Antibodies to *Toxoplasma gondii* in Patients With Schizophrenia: A Meta-Analysis

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Recent studies have linked infectious agents to schizophrenia. The largest number of studies has involved the analysis of *Toxoplasma gondii*; these studies were subjected to a meta-analysis. Published articles and abstracts were identified by searches of MEDLINE, Ovid, and Google Scholar; by a search of Chinese publications; through letters to researchers; and by visiting China. Published and unpublished controlled studies that used serological methods for measuring *T. gondii* antibodies to assess inpatients and/or outpatients diagnosed with schizophrenia were selected for analysis, and source documents were translated as needed. Forty-two studies carried out in 17 countries over 5 decades were identified; 23 of these (6 unpublished) met selection criteria. The combined odds ratio (OR) was 2.73 (95% confidence interval, 2.10 to 3.60; chi-square with 1 *df* 263; *P* < .000001). Seven studies that included only patients with first-episode schizophrenia (OR 2.54) did not differ significantly from 16 studies that included patients in all clinical phases (OR 2.79). The results suggest that individuals with schizophrenia have an increased prevalence of antibodies to *T. gondii*. This association is consistent with other epidemiological studies as well as with animal studies. Although the OR of 2.73 is modest, it exceeds that for genetic or other environmental factors identified to date and suggests that *Toxoplasma* is in some way associated with a large number of cases of schizophrenia. If an etiological association can be proven, it would have implications for the design of measures for the prevention and treatment of this disease.

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Introduction

In 1896, the *Scientific American* published an article, "Is Insanity Due to a Microbe?," thereby initiating interest in a possible infectious etiology of schizophrenia. Interest in the hypothesis was widespread in the early years of the 20th century, then waned until the closing years of the century. Recent studies have linked schizophrenia with perinatal exposure to viruses such as influenza A virus,[1] rubellavirus,[2] herpes simplex virus type 2,[3] and polioviruses[4] and with postnatal exposure to viral and bacterial agents causing meningitis and encephalitis.[5] The largest number of studies linking an infectious agent to schizophrenia, however, has involved *Toxoplasma gondii*.

Toxoplasma gondii, a coccidian protozoa of the apicomplexa family, was first described in 1908. In 1939, it was linked to a congenital syndrome that includes deafness, retinal damage, seizures, mental retardation, and intracranial calcifications.[6] Postnatal transmission may produce lymphadenopathy and nonspecific symptoms of infection, but most cases are thought to be asymptomatic. The definitive hosts of this organism are cats and other felines. Transmission of *T. gondii* to humans may come about through ingestion or inhalation of oocysts shed by infected cats into litter boxes, gardens, sandboxes, or other children's play areas. The organism may also be transmitted through the ingestion of tissue cysts by the eating of undercooked meat containing tissue cysts from sheep, goats, or other animals that have been infected from cats.[7] The availability of serological assays has allowed for the testing of exposure to *T. gondii* in large numbers of individuals. Studies using these assays have indicated that *Toxoplasma* infection is widespread and varies in geographic regions and among individuals with different demographic characteristics.

Given *T. gondii*'s neurotropism and association with congenital brain dysfunction, there has been long-standing interest in investigating a possible association between exposure to this organism and the development of severe psychiatric disorders. The first study of *T. gondii* antibodies in psychiatric patients was published in 1953 by Kozar[8] in Poland. Since that time, 41 additional published and unpublished studies have been identified by the authors and were subjected to a meta-analysis

directed at defining the association between *Toxoplasma* exposure and the risk of schizophrenia.

Methods

Data Sources

Through previous analysis of several Eastern European and Chinese publications directed at the association between *Toxoplasma* antibodies and psychiatric disorders,[9] the authors were aware that many of the studies needed for a meta-analysis had been published in languages other than English. A keyword search of MEDLINE, Ovid, and Google Scholar found only 4 of the 34 published articles eventually identified. Most of the studies were identified through a survey of Chinese publications (Z.R. Lun, PhD, unpublished data, 2005), letters to Chinese and Eastern European researchers, a visit to China by two of us (EFT and RHY), and citations of earlier publications by those who published later. The earliest studies were published in Eastern Europe, and these studies were cited by the first researcher to carry out studies in China.[10,11]

Of the 42 studies ultimately identified, 35 were published and 7 were unpublished. Among those published, only 6 had been written in the English language. The studies were carried out between 1953 and 2005 in 17 countries: China (17); Germany (4); Australia, Bulgaria, Czechoslovakia, Italy, Mexico, and the United States (2 each); and Cuba, Egypt, Ireland, Korea, Peru, Poland, Russia, Spain, and Turkey (1 each).

The studies were translated as needed and then summarized regarding psychiatric diagnoses, control groups, and method of assessing exposure to *T. gondii*. It was decided to include in the meta-analysis only those studies that met the following criteria: (1) a clear diagnosis of schizophrenia, (2) inclusion of a defined control group, and (3) use of one of the following diagnostic assays: Sabin-Feldman dye test, complement fixation (CF), immune hemagglutination (IHA), immune fluorescence (IFA), or enzyme-linked immunosorbent assay (ELISA). 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.

In one study, antibodies were assessed serologically using both the dye test and CF.[12] Because studies can be counted only once in a meta-analysis because analysis is based on the assumptions of independence, we utilized the results of the assay that showed the smaller difference between cases and controls.

Statistical Methods

The data summarized by meta-analysis in this report originate from a series of classic two-group, binary-event studies. For our study, we are looking at the exposure rate of positive *T. gondii* antibodies in individuals with a diagnosis of schizophrenia versus a group of controls without that diagnosis. The results of each study are reported in a classic two-by-two contingency table. The proportion of infected individuals in each group is denoted by p_t and p_c, respectively, for the exposed group (t), and the control group (c).

For two-by-two binary-event studies, the statistic summarized is the odds ratio (OR), defined as $[p_t/(1 - p_t)]/[p_c(1 - p_c)]$. An OR of unity implies no difference between the two groups. An OR of two, for example, implies that the numerator group is at a twice higher risk than the denominator group. The graphics in this report present the OR and the length of the confidence interval (CI) for each study as well as the combined results. The software program NCSS (*NCSS Statistical System for Windows*, Kaysville, UT: Number Cruncher Statistical Systems, 2004) was used to analyze the raw data for the meta-analysis. We used the random effects model, which incorporates a weighted method of analysis; this is not the inverse variance-weighted method that has known limitations. The random model is also more conservative than the fixed model with wider CIs, a decision supported by statistically significant chi-square heterogeneity tests. In addition, basic science supports this decision in that we expected the rate of positive test results to vary from site to site as it would on exposure, hence, the use of the random model. The Mantel-Haenszel method described in the NCSS software uses the stratified method and the raw counts for a combined OR estimate. We used the Woolf heterogeneity test for testing the general hypothesis that all ORs are equal but not necessarily equal to unity. Because opinions vary on the appropriate methods for performing a particular meta-analysis, we examined the robustness of the findings by using a sensitivity analysis. In addition, because statistically significant results are more likely to get published, this can distort the findings in a meta-analysis. Sensitivity was thus assessed by exploring the correlation association of the size of the OR and its CI versus the size of the study because smaller ORs can be statistically significant in larger studies.

Results

A total of 23 of the 42 identified studies met the criteria established for the meta-analysis (table 1).[10,12–27] They included 3873 individuals with schizophrenia and 7046 controls. The reasons for