

Does *Toxoplasma. gondii* related to Schizophrenic symptoms? A Narrative Systematic review.

A dissertation submitted to University of Manchester for MSc degree in Faculty of Biology.

Abstract:

Background: Accumulating evidence associated infectious agents with schizophrenia. Majority of these studies analyzed *Toxoplasma. gondii* association with schizophrenia.

Aims and objectives: the present study aimed to perform systematic search on studies conducted on investigating association between *T. gondii* and schizophrenia using IgG antibodies against *T. gondii*. Secondary objective was to discuss possible mechanisms by which *T. gondii* linked to schizophrenia.

Methods: Systematic search performed using Google Scholar, PubMed, Web of Science and University of Manchester databases. Key words Schizo* AND Toxoplasm* used to find articles published from years 2010-2020, used IgG antibodies against *T. gondii*, and patients participated in these studies definitively diagnosed with schizophrenia using DSM-IV or ICD- 10.

Result: Total of 122 articles was identified after duplicated were removed, of these 24 were included in review. Two-third of studies found that schizophrenic patients had significantly higher IgG antibodies versus controls.

Conclusion: These findings suggest that *T. gondii* is associated with schizophrenia and that *T. gondii* might be risk factor for schizophrenia development. If causative link is ascertained, then it would be possible to treat and prevent schizophrenia.

1-Introduction:

Behavioral and psychiatric disorders significantly affect public health since they frequently occur and affect 10-16% of the community world-wide (Demyttenaere et al, 2004; Wang et al, 2007a). They are not only associated with increased levels of individual's distress, premature mortality, and disability, but also lead to a substantial increase in costs related to lost productivity and utilization of health services. These diseases constitute 12% of the global disease burden (World Health Organisation, 2001).

1.1. Schizophrenia:

1.1.1 : Definition and Burden:

Schizophrenia is a serious neuropsychiatric disorder of unknown origin (Cetinkaya et al, 2007), which affects approximately fifty million individuals worldwide. The disease burden on the economy, either directly or indirectly. The direct impact of the disease constitutes 1.5-3% of the total national healthcare budget worldwide, which includes hospitalization, medications, procedures, diagnosis and prolonged care services (Nicholl et al, 2010), whereas the indirect burden includes increased premature mortality rates as a result of suicide and unemployment rates and reduced productivity in the workplace. The disease's indirect burden exceeds those of direct costs by 20% (Goeree et al, 2005; Chang et al, 2008).

1.1.2 : Symptoms and Clinical Manifestation:

Schizophrenia onset times differ between males and females. In females, disease onset usually begins in late adolescence to middle adulthood, while in men disease onset usually develops earlier (Hafner et al, 1993). The disease is characterized by two types of symptoms: negative and positive. Positive symptoms manifest as hallucinations, delusions and unusual motor behaviors with different severity grades, whereas negative symptoms are presented as a reduction in emotion expression, induction of goal-directed behavior and hostile thinking style to the people. In addition, avolition and anhedonia are present in some patients. Cognitive symptoms occur and are grouped as a third category. These symptoms include disorganized thought, speech, and potentially attention, eventually debilitating a person's capability to communicate (Patel et al, 2014).

1.1.3 Risk Factors:

Unfortunately, until now no causative agent discovered in relation to schizophrenia, however, there are some risk factors that play role in causing disease. These include: abnormalities in neurons development, genetic susceptibility, and environmental associated factors (Fuglewicz et al, 2017). Pathogens as cytomegalovirus, *Herpes simplex* virus, influenza virus, and *Toxoplasma. gondii*, contribute in causation of some behavioral and psychiatric disorders. Many studies focused on schizophrenia association with *T. gondii* infection (Park et al, 2012).

1.2. *Toxoplasma. gondii* (*T. gondii*):

1.2.1 Definition and Background:

T. gondii is commonest protozoan parasite that belongs to Apicomplexa phylum, a phylum that contains 5000 species. Only minority of species (e.g. *Plasmodium* spp. and *Cryptosporidium* spp.) responsible for causing disease in humans (Xiao and Yolken, 2015). Parasite is categorized into three major genotypes, which vary in their virulence characteristics and distribution (epidemiology). For instance, type I strain is highly virulent in mice and commonly found in patients with ocular toxoplasmosis (Dalimi and Abdoli, 2012). Both type II and III strains are not virulent in mice, but frequently involved in human infections in Europe and North America, although type III is less frequent than type II (Maubon et al, 2008). Type I and II involved in congenital diseases and HIV patients (Ajzenberg et al, 2002; Khan et al, 2005).

