Systematic Review

Systematic Review on the Relationship between Toxoplasmosis and Mental Disorders

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Abstract

Background: Toxoplasmosis is a worldwide parasitic zoonosis caused by the protozoan *Toxoplasma gondii*. In cases of vertical infection, and in immunosuppressed people by the human immunodeficiency virus (HIV) serious clinical conditions may appear, while immunocompetent people do not present symptoms. However, *T. gondii* infection has been linked to several mental disorders for decades.

Objective: To substantiate the possible relationship between *T. gondii* and mental disorders and suggest control and prevention strategies.

Material and Methods: A systematic review has been carried out to analyze the relationship between *T. gondii* exposure (presence of IgG) and the onset of mental disorders in minors and adults. The etiopathogenic mechanisms described by the authors have also been included and the systems of surveillance, prevention and control of infection have been evaluated.

Results: Several processes linked to the presence of cysts and the reactivation of the parasite in certain situations produce an immune and inflammatory response. Also, direct and indirect actions on different neurotransmitters. These mechanisms, together with other environmental and genetic factors, would predispose to different psychiatric pathologies.

Conclusions: Due to the limits of the study, no conclusions can be drawn in childhood and adolescence. However, the results of this systematic review show a possible association of schizophrenia, bipolar disorder and compulsive disorder with *T. gondii* infection in adults. There is a need to improve control, integrated surveillance and extend prevention measures to the entire population.

Keywords

Toxoplasma gondii; mental disorders; neuropathology; primary prevention; public health surveillance

Introduction

Toxoplasmosis is a worldwide zoonosis caused by the protozoan *T. gondii* (Apicomplexa group). Infection occurs through the ingestion of infective forms present in food and in the environment. The seroprevalence according to countries and areas exceeds 60% [1]. Data on the prevalence of toxoplasmosis come from epidemiological studies in the general population and mainly in pregnant women, which indicate that seroprevalence varies according to countries and even areas (higher in rural areas) due to climatic or cultural differences, among other factors.

The causative agent was identified in 1908 by Nicolle and Manceaux [2] but it was not until the mid-1950s when more importance was given to the pathogenesis, clinic and prevalence. During those years in Poland, studies were carried out where a higher rate of *T. gondii* infection was observed among patients in the psychiatry department compared to controls [3].

Since then, several prevalence and case-control studies have been carried out showing discordant results in patients with different mental disorders (such as schizophrenia [4], bipolar disorder [5], obsessive-compulsive disorder (OCD), depression [6], epilepsy, anxiety [6], personality changes and behavioral disorders, among others. The etiology of mental disorders remains uncertain, presenting a multifactorial trait which would include a genetic predis-

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position, environmental factors and exposure to certain infectious agents being *T. gondii*, perhaps, one of them [7].

Many drugs used for these mental disorders (haloperidol, valproate, risperidone, fluphenazine) have a parasiticidal activity and can eliminate the protozoan [8]. Some studies show that treatments with antiprotozoal drugs in children and human immunodeficiency virus (HIV) positive patients reduced the presence of antibodies and the symptoms caused by these disorders, such as OCD, which promoted other studies on the matter [7].

The three evolutionary forms present in the life cycle of *T. gondii* are infectious for intermediate (potentially any mammal) and definitive (felids) hosts, which can be infected by ingestion of sporulated oocysts containing sporozoites, through bradyzoites contained in tissue cysts or by transplacental transmission of tachyzoites.

In most cases, infections occur asymptomatically in immunocompetent people or presenting mild and nonspecific symptoms. However, the symptoms can be serious in immunosuppressed people, even fatal, affecting the nervous system (encephalitis), myocardium and retina. In pregnant women who become infected, vertical transmission of the parasite might occur, causing abortion, neonatal death or a series of alterations in the fetus. These alterations vary depending on the period of pregnancy when the infection occurs, being much slighter at the end of the pregnancy. Among these alterations, encephalomyelitis, chorioretinitis, cerebral calcifications, hydrocephalus, ocular alterations, psychomotor retardation and other non-specific signs have been observed [8].

Regarding diagnosis and treatment, usually serological techniques are used to detect antibodies (IgG and IgM) and, sometimes, direct techniques, such as polymerase chain reaction (PCR) or histopathological studies are performed. The drugs commonly used to treat toxoplasmosis are pyrimethamine combined with sulfadiazine or clindamycin combined with spiramycin [9].

Prophylactic measures include cooking meat at high temperatures, washing vegetables carefully, and consuming pasteurized milk. Also, wearing gloves when gardening or doing other work that involves handling soil, washing hands thoroughly after contact with cats and wearing gloves when changing the litter box of cats. In addition to these measures, preventing cats from accessing areas where food is produced or handled [10].

However, it does not seem that *T. gondii* is considered in the management of patients with mental disorders. There are also no prevention programs that alert the general population to avoid possible infections in groups not identified as at risk.

Therefore, the objective of this systematic review is to substantiate the possible relationship between *T. gondii* and mental disorders and to suggest control and prevention strategies derived from the information obtained.

