

# Assessing the Relationship Between Exposure to *Toxoplasma gondii* and the Development of Schizophrenia: Is There Really Something Up with Cat People?

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## Abstract

**Background:** Multiple studies have proposed a relationship between infection with the parasite *Toxoplasma gondii* (*T. gondii*) and the onset of schizophrenia. Humans are infected with this parasite via exposure to cat feces, ingesting contaminated food and water or through transplacental transmission. It is estimated that roughly 11% of the world population is infected with *Toxoplasma*<sup>1</sup>. Schizophrenia is a psychiatric disorder, and affects approximately 1.1% of the population over 18 years old worldwide<sup>2</sup>. We hypothesize that individuals infected with *Toxoplasma* may be at an increased risk of developing schizophrenia.

**Objective/Purpose:** To elucidate the relationship between exposure to *Toxoplasma gondii* and the development of schizophrenia.

**Methods:** Journals such as: Nature, Annals of General Psychiatry, The Journal of Psychoses and Related Disorders, Acta Psychiatrica Scandinavica, Infectious Diseases Society of America, Schizophrenia Research and The U.S. National Library of Medicine National Institutes of Health were used to collect information regarding exposure to *T. gondii* and the development of schizophrenia. Limits of our search involved language filters. Only English journals that contained our keywords: infection, schizophrenia and *Toxoplasma gondii*, were selected.

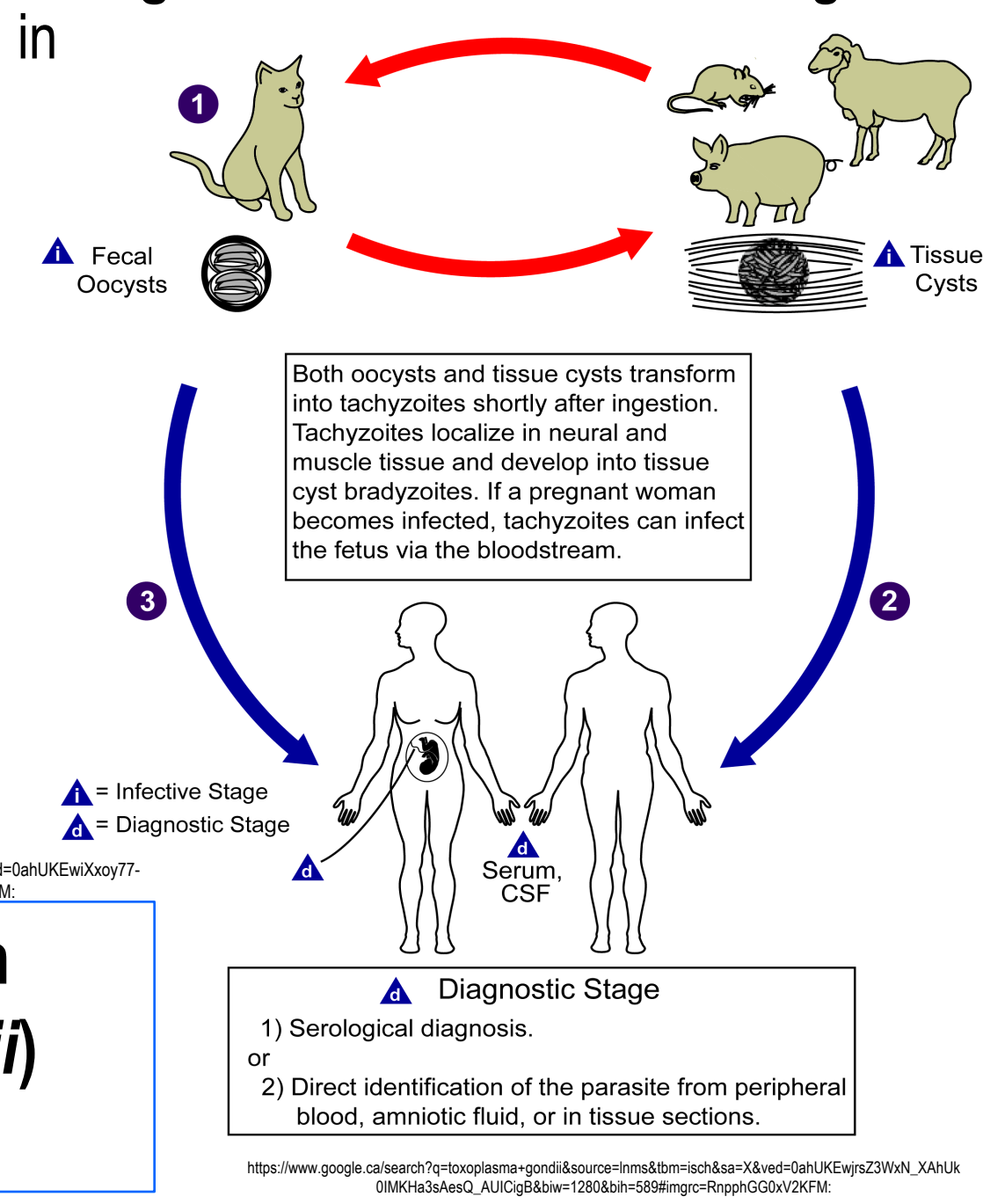
**Results:** 9 relevant studies were found. The type of reviews and study designs varied, including 2 meta-analysis, 4 case controls, 1 cross sectional analysis, 1 prospective cohort study and 1 narrative review. 8 of the 9 studies reported statistically significant data showing increased levels *T. gondii* in schizophrenic patients. P-values, chi-square, and odds ratio measures of association were used to determine statistical significance.