1.2.2. Prevalence:

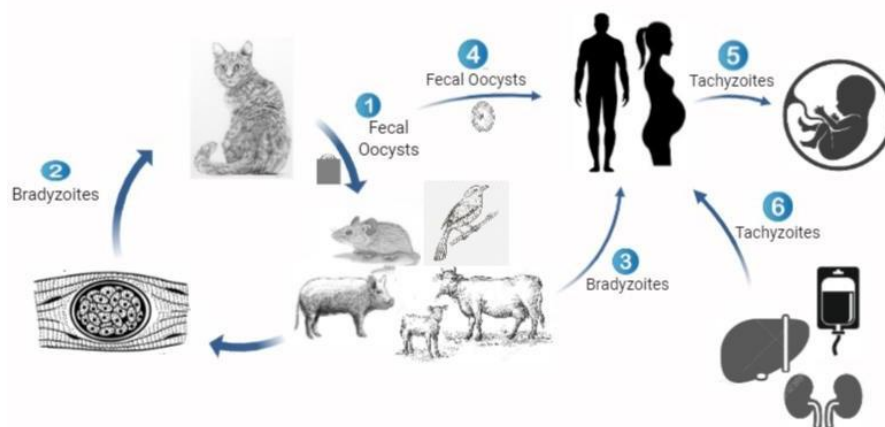
T. gondii infection is widely distributed and approximately one third of world's population infected with *Toxoplasma* (Fekadu et al, 2010). Disease incidence differs depending on weather, hygienic and nutritional habits and geographical area (Fuglewicz et al, 2017). Antibodies prevalence to *T. gondii* in London was 22%. In New York City prevalence achieved 32% (Esshili et al, 2016). While prevalence in France reached 84% that explained by French people's nutritional habits, as they frequently consume lightly-cooked meat (Hill et al, 2005).

Life cycle of *T. gondii*:

T. gondii life cycle characterized by its complexity and heterogenicity; with members of feline family (e.g. domestic cat) as primary hosts, and all warm-blooded animals including humans acting as secondary hosts (Da- Silva et al, 2009). Parasite has three infectious stages; resistant and immature form oocyst, which shed in felines feces;

bradyzoites; slow replicating form of parasite, which generates during chronic infection and localized in tissue cysts; and finally tachyzoites; rapidly replicating form that occurs during acute infection and excreted in all body fluids (Tenter et al, 2000):

These different stages vary in their resistance to environmental conditions. Tachyzoite is most sensitive form to extreme environmental condition as temperature, high salt and proteolytic enzymes (e.g. pepsin found in GIT of both secondary and primary host). Because of this high sensitivity, they rarely survive outside host and hence, they are of less concern epidemiologically except for vertical transmission (mother to baby) (Tenter et al, 2000). Bradyzoites resist effect of proteolytic enzymes and survive in this environment more than tachyzoites (Dubey et al, 1998). They remain infectious for approximately three weeks even with environmental changes like heating or freezing (Tenter et al, 2000). Regarding oocysts, this stage considered highly resistant as it can survive in dehydration and cold and remain infectious in humid sand or soil for one and half year (Tenter et al, 2000). These three stages linked together in complex life cycle shown in Figure 1, including transmitted mode to human.



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Figure 1. *T. gondii* life cycle and transmission to human.

Definitive hosts of *T. gondii* are felines as domestic cats (Jackson and Hutchison, 1989). Parasite was reproduced sexually only in felines, who shed infectious oocyte into environment (Yolken et al, 2017). 1) Oocyte contaminates food stuffs e.g. grass of other warm-blooded animal act as intermediate hosts (Tenter, 2000). When intermediate host ingests oocyst, *T. gondii* initiates two stages of asexual reproduction. Primary stage (tachyzoites) replicates rapidly by frequent endogeny in all body cells. Once immune system starts to suppress infection, final generation of tachyzoites

generates second stage of asexual reproduction, which results in tissue cysts generation. In tissue cysts, cystozoites or bradyzoites replicate slowly by endodyogeny (Jackson and Hutchison, 1989; Dubey et al, 1998). Tissue cysts increased tropism to muscular and neural tissues.