Materials and Methods

In order to obtain the necessary information to substantiate the possible relationship between *T. gondii* and mental disorders and suggest control and prevention strategies derived from the information obtained, a systematic review was carried out to answer the following Problem/Population, Intervention, Comparison, Outcome (PICO) question: is the appearance of mental disorders more frequent in adults and minors with *T. gondii* infection than in non-infected ones?

The bibliographic search was conducted using the Plos One, ProQuest Central and Pubmed databases, by means of the following strategy: Plos One: (title: Toxoplasm*) AND everything: “mental disorders”; Proquest Central: (Title-Combined: (toxoplasm*)) AND (“mental disorders”) and Pubmed: “Toxoplasmosis/psychology” [Mesh].

The publication period of the articles was limited to 6 years (April 5th, 2015–April 5th, 2021). In Proquest Central, only “*Weekly Article*” publications were selected.

Studies that analyzed the relationship between *T. gondii* and mental illnesses (listed in the Diagnostic and Statistical Manual of Mental Disorders, DSM) were included. Also, those that indicated possible pathogenic mechanisms.

Duplicate articles and those that, after reading the title or abstract, did not meet the objective, were identified and eliminated. Subsequently, after reading the full text, studies that did not provide relevant information about the topic were excluded.

The assessment of the methodological quality of the preselected articles was carried out independently by two researchers by means of the STROBE [11] statement (for observational studies) and the PRISMA [12] checklist (for meta-analyses). Articles that obtained less than 60% of the maximum score (13/22 STROBE and 16/27 PRISMA were not included in the systematic review. This systematic review is reported according to PRISMA 2020 guidelines (**Supplementary File 1**).

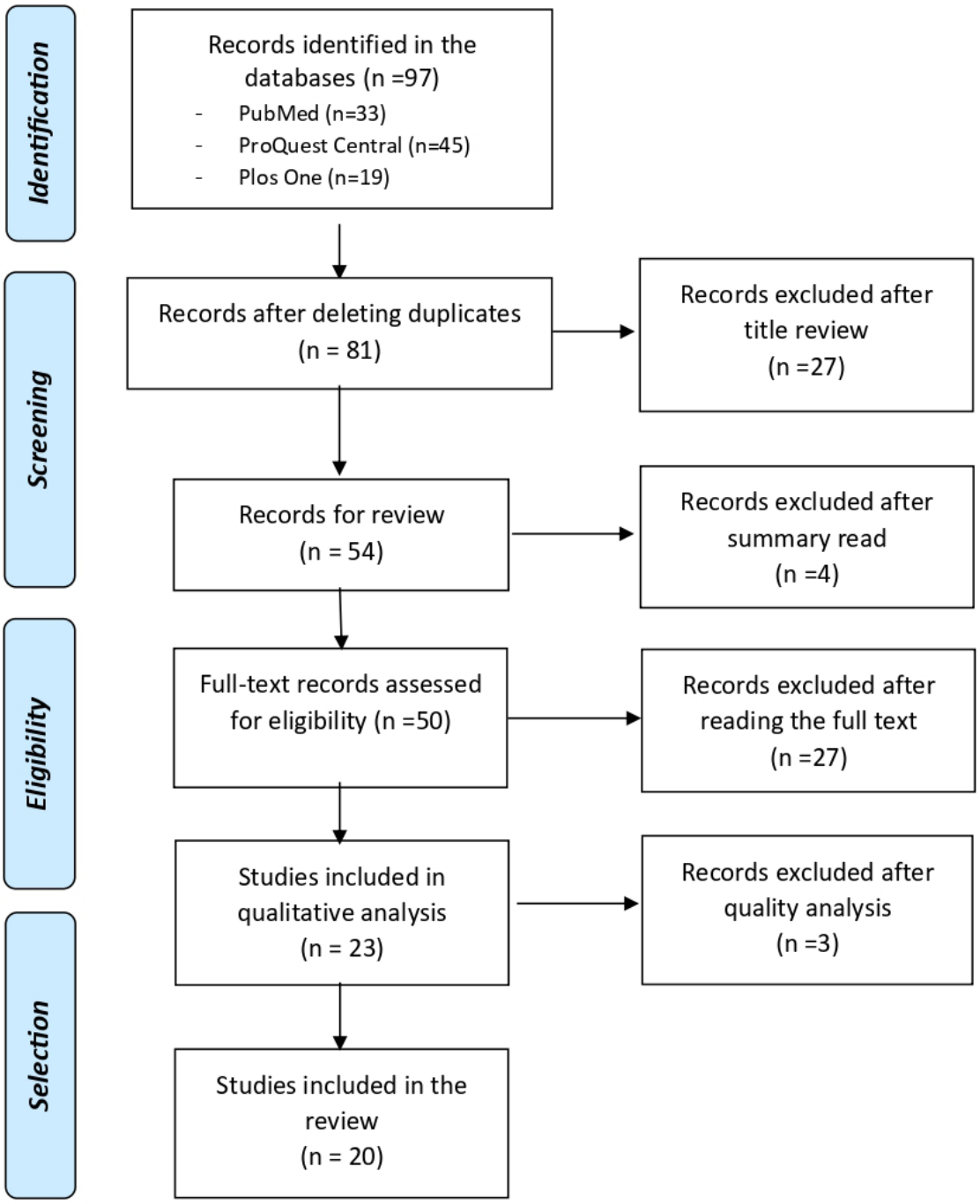

Fig. 1. PRISMA flowchart.