**Conclusion:** There is a growing body of data to indicate that *T. gondii* infection may be associated with the development of schizophrenia. Further study is needed to determine a concrete association between *T. gondii* infection and schizophrenia, as well as to elucidate the mechanism relating infection with *T. gondii* to the development of schizophrenia.

## Background

- Toxoplasma gondii* is a prevalent neurotropic parasite: 11% of world population<sup>1</sup>
  - In developing regions, it is estimated that 95% of the population may be infected with the parasite<sup>1</sup>
  - T. gondii* is transmitted through poor food and water, congenitally and cat feces<sup>1</sup> (Figure 1)
- Schizophrenia is a psychiatric disorder of unknown etiology, and affects approximately 1.1% of the world's population over 18 years old<sup>2</sup>
- It is proposed that genetic, as well as environmental factors may influence the onset of schizophrenia
- Increased levels of antibodies to neurotropic pathogens are found in multiple mental illness
- It has been postulated that *T. gondii* may confer a substantial environmental risk to the development of schizophrenia

Figure 1. Transmission of *T. gondii*



- Levels are measured by antibody titer
- Many studies have proposed a relationship between infection with the parasite *Toxoplasma gondii* (*T. gondii*) and the onset of schizophrenia.

## Research Question

Are individuals who are infected with *Toxoplasma gondii* at a significantly increased risk of developing schizophrenia?

## Methods

### Structured Literature Review (Figure 2)

#### Inclusion Criteria

- Humans
- Schizophrenia
- English
- Articles

#### Exclusion Criteria

- Other languages
- Non-article sources

#### Keywords:

- "*Toxoplasma gondii*"
- "Toxoplasmosis"
- "Antibodies"
- "Infection"