They are mainly found in eyes, CNS and skeletal and cardiac muscles; however, they may locate in kidney, lung and liver, but less common (Dubey et al, 1998). Tissue cysts remain infectious and persist for life-span of intermediate hosts (Tenter, 2000). 2) Cats can be infected by eating prey animal whose tissues contain *T. gondii* cysts. Once cat infected by tissue cysts, bradyzoites undergo asexual dissemination which consist of many stages of endopolygeny in feline's small intestine. Final stages of this dissemination create sexual life cycle replication phase. Oocysts and gamogony also formed in small intestine epithelium. Unsporulated oocysts discharged into intestinal lumen and excreted into environment via cat feces. Sporogony happens in environment and result in infectious oocysts formation which possess 2 sporocysts and four sporozoites in each (Jackson and Hutchison, 1989; Dubey et al, 1998). Not only bradyzoites cause infection to cats, but also tachyzoites and oocysts. Successful infection rate is not as high as with bradyzoite cysts (Dubey et al, 1998). While in humans, *T. gondii* infection acquired via four routes: 3) by ingesting meat from cattle, pigs, sheep or poultry whose tissues contain bradyzoites cysts. 4) by ingesting oocysts after handling cat feces or materials contaminated with cat feces. 5) from mother to baby via placenta if mother infected with *T. gondii* during pregnancy (by tachyzoites stage) (Yolken et al, 2017). 6) by organ transplantation where *T. gondii* can be in form of tachyzoites or bradyzoites. *T. gondii* transmission in tachyzoites form occurs during blood transfusion. Infection chances via this route are rare and occur mainly if blood donor has acute infection (Tenter et al, 2000).

1.2.3. Prevalence of different infection routes in human:

Both ingesting sporulated oocysts after handling cat feces and ingesting lightly-cooked meat from cattle and pigs are common infection routes in human. Determining major infection route differs among human population with diverse eating, cultural habits and climate conditions (Cook et al, 2000). In Poland, ingesting lightly-cooked meat containing bradyzoites identified as major infection source, nearly 80% of live stocks reported as *T. gondii* seropositive (Flegr et al, 2014a). In some parts of Brazil, weather conditions (warmth and humidity) enhance long-term oocysts survival and most people live in low-socioeconomic status (Yan et al, 2016), ingesting oocysts largely attributed for most cases (Bahia- Oliveira et al, 2003).

1.2.4. *T. gondii* infection in human:

Primary *T. gondii* infection in healthy individuals is subclinical in >80% of individuals, and in remaining 20%, only transient symptoms seen. However, infection is more severe in immunocompromised patients who experience

neuropsychiatric symptoms (e.g. schizophrenic psychosis, depression, anxiety, and disorientation) (Fabiani et al, 2013).

Chronic infection result in behavioral and personality disorders (Fabiani et al, 2013), decline in psychomotor performance and intelligence quotient (Flegr et al, 2003; Havlicek et al, 2001; Fabiani et al, 2013), and mental health problems development (e.g. parkinsonian manifestations, schizophrenia, schizophrenia-spectrum disorder) in persons with genetic susceptibility to these disorders (Fabiani et al, 2013). Many studies performed to discover etiopathogenetic relationship between these disorders and *T. gondii* (Fabiani et al, 2013). Most common method used higher titers of anti-*T. gondii* antibodies in schizophrenic patients versus controls (Del Grande et al, 2017). Although some investigations revealed association, others did not find. It is still debatable whether *T. gondii* causes schizophrenia or behavioral changes caused by disease favored *T. gondii* acquisition (Sutterland et al, 2015).

Primary objective of the present study was to evaluate association between schizophrenia and *T. gondii* by performing systematic search on studies conducted in last ten years (2010-2020). Second objective was to discuss possible mechanisms by which *T. gondii* linked to schizophrenia.

2- Materials and Methods:

Studies included:

Databases

Studies that investigated association of *T. gondii* with schizophrenia were retrieved using PubMed, Google Scholar, Web of Science, and University of Manchester Library databases. Key words used were Toxoplasma* and Schizo*. Title and abstract of articles were examined and selection made based on inclusion/ exclusion criteria. Additionally, reference lists of reviews and retrieved articles were screened and relevant articles were cross-referenced. Only 24 studies were included in the study.

3. Procedure

The total 24 research articles that met inclusion criteria were subjected to the review study. Firstly, it was identified 122 articles after duplicates removed. Of these 32 were reviews. Title and abstract of remaining 90 articles screened and 49 were assessed for eligibility. In total, articles number that met all bellow- mentioned criteria were 24. Flow chart (PRISMA.