Results

A total of 97 articles were identified, of which 16 were in duplicate. After reading the title and abstract, and the evaluation of the full text reading, 58 were removed. Finally, after the evaluation of the methodological quality of 23 documents, 3 articles were eliminated, remaining 20 papers that were included in the present systematic review. The process of identification, screening and selection of articles is described in the PRISMA flowchart (Fig. 1).

Table 1 (Ref. [7,8,13–30]) summarizes the characteristics of these 20 articles. Of these, 7 studies were carried out on children and adolescents (Table 2, Ref. [13–19]). In 4 of these 7 studies, a statistically significant association was observed, with *T. gondii* infection being related to de-

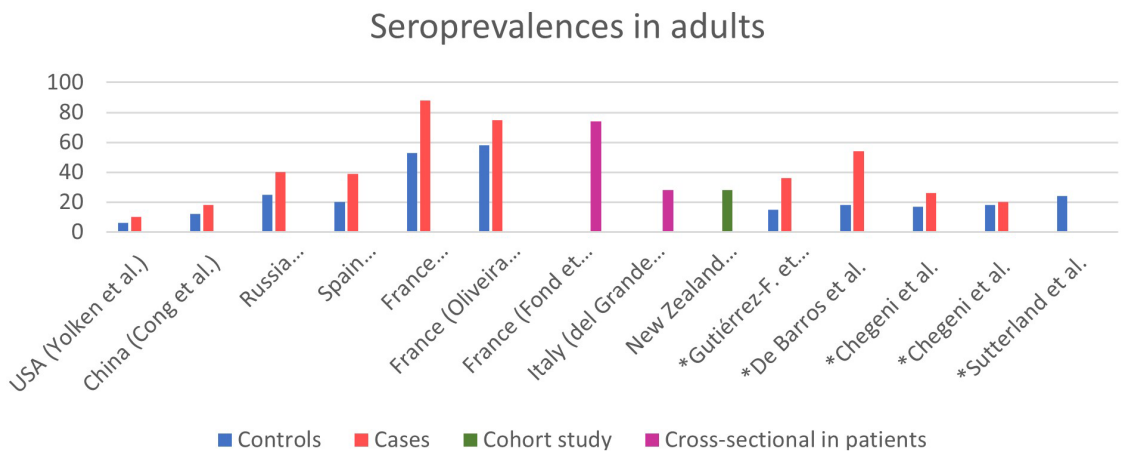

Fig. 2. Summary of seroprevalences described in the different studies carried out in adults. The graph shows seroprevalence (percentage) by country in case-control studies, cross-sectional studies in psychiatric patients, cohort studies, and case-control studies in meta-analysis studies involving several countries (*).

pression [13], OCD and generalized anxiety [14]. A statistically significant association was also found with disorders that began in infancy, childhood or adolescence: stuttering [15] and Tourette syndrome and vocal and motor tics [16].

In the two other studies, an association between *T. gondii* infection and mental disorders (autism and hyperactive disorder [17] and OCD [18]) was not found. However, it was observed a significant association between the severity of the hyperactive disorder and the presence of IgG (being more severe in the serologically positive patients), determining that *T. gondii* is probably not a direct cause but contributes to exacerbating the clinical picture [19].

Miman *et al*. [18] in Turkey did not find an association between infection and OCD, although they mention in their study that other experts suggest that childhood-onset OCD is a phenomenologically and etiologically distinct subtype from adult OCD, which would have a close genetic relationship with tics disorders. Thus, the OCD diagnosed in the children in this study would be a mix of the two types and could either remit or persist into adulthood, being two different but indistinct pathologies at this age.

The possible interaction of other factors was also analysed. Only a study showed a significant association between hyperactivity disorder and gender, being more prevalent in men [19]. No significant differences related to area of residence [15] or socioeconomic status [13,18] were identified. However, significant differences were found in the assessments of the scales measuring the severity of Tourette [16], autism [17], hyperactivity [19], and anxiety and OCD [14], observing more severe symptoms in seropositive patients.

Discussion

In this systematic review, we have studied the possible association between *T. gondii* infection and mental disorders. It has been possible to determine the association between infection and mental illnesses in children and adolescents. Few articles address the problem in these population groups. Furthermore, the papers analyze different pathologies, with small sample sizes and contradictory results. In addition, all of them were carried out in Turkey, where the seroprevalence in the general population is high, estimated between 23–35% [17]. Although lower prevalences are observed in these results, probably due to the young age of the participants, which leads to a shorter exposure time to the parasite together with the cumulative effect of the IgG measured.