Figure 3. Study designs included in analysis

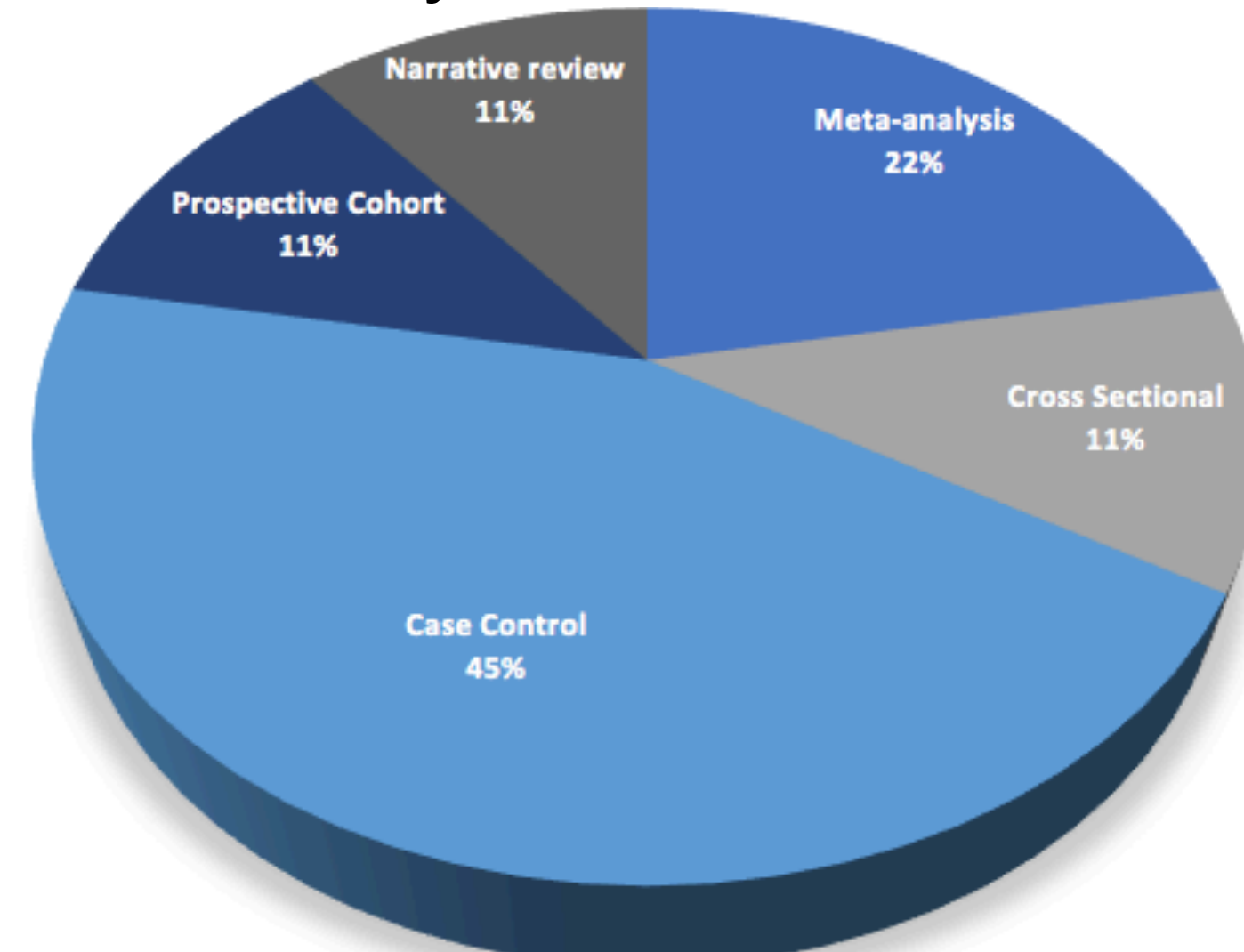
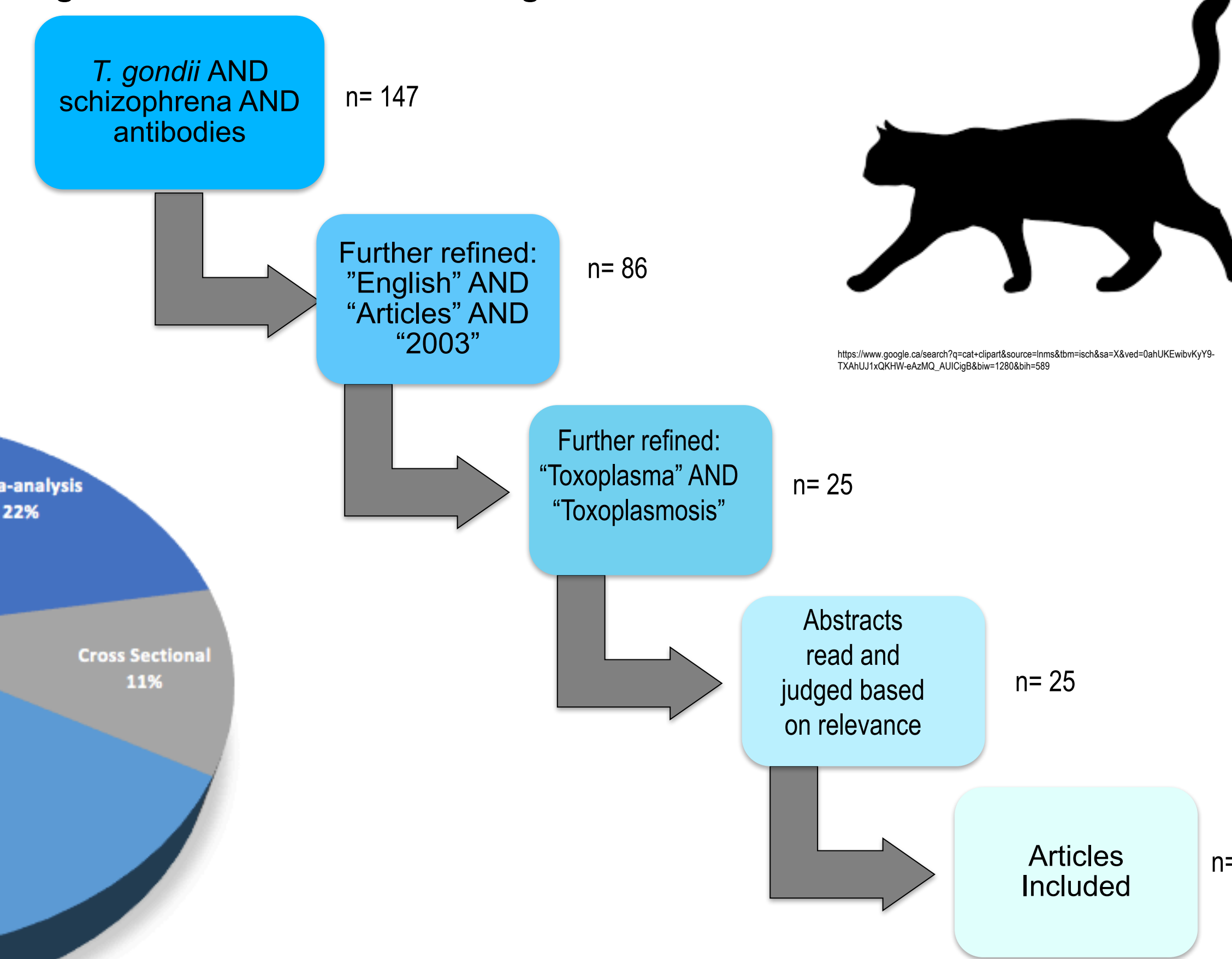


