Abingdon)* **3**, 115–119.

Ybanez RHD, Busmeon CGR, Viernes ARG, Langbid JZ, Nuevarez JP, Ybanez AP and Nishikawa Y (2019) Endemicity of *Toxoplasma* infection and its associated risk factors in Cebu, Philippines. *PLoS One* **14**, e0217989.

Yolken R, Torrey EF and Dickerson F (2017) Evidence of increased exposure to *Toxoplasma gondii* in individuals with recent onset psychosis but not with established schizophrenia. *PLoS Neglected Tropical Diseases* **11**, e0006040.

Zulpo DL, Sammi AS, Dos Santos JR, Sasse JP, Martins TA, Minutti AF, Cardim ST, de Barros LD, Navarro IT and Garcia JL (2018) *Toxoplasma gondii*: a study of oocyst re-shedding in domestic cats. *Veterinary Parasitology* **249**, 17–20.

https://doi.org/10.1017/S0031182020001183 Published online by Cambridge University Press