Regarding the possible relationship between toxoplasmosis and mental disorders in adults, 13 articles (observational studies and meta-analysis) have been reviewed, being schizophrenia, bipolar disorder, OCD and major depression the most studied psychiatric pathologies (see results in Table 3, Ref. [7,8,20–30]).

In general, the studies in this block included data from different countries and presented a prevalence in the control groups under 20%. The lowest prevalence was recorded in USA (6%) [20] and in China (12%) [21], meanwhile the highest prevalences (over 50%) were found in France [22,23]. In Spain, 20% was found in the control group [8]. These prevalence data agree with those reported by Paris in its 2019 study [1]. Fig. 2 shows the seroprevalence data in adults reported in these articles. Meta-analysis studies that include several countries determine average seropreva-

Table 1. Characteristics of the articles included in the study.

Author & Year	Title	Country	Type	Methodological assessment
Akaltun *et al*. [14], 2018a	The relationship between *Toxoplasma gondii* IgG antibodies and generalized anxiety disorder and obsessive-compulsive disorder in children and adolescents: a new approach.	Turkey	C-C	15 [a]
Akaltun *et al*. [16], 2018b	Seroprevalance Anti-*Toxoplasma gondii* antibodies in children and adolescents with Tourette syndrome/chronic motor or vocal tic disorder: A case-control study.	Turkey	C-C	16 [a]
Akaltun *et al*. [19], 2019	The relation between serum *Toxoplasma gondii* IgG antibody in children and ADHD and its severity.	Turkey	C-C	15 [a]
Celik *et al*. [15], 2015	The prevalence of anti-*Toxoplasma gondii* antibodies in stutterers is higher than in the control group.	Turkey	C-C	13 [a]
Chegeni *et al*. [7], 2019a	Relationship between toxoplasmosis and obsessive-compulsive disorder: A systematic review and meta-analysis.	Several [1]	MA	25 [b]
Chegeni *et al*. [29], 2019b	Is there any association between *Toxoplasma gondii* infection and depression? A systematic review and meta-analysis.	Several [2]	MA	26 [b]
Cong *et al*. [21], 2015	Seroprevalence and associated risk factors of *Toxoplasma gondii* infection in psychiatric patients: A case-control study in eastern China.	China	C-C	18 [a]
de Barros *et al*. [30], 2017	Is there any association between *Toxoplasma gondii* infection and bipolar disorder? A systematic review and meta-analysis.	Several [3]	MA	21 [b]
Del Grande *et al*. [25], 2020	Toxoplasmosis in a Cohort of Italian Patients with Bipolar and Psychotic Disorders: How Infection May Affect Clinical Features?	Italy	C-S	16 [a]
Esnafoglu *et al*. [17], 2017	The seroprevalence of antibodies to *Toxoplasma gondii* among children with autism.	Turkey	C-C	14 [a]
Fond *et al*. [28], 2018	Latent toxoplasma infection in real-world schizophrenia: Results from the national FACE-SZ cohort.	France	C-S	18 [a]
Gutiérrez-Fernández *et al*. [8], 2015	Different presence of *Chlamydia pneumoniae*, herpes simplex virus type 1, human herpes virus 6, and *Toxoplasma gondii* in schizophrenia: Meta-analysis and analytical study.	Several [4] Spain	MA C-C	18 [b]
Hamdani *et al*. [22], 2015	Cognitive deterioration among bipolar disorder patients infected by *Toxoplasma gondii* is correlated to interleukin 6 levels.	France	C-C	17 [a]
Miman *et al*. [18], 2018	*Toxoplasma gondii*–obsessive –compulsive disorder relationship: is it different in children?	Turkey	C-C	15 [a]
Oliveira *et al*. [23], 2016	*Toxoplasma gondii* exposure may modulate the influence of TLR2 genetic variation on bipolar disorder: a gene–environment interaction study.	France	C-C	17 [a]
Sapmaz *et al*. [13], 2019	Relationship between *Toxoplasma gondii* seropositivity and depression in children and adolescents.	Turkey	C-C	18 [a]
Stepanova *et al*. [27], 2019	Toxoplasmosis and mental disorders in the Russian Federation (with special reference to schizophrenia).	Russia	C-C	18 [a]
Sugden *et al*. [26], 2016	Is *Toxoplasma gondii* Infection related to brain and behavior impairments in humans? Evidence from a population-representative birth cohort.	New Zealand	Cohorte	18 [a]
Sutterland *et al*. [24], 2015	Beyond the association. *Toxoplasma gondii* in schizophrenia, bipolar disorder, and addiction: Systematic review and meta-analysis.	Several [5]	MA	26 [b]
Yolken *et al*. [20], 2017	Evidence of increased exposure to *Toxoplasma gondii* in individuals with recent onset psychosis but not with established schizophrenia.	USA	C-C	16 [a]

C-C, case-control; MA, meta-analysis; C-S, Cross-Sectional; ADHD, Attention Deficit Hyperactivity Disorder; TLR2, Toll Like Receptor 2.

[a] assessed with the STROBE scale (maximum 22 points).

[b] assessed with the PRISMA scale (maximum 27 points).

[1] Turkey, Saudi Arabia, Iran, China, USA, Mexico and Czech Republic.