Figure 2. Flowchart describing literature review



## Results

Table 1. Summary of findings from literature review

Author	Study Design	Sample Size	Findings	Statistical Significance
Torrey, E. and Yolken, R. (2003)	Narrative review	n = 798	- <i>T. gondii</i> has high affinity for brain tissue (e.g. astrocytes, glia) - The infection is associated with early brain development resulting in disease pathogenesis - Higher exposure to cats in childhood among those with schizophrenia - <i>T. gondii</i> has affected levels of NTs known to be associated with schizophrenia - <i>T. gondii</i> should be considered in the etiological pathway for schizophrenia	N/A
Mokhtari, M. (2006)	Case-control	n = 460	- ELISA was used to measure IgG and IgM of <i>T. gondii</i> in schizophrenic and non-schizophrenic patients - Statistical significant differences were found between case and control groups	P < 0.05
Bartko, J. et. al. (2006)	Meta-analysis	n = 10 919	- Results indicated that people with schizophrenia have increased prevalence of antibodies to <i>T. gondii</i> - Consistent with animal studies	OR 2.73 p = 0.000001 (95% CI) 2.10 to 3.60 chi-square with 1 df 263
Sutherland, A. L. et. al. (2015)	Meta-analysis	n = 83 450	- Association between higher antibody titer and schizophrenia - Studied <i>T. gondii</i> presence in multiple psychiatric disorders but schizophrenia had greatest significance	OR 1.81 P < 0.00001
Yolken, R. H. et. al. (2001)	Case-control	n = 76	- Measured antibody serum samples of IgM, IgA and IgG - Higher levels of each immunoglobulin were found in cases than controls	p = 0.02 IgG p = 0.007 IgM
Holub, D. et. al. (2013)	Cross sectional	n = 251	- <i>T. gondii</i> infected schizophrenic patients showed more severe positive, disorganized and manic behaviour than <i>T. gondii</i> uninfected schizophrenics (measured on PANSS scale) - Negative correlation between PANSS scores and concentration of antibodies: cumulative effect of infection	p = 0.032 (95% CI)
Okusaga, O. et. al. (2011)	Prospective cohort study	n = 950	- Infection with <i>T. gondii</i> was associated with increased suicidal behaviour in schizophrenic patients under 38 years of age - Higher infection increased schizophrenic symptoms and suicide	p = 0.001 (95% CI)
Kannan, G. et. al. (2017)	Case-control cohort (human) Longitudinal cohort (mice)	n = 899 (humans) n = 41 (mice)	- <i>T. gondii</i> crossed blood brain barrier leading to infection in schizophrenic patients - Controls did not show similar autoantibodies against <i>T. gondii</i> - Increased infection lead to compromised NMDA-R immune response: proposed mechanism - Positive tests for NMDAR and pathogen antibodies lead to reduced scores on measures of cognition	p = 0.0001 (human) p = 0.04 (mice) (95% CI for both)
Mortensen, P. et. al. (2007)	Case-control	Potential cases consistence of all people born in 1981 or later who, as of October 1991, had been registered in the Danish Psychiatric Case Register	- Samples of those who were later diagnosed with schizophrenia had significantly higher levels than control subjects of IgG antibodies against <i>T. gondii</i> ; focused on early onset schizophrenia - Reported a relationship between <i>T. gondii</i> infection and early onset schizophrenia	p = 0.045 (95% CI) OR 1.79