<http://www.prisma-statement.org/>) presenting information through different stages of systematic review was shown in Figure 2.

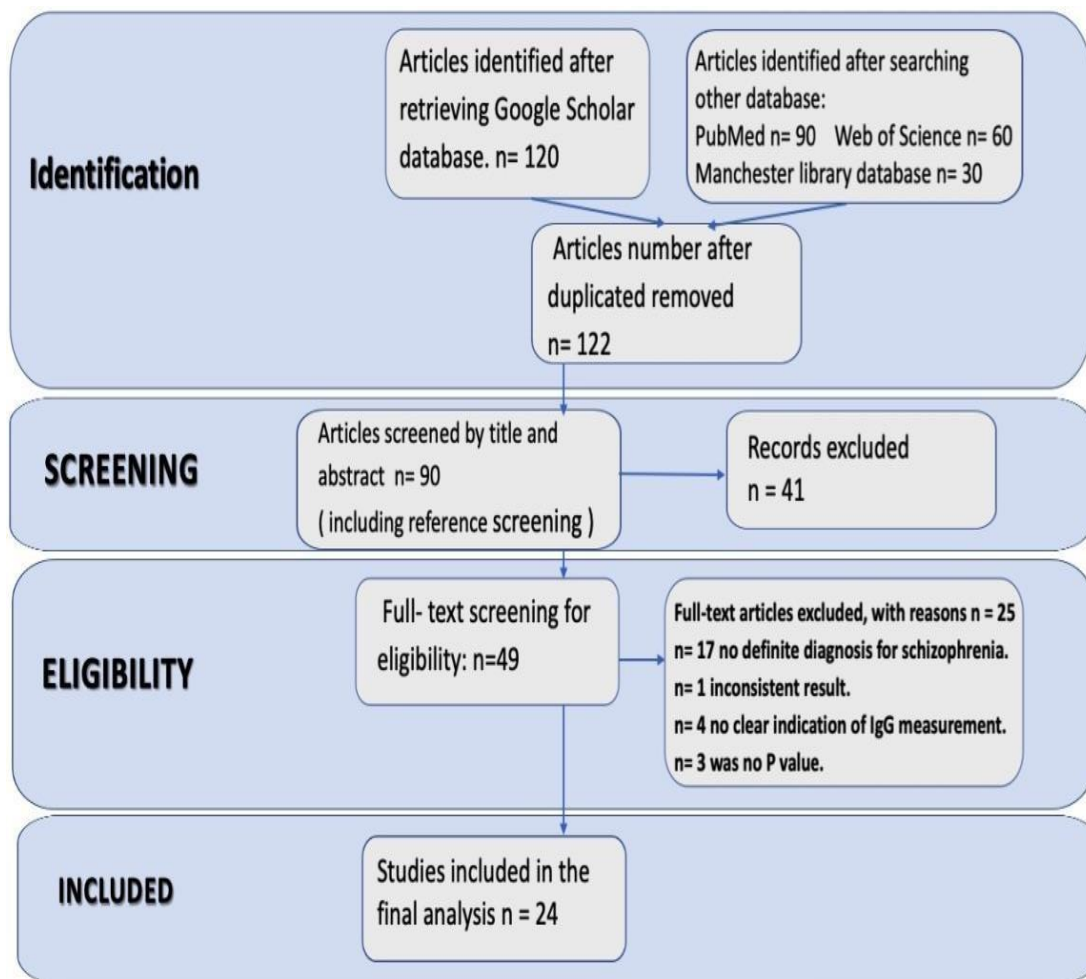


Figure 2. Flow chart Prisma for strategies used for articles selections including list of references screening. adapted from Moher et al (2009).

3.1 Inclusion/ exclusion criteria:

Inclusion criteria were; case- control study, primary research, published in English, published in last ten years (2010 to 2020), cases in studies definitely diagnosed by schizophrenia according to DSM-IV or ICD-10 criteria, specifically examining association of *T. gondii* with schizophrenia, included measurement of anti- *T. gondii* IgG antibodies titer rather than IgM antibodies as IgM antibodies affected by presence of high IgG level, which leads to false-negative results. Rheumatoid factors existence influences IgM titers, resulting in false-positive results (Filice et al, 1983), Presence of statistical comparison between control and schizophrenia.