[2] USA, Mexico, Finland, Germany, Austria, UK, Czech Republic, Iran, Turkey, Saudi Arabia, China, Egypt and New Zealand.

[3] USA, Cuba, France, Germany, Denmark, Iran and Ethiopia.

[4] USA, Mexico, Turkey, Denmark.

[5] USA, Mexico, Brazil, Peru, Germany, Czech Republic, Denmark, Ireland, France, Spain, Sweden, Iran, Turkey, China, South Korea, Malaysia, Vietnam, Egypt and Ethiopia.

Table 2. Summary of studies conducted in children and adolescents.

Child and Adolescent Studies	Individuals Included (% HIV-positive)			Childhood, juvenile, adolescent onset disorder	OCD	Depression	Anxiety
	Patients	Controls	*p*-value				
Akaltun *et al.* [14], 2018a	OCD 60 (35%) Anxiety 60 (32%)	60 (10%)	**0.0001** **0.0001**		**4.85 (1.79–3.13)**		**4.17 (1.53–11.38)**
Akaltun *et al.* [16], 2018b	Tourette 43 (37%) Tics 87 (31%)	130 (9%)	**0.001**	**Tourette 5.83 ($p < 0.001$)** **Tics* 4.43 ($p < 0.001$)**			
Celik *et al.* [15], 2015	65 (28%)	65 (5%)	**0.005**	**Stammer 7.91 (2.2–28.5)**			
Sapmaz *et al.* [13], 2019	37 (22%)	36 (6%)	**0.046**			**4.68 (0.97–33.88)**	
Akaltun *et al.* [19], 2019	107 (7%)	107 (3%)	0.235	Hyperactivity OR not available			
Miman *et al.* [18], 2018	55 (22%)	59 (15%)	0.63		OR not available		
Esnafoglu *et al.* [17], 2017	102 (3%)	51 (2%)	0.593	Autism OR not available			

Statistically significant results are highlighted in bold ($p < 0.05$). The table shows the Odds ratio (ORs) with confidence intervals or the *p*-value in the boxes for each disorder. * Tics were motor and vocal. HIV, human immunodeficiency virus; OCD, obsessive-compulsive disorder.

Table 3. Summary of studies conducted in adults.

Adult Studies	Individuals Included (% HIV-positive)			Various disorders	Schizophrenia	Bipolar Disorder	OCD	Depression	Other
	Patients	Controls	*p*-value						
Sutterland *et al.* [24], 2015	12,009	71,441 (24%)	**Significant**	Yes	**1.81 (1.51–2.16)**	**1.52 (1.06–2.18)**	**3.4 (1.73–6.68)**	1.21 (0.8–1.70)	X
Yolken *et al.* [20], 2017	1481 (10%)	571 (6%)	**0.017**	Yes	**2.44 (PIR) (1.36–4.38)** **1.91 [a] (1.28–2.93)**	**1.9 [a] (1.23–3.07)**		1.3 [a] (0.44–3.26)	
Cong *et al.* [21], 2015	445 (18%)	445 (12%)	**0.038**	Yes	**3.39 [a] (1.51–7.26)**		2.25 [a] (0.86–5.39)	0.59 [a] (0.14–1.8)	X
Del Grande *et al.* [25], 2020	101 (28%)	0	>0.4	X	X	X		X	
Sugden *et al.* [26], 2016	837 (28%)		Not significant	Yes	1.31 (0.55–3.12)			1.01 (0.66–1.54)	X
Stepanova *et al.* [27], 2019	155 (40%)	152 (25%)	**0.007**		**1.93 (1.16–3.23)**				
Fond *et al.* [28], 2018	250 (74%)	0	**<0.05**		**3 [b]**				
Gutiérrez-Fernández *et al.* [8], 2015	767 (36%) 142 (39%)	1714 (15%) 142 (20%)	**0.001**		**2.5 (1.40–4.47)**				
Hamdani *et al.* [22], 2015	42 (88%)	36 (53%)	**0.005**			**6.45 [a] (2.12–22.28)**			
Oliveira *et al.* [23], 2016	138 (75%)	167 (58%)	**0.002**			**1.77 (1.00–3.11)**			
de Barros *et al.* [30], 2017	797 (54%)	8090 (18%)	**0.0004**			**1.27 (1.08–1.47)**			
Chegeni *et al.* [7], 2019a	389 (26%)	9484 (17%)	**Significant**				**1.96 (1.32–2.90)**		
Chegeni *et al.* [29], 2019b	4964 (20%)	18,654 (18%)	Not significant					1.15 (0.95–1.39)	

Statistically significant results are highlighted in bold ($p < 0.05$). In the columns for diseases, the ORs with confidence intervals are showed. [a] calculated with the OpenEpi program using the data indicated in the article; [b] value indicated by the authors without reference values.

lences of 15 to 24% in the control groups. However, in almost all patient groups the seroprevalence increased notably (see Fig. 2).