## Discussion

- All articles supported the relationship
- Substantial evidence linked infection with *T. gondii* to the development of schizophrenia
  - Molecular evidence (i.e. affinity to brain tissue, antibody levels)
  - Cumulative effects (Holub et. al., 2013)
  - Statistically significant findings
- All studies analyzing antibodies (n=7) found that the prevalence of antibodies to *T. gondii* in individuals with schizophrenia is significantly higher than the prevalence of antibodies in control populations
  - Serological in nature and are not based on the direct detection
- Satisfactory evidence is provided which elucidates the pathophysiology and mechanism by which *T. gondii* contributes to the development of schizophrenia
  - May lead to novel treatments/new understanding of schizophrenia or other related disorders
- Schizophrenia has not been found to be unusually prevalent in these countries
- Several studies measured antibody levels subsequent to diagnosis

### Limitations

Future research should focus on the timing of the infection

However: only relationship provoking evidence was provided No RCT: ethical limitations

- Validity, Reliability, Sensitivity, Specificity Non-differential misclassification bias
- Schizophrenia is a complicated disease; no blood test
- Not everyone with schizophrenia can be diagnosed/identified

\*The diagnostic criteria for schizophrenia used in the United States (*Diagnostic and Statistical Manual of Mental Disorders*), Europe (*International Classification of Diseases*), and China (*Classification and Diagnostic Standards of Mental Disorders in China*) are very similar

- Undefined patient populations: in several studies the patient selection and how the patients were enrolled is not indicated
  - Mortensen et. al., (2007) focused on early onset schizophrenia (18 under)
- Association between schizophrenia and *T. gondii* reflects an underlying noncausal association schizophrenia and the exposure to *T. gondii* rather than a causal association

### Bias

- Reporting
- Foreign exclusion bias
- Ease of access
- Non-disclosure of patient selection
- Berkson's bias

## Conclusion

- Many causes of schizophrenia are hypothesized including a likely genetic component<sup>2</sup>
- Bradford Hill Criteria
  - Strength
  - Consistency
  - Specificity
  - Temporality
  - Biological gradient
  - Plausibility
  - Coherence
  - Experiment
  - Analogy
- There may be a latent period between initial infection and experience of symptoms making it difficult to prove causality<sup>1</sup>
- T. gondii* is highly prevalent in the general population<sup>1</sup>
  - reduces the strength of association between *T. gondii* being a causal factor for schizophrenia; however, etiology remains uncertain
  - No indication that schizophrenia incidence is narrowly linked to endemic variations in *T. gondii* infections
- Further study is needed to ascertain the relationship between *T. gondii* and the outcome of schizophrenia
- A double-blind randomized control trial would produce the most conclusive results however due to ethical issues it is unlikely this will occur

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