Exclusion criteria

Exclusion criteria were; review articles, articles that are not completed (e.g. letter to editor), maternal or neonatal studies, animal studies (but these referred to in discussion sections), cohort studies, studies investigating effects of *T. gondii* seropositivity on schizophrenic patients without controls, studies measured risk ratio of schizophrenia development.

4- Results:

Twenty-four studies included in this report summarized in Table 1. They carried out in different countries with most being in Iran (n=4), Malaysia (n=3), Turkey (n=3), Germany (n=2), Egypt (n=2), Brazil (n= 2), and one for each; Nigeria, Spain, Korea, Saudi Arabia, Tunisia, Mexican, Iraqi Kurdistan and Lebanon.

Table 1. Summary of reviewed studies.

Author/ Year	City	Patients number	Controls number	Mean age of patients	Mean age of controls	Schizophrenia Diagnosis	Patients number with IgG+	Controls number with IgG+
Al- Hussainy et al (2015) *	Saudi Arabia	63	55	NA	NA	DSM-5	20 (31.57 %)	8 (14.55 %)
Esshili et al (2016)*	Tunisia	246	117	40.5	38.6	DSM-5	184 (74. 8%)	63 (53.8 %)
Emelia et al (2012)	Malaysia	144	144	NA	NA	DSM-IV	54 (37.5 %)	49 (34.0 %)
De Campos- Carli et al (2017)	Brazil	40	48	40.21	40.62	DSM-IV	27 (56.25%)	22 (56.41%)
Alvarado- Esquivel et al (2011)*	Mexican	50	150	45.12	45.1	ICD-10	10 (20%)	8 (5.3 %)
Hamidinejat et al (2010)*	Iran	98	48	33	33	DSM-IV	56 (57.14%)	14 (29.2%)
Bakre et al (2015)*	Erbil	93	93	34	34	DSM-IV	30 (32.3 %)	4 (4.3%)
El- Sayed et al (2012)*	Egypt	60	30	38	37.76	DSM-IV	34 (56.7 %)	6 (30 %)
Alipour et al (2011)*	Iran	62	62	37.54	37.24	DSM-IV	42 (67.7%)	23 (37.1%)
Juanah et al (2013)*	Malaysia	88	88	39.42	39.42	DSM-IV	45 (51%)	27 (30.7 %)
Park et al (2012)*	Korea	96	50	46.14	44.8	DSM-IV	21 (21.9%)	4 (8.0%)
Yuksel et al (2010)*	Turkey	300	150	42.6	42.6	DSM-IV	182 (60.7 %)	68 (45.3 %)
Karabulut et al (2015)	Turkey	85	60	41.73	40.45	DSM-IV	37 (43.5%)	26 (43.3%)
Omar et al (2015)*	Malaysia	101	55	41.1	45.3	DSM-IV	52 (51.5%)	10 (18.2 %)
Gutierrez- Fernandez et al (2015)*	Spain	143	143	28.69	30.42	ICD-10	56 (39.4 %)	29 (20.4%)
De- Witte et al (2015)	Germany	368	282	30.5	34.5	DSM-IV	68 (18.5 %)	50 (17.7%)
El- Mouhawess et al (2020)	Lebanon	150	150	56	58	DSM-IV	117 (79.1%)	74 (79.6 %)
Ansari- Lari (2017)*	Iran	99	152	40.3	40.6	DSM-IV	42 (42%)	
James et al (2013)*	Neigeria	140	140	28.2	29.1	mini international psychiatric interview based on DSM-IV	43 (30.7 %)	
Morais et al (2019)*	Brazil	34	85	40.6	35.9	DSM-IV	31 (91.18)	
Khademvatan et al (2014)	Iran	100	95	NA	NA	DSM-IV	34 (34%)	

El- Gebaly et al (2019)	Egypt	120	120	35.5	35.5	DSM-IV	54 (45 %)	
Kruase et al (2010)	Germany	31	30	36.7	33.7	DSM-IV	12 (38.70%)	
Cevizci et al (2015)	Turkey	30	60	NA	NA	DSM-IV	10 (33.3 %)	

NA= Not indicated

* P value indicates that difference of antibodies to *T. gondii* between controls and schizophrenic patients is statistically significant. Indicates that study used different method than Elisa for anti- *T. gondii* IgG antibodies detection. i.e. James et al used chromatogram immunoassay while Morais used chemiluminescence method.