Some studies included patients with different pathologies. Of these, the meta-analysis carried out by Sutterland *et al*. [24] analyzed the association between infection and mental disorders in groups of patients and control groups from different countries, observing a significantly higher seroprevalence in patients compared to the control group. Similar results are observed in case-control studies carried out in USA [20] and in China [21]. However, the cross-sectional study carried out in Italy [25] and the cohort study performed in New Zealand [26] did not find significant differences in seroprevalence between patients and controls.

All these studies involved patients suffering from schizophrenia, bipolar disorder, obsessive-compulsive disorder, and depression, and others (addictions, behavioral disorders, suicide...). The most common disorder was schizophrenia, although in the Italian cross-sectional study [25] patients with bipolar disorder were the most numerous, since the study center was a reference hospital for this condition.

These results are similar to those reported by Bisetegn *et al*. [31] in the systematic review and meta-analysis they conducted in 2023. In that review authors observed a higher IgG seroprevalence of *T. gondii* among neuropsychiatric patients (38%) compared to control subjects (25%). In addition, they observed a higher IgG prevalence in men than in women (17.5% vs. 12.4%, respectively).

Analyzing the different disorders separately, schizophrenia is the pathology that has been studied the most in relation to this parasitosis, which is why it is the one on which the most articles have been found, mostly describing a statistically significant relationship with the infection, identifying toxoplasmosis as a risk factor for schizophrenia.

In 2015, Gutiérrez-Fernández *et al*. [8] carried out a meta-analysis and a case-control study in Andalusia (Spain), finding in both a significant association between the presence of antibodies and the disease. Similar results are described in a Russian case-control study [27] and in a French cross-sectional study [28]. This relationship was also observed in the subgroups of schizophrenic patients within the aforementioned studies that included other psychiatric pathologies [20,21,24], being particularly striking the increase in odds ratio (OR) in patients with recent onset psychosis compared to schizophrenics in an advanced stage of the disease [20]. Other relatively high ORs are observed in studies from Spain [8], China [21] or France [28] (OR 2.5; 3.39 and 3 respectively). Similar results are showed in recent publications. For instance, Nessim *et al*. [32] observed a significant risk of schizophrenia in subjects with toxoplasmosis (OR = 2.39; 95% confidence interval CI 1.71–3.33). Rovira *et al*. [33] conducted a case-control study and also found a significant association between infection and schizophrenia, with an increased risk of this mental disorder in subjects with toxoplasmosis (OR = 2.5; 95% CI 1.47–4.23). However, not all studies show this association. Among the articles included in this systematic review, two of them failed to verify the association between schizophrenia and toxoplasmosis [25,26]. Likewise, other publications do not confirm the association. As the case-control study conducted by Ademe *et al*. [34], in which no significant differences were found in the prevalence of toxoplasmosis between subjects with schizophrenia and control subjects (87.2% vs 80.9%, $p = 0.398$).

Regarding bipolar disorder, several independent studies carried out in France show a significant relationship with infection. The study by Oliveira *et al*. [23] approaches the problem from a genetic point of view, finding a significant association between *T. gondii* infection and a polymorphism in the TLR2 gene. This polymorphism could modulate the association of the parasite with the pathology, although other environmental factors would be influencing it as well. Another study found a significant association between high expression of interleukin (IL)-6 and cognitive dysfunction, suggesting that the quantification of IL-6 could be used as a marker of this disorder [22]. However, the conclusions of this study should be interpreted with caution since, despite showing the highest OR (>6), the sample size of this study is small.

In the same way, studies that analyzed several psychiatric disorders simultaneously showed that patients with bipolar disorder had significantly higher seroprevalences than controls [22,23] (88–53%, $p = 0.005$; 75–58% $p = 0.002$). Only the study carried out in Italy [25] did not report significant differences.

Three studies found a significant positive correlation between obsessive-compulsive disorder and toxoplasmosis, with relatively high ORs [24] (>3). Two of these studies included other psychiatric pathologies [21,24], and one of them only OCD [7].

No study found an association between major depression and infection [20,21,24,26,29]. Nor were any statistically significant relationships observed between other psychiatric pathologies other than those mentioned and the protozoan [21,24,26].

In these studies, other factors have also been statistically analyzed to establish their possible influence on the presence of these pathologies.

The effect of gender has been determined in most articles since it could be related to these diseases, in many cases linked to a hormonal effect or predisposition to certain types of pathologies. However, studies on bipolar disorder [22], schizophrenia [27,28] and in studies that analyze various mental disorders [27,28] have not found significant differences by gender.

Age has not been statistically associated either [20, 28]. However, in bipolar disorder, a higher average age and significant differences in this regard were observed [22,23].

In schizophrenic patients [28], differences were observed related to the severity of the condition Positive and Negative Syndrome Scale (PANSS) subscores and a greater presence of certain specific symptoms, such as extrapyramidal symptoms, which were found associated with the negative syndrome of schizophrenia.

No differences were found in the education level [20, 22]. Only one study reported these differences [23], which should be confirmed by further research.

In a study carried out in China [21], the authors reported the influence of the presence of cats at homes and of the ingestion of raw or undercooked meat on the association between the level of antibodies and psychiatric patients.

Chegeni *et al*. [7] and Sutterland *et al*. [24] studied the Rhesus factor, finding a lower prevalence of depression and other psychiatric disorders in Rh-positive women.

The individual genetic characteristics that influence the presence of different disorders such as OCD or bipolar disorder [7,22] and the influence of the type of *T. gondii*, which in addition to presenting a different distribution depending on the geographical area, has been related to different pathogenicity. It seems that type I is more linked to the presence of psychotic affective disorders and types II and III, less related to psychiatric disorders [8,24,27].

Since the 1950s, the relationship between *T. gondii* and mental illness has been studied. However, some authors explain the higher seroprevalence found in psychiatric patients as a consequence of the cognitive loss and behavioural changes associated with these mental pathologies. Furthermore, they highlight that many of these patients came from low socioeconomic levels and lived with worse hygienic-sanitary conditions, which could explain the higher seroprevalence. This approach changed and, based on the advances made in different fields about the etiopathogenic mechanisms, *T. gondii* was once again considered the cause of these pathologies [27].

The etiopathogenic mechanism that links toxoplasmosis and the different mental diseases that have been described is complex and would include different processes connected with the presence of cysts, the reactivation of the parasite in certain situations, immune and inflammatory response, and direct and indirect action on different neurotransmitters. All together with other environmental and genetic factors would predispose to the described psychiatric disorders [13,23].

Brain lesions caused by the parasite or cysts in the cerebral hemispheres, hippocampus, amygdala, basal ganglia, cerebellum, cortex and brain stem can cause psychiatric symptoms and modify paracrine secretion, which would affect brain functions in the surrounding area [19, 29]. Likewise, cysts containing *T. gondii* are distributed in a wide variety of brain regions and can cause neurodegeneration [18].

Processes such as immune reactions, neuronal damage with changes in the hypothalamic-pituitary-adrenal axis, genetic interactions or hormonal dysfunctions have been related to the etiology of some mental disorders, like OCD, bipolar disorder, schizophrenia, anxiety and other behavioural disorders. All these processes also occur during toxoplasma infection [17]. Furthermore, there is evidence that infection with *T. gondii* has a greater impact on the hippocampus and amygdala [15]. A relationship has been observed with the synthesis of neurotransmitters such as dopamine and serotonin, also related to the other pathologies cited in this work (dopamine in Tourette, autism, hyperactivity, and serotonin in depression), combined impairment of dopaminergic regulation and presynaptic serotonergic with dopaminergic transmission dysfunction [17,19].

T. gondii infection has also been observed in cross-reactions with NMDA receptors that are involved in the onset and maintenance of schizophrenia, as well as disruption of neuronal circuits and cognitive deficits [28].

The parasite, particularly the virulent varieties (type I), produces hyaluronidases that facilitate its penetration [27] and in response to the damage caused to the tissue by the protozoan, astrocytes can be activated, which will increase the levels of intracerebral kynurenic acid, which produces toxicity. which acts by inhibiting glutamine and nicotine receptors [8]. Also, the release of T lymphocytes and natural killer cells, inflammatory cytokines, such as tumor necrosis factor (TNF)-alpha and interferon (IFN)-gamma, induce the

secretion of the enzyme indolamine, which activates tryptophan in the kynurenine pathway [24]. These changes would be related to deficits in tryptophan, serotonin and melatonin that would contribute to increasing cognitive dysfunction [13].

As mentioned, alterations in dopamine seem to be involved in processes linked to the presence of mental disorders. In relation to these dopaminergic alterations, involved in processes linked to the presence of mental disorders, the following has been observed:

- the parasite genome has two genes that encode two aromatic amino acid hydroxylase enzymes (tyrosine hydroxylase) that potentially would directly modulate the biosynthesis of dopamine and/or serotonin [13,15,16,18].

- brain cells with cysts contain high concentrations of dopamine, being observed *in vitro* that they in turn stimulate the production of high levels of dopamine [15,16].

- inflammatory cytokines that increase dopamine release (i.e., nitrogen monoxide, IL-2 and IL-6) are important in controlling *T. gondii* infection [22,30].

- it has been reported higher levels of testosterone in men with latent toxoplasmosis compared to control subjects, which could be due to a relationship between testosterone and dopamine release [19].

- dopamine-regulated functions in the prefrontal cortex are mediated by D1/D5 and D4 receptors. In mice, *T. gondii* infection leads to altered dopamine signalling and reduced expression of genes related to dopaminergic transmission, like Dopamine D1 Receptor (DRD1), Dopamine D1 Receptor 5 (DRD5) and Monoamine oxidase A(MAOA), which encode these dopamine receptors [26]. Furthermore, changes in hypersensitivity in postsynaptic D2 receptors, a decrease in D2 receptors in the left caudate nucleus, have been determined in patients [19].

- it has been observed that miR-132 expression increases with *T. gondii* infection, and that this increase could be associated with changes in dopamine receptor signalling [19].