5- Discussion:

This systematic review was carried to find studies that examined association between schizophrenia and *T. gondii* using IgG antibody titers, aiming to investigate whether there is an association between *T. gondii* and schizophrenia. Further, it aimed to discuss the nature of this association (whether *T.gondii* causes schizophrenia or behavior changes caused by schizophrenia increased the acquisition of *T. gondii*). As indicated in studies summarized in Table 1 that in most studies, there is an association between schizophrenia and *T. gondii*, with two thirds of studies indicated that schizophrenic patients were more likely to have anti- *T. gondii* IgG antibodies versus controls with statistically significant, *P* value ranging from $P=0.00006$ to <0.05 . This finding of reviewed studies consistent with other meta-analysis examining association between schizophrenia and *T. gondii*, that were out of current research scope, despite having some of studies from these meta-analyses in this review. Torrey et al (2007) reported in their meta-analysis that schizophrenic patients had higher seroprevalence of *T. gondii* seropositivity than controls with odd ratio 2.73, and 2.54 for first episodes. The meta-analysis covered 38 studies reported odds ratios of 2.71 (95% confidence interval (CI) 1.93-3.78), acknowledging relation between *T. gondii* and schizophrenia disorder (Torrey et al, 2012). Sutterland et al (2015) carried meta-analysis on 42 studies and found significant association between *T. gondii* and schizophrenia with odd ratio 1.81, $P<0.00001$. Taken together, current study and past meta-analyses point clearly to presence of association. Indeed, association between schizophrenia and *T. gondii* observed in many other study types, not only epidemiological studies. Studies summarized in two main categories; first category is association could be explained by *T. gondii* being risk factor for schizophrenic symptoms development, or alternatively schizophrenia might favor *T. gondii* acquisition via behavioral changes caused by schizophrenia.

Behavioral changes that *T. gondii* causes in infected individual observed clinically in schizophrenic patients, leading to hypothesis that *T. gondii* might proceed to schizophrenia. However, these findings comes from descriptive studies, not causative ones. There is a need

of the causative research dealing with DOPA release with the *T. gondii* infection.

Schizophrenia is multifactorial disease, and needs combination of both genetic and environmental factors explanations. *T. gondii* is important risk factor for its development in individuals with both genetic and environmental susceptibility (Flegr, 2015), and risk exceeded risk of any other human gene with $OR < 1.40$, as reported by genome-wide linkage study (Webster et al, 2010).

Improvement in both sensitivity and specificity of results needed to solve these differences. This achieved by conducting studies that uses IgG antibodies and PCR. Only few studies used both methods to investigate association.

Exposure to cats and eating lightly-cooked meat effects investigated only in few studies and significant effect on association was found. Research could be conducted on psychiatric outpatients with healthy controls in same area of residence or carrying out cohort studies using PCR and IgG antibodies to ascertain association.

Another question for future research is determining infection time as this would identify relation between schizophrenia and *T. gondii*. Niebuhr et al (2008) found association before schizophrenia onset, it was difficult to ascertain this association due to nature of military personnel's lifestyles that made them more exposed to *T. gondii* (Gutierrez- Fernandez et al, 2015). It would be interested to examine combination of antimicrobial effects of antipsychotic drugs with antiparasitic treatment. This might provide possible cure for disease.

Finally, prenatal infection with *T. gondii* results in severe consequences on fetus. Hence, determining exact mechanism by which *T. gondii* cause these consequences is point that needs further research.

6- Limitations:

There are two major limitations **for the present study**. First, review did not include studies that published in languages other than English, which could lessened methodology power. However, exclusion of these studies aimed to construct a replicable systematic search, which is regarded as gold standard. **Second** limitation was the limiting date of included studies to years 2010 to 2020. This could also affect methodology power. Nevertheless, this aimed to clearly indicate association between *T. gondii* and schizophrenia, as serological methods sensitivity improved during last ten years.

7- Conclusion:

Many epidemiological studies associated *T. gondii* with schizophrenia. However, other epidemiological studies did not find this association. So, it was difficult to confirm aetiopathogenesis association between *T. gondii* and schizophrenia. However, given that schizophrenia is multifactorial disease and not all schizophrenic patients infected with *T. gondii*, *T. gondii* identified as an important risk factor for schizophrenia development. Therefore, upcoming research should ascertain association between *T. gondii* and schizophrenia, to open up new perspective in treatment and prevention of this disease. It is vital to continue research on this area.

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Conflict of interest:

None

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