Other immune reactions have been described relating toxoplasmosis to certain mental alterations [7,25]; these would occur in neurons in the areas of the caudate, putamen and globus pallidus that have been associated with disorders that influence movement, tics and OCD [14]. The arachidonate 12-lipoxygenase (ALOX12) gene, which encodes for arachidonate 12-lipoxygenase, has been associated with the immune response to *T. gondii* infection [28].

All this information on pathophysiological mechanisms involved in some way with mental disorders seems to confirm the association of infection and these disorders in the adult population, since the etiopathogenic mechanisms of several of these diseases are referable to the effects of the parasite on the central nervous system, caused by changes in neurotransmitters and immune-mediated responses. Similar observations have been reported by different authors relating *T. gondii* to schizophrenia [35], bipolar disorder and other mood disorders, in addition to schizophrenia [36] or obsessive-compulsive disorder [37].

As is the case with studies carried out on young people and adolescents, the presence of various selection biases is intuited in case-control studies and publication biases in meta-analyses. It is no coincidence that in the assessments of methodological quality the essential points that refer to the eligibility, representativeness and bias criteria obtain a lower score in general although they meet all the other items. In general, meta-analysis articles have received better score.

Regarding the current situation, it seems that the prevalence has been reduced in recent years due to better hygienic-sanitary measures [3]. In a study carried out in Spain, the seroprevalence was 20% in the control group [8]. The incidence of congenital toxoplasmosis in Spain is also lower than in Europe, but integrated surveillance in animals and food is scarce and disorganized.

Some authors indicate that it is necessary to take more drastic measures to control this zoonosis. Some of these measures could be limiting cats' access to certain environments, sampling soils for oocysts, improving food detection techniques [38], and proposing systematic diagnosis and preventive treatment against *T. gondii* in all patients with mental problems [39]. However, to improve control without the need for large investments, it would be very useful to extend the simple prevention measures currently applied to risk groups, since no one is exempt from experiencing situations of immunosuppression throughout their life.

The greatest limitation of this review has been the breadth of the argument and the heterogeneity of the articles included, in terms of their content.

If we analyze the scores on the methodological quality of observational studies, a large gap is determined with regard to eligibility criteria, representativeness of the samples, and biases and measures to address them. Other limitations of this type have also been found in meta-analysis articles and have been described by the same authors.

The parameter that was evaluated in all articles was IgG, using different techniques. However, no reference methods or characteristics of the techniques (in terms of sensitivity or specificity) were mentioned. Nevertheless, to find a relationship between latent forms of toxoplasmosis and mental illness, the measurement of IgG may not be a good indicator to obtain enlightening results since, in theory, these antibodies last throughout life, do not provide information about the presence of cysts or when the infection occurred and do not allow it to be related to the onset of mental illnesses.

It was also missing many details that could have been useful and important, such as the seroprevalence in the geographical areas that served as a reference, the quantification of antibody titres, the varieties isolated or most present in the areas in order to relate them to pathogenicity, information about patients (Rhesus factor (Rh), genetic predisposition, phase of the disease), treatment used (Treatment with anti-toxoplasmic activity (TATA+ drugs) or whether they had other pathologies.

As a prospective approach, it arises the need to better understand the interactions responsible for the multifactorial etiology of mental disorders, whether genetic, environmental or infectious.

In the particular case of toxoplasmosis, further studies more complete, more representative and that provide more information are necessary as well. Also, it would be interesting studies with markers that can better correlate toxoplasmosis with the onset of a mental disorder and integrating other predisposing factors.

Regarding control and prevention of the infection, hygiene, hand washing, and the consumption of correctly washed and cooked food should be promoted in all groups of people, just as risk groups do. In this way, the incidence of infection would be significantly reduced.

Other necessary measures would be the increase of integrated surveillance in animals and food, which involves the consolidation of communication systems already designed, and improvement of diagnostic techniques in food.

In the case of cats, it would be appropriate to perform detection tests on animals that have access to open areas or those that live in communities in order to control the excretion of carrier animals and to prevent infection in cats, humans or other intermediate hosts.

Conclusions

Based on the analyzed studies, it cannot be established a clear relationship between toxoplasmosis and the presence of mental disorders in young people and children. In adults, the relationship between *T. gondii* and certain pathologies such as schizophrenia, bipolar disorder and obsessive-compulsive disorder could be justified by the effect of the parasite, its forms of resistance, the immune response, and the alteration of neurotransmitters (mainly dopamine) which occurs and shares pathogenic mechanisms with this type of diseases. This association has not been demonstrated in major depression.

Neuropsychiatric disorders derive from the interaction between environmental, individual, genetic and immune factors, and also from epigenetic modifications. Therefore, further studies are necessary to verify these processes.

Despite its high prevalence, toxoplasmosis is an almost forgotten parasitosis, since prevention measures are only applied in risk groups and there are no specific standards developed on surveillance in animals and foods, which makes it necessary to improve the strategies for prevention and control.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

Author Contributions

LBP and VZ designed the research study. LBP performed the research. LBP and VZ carried out the assessment of the methodological quality of the preselected articles. VZ improved the discussion and reviewed the document. Both authors contributed to editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.62641/aep.v52i2.1658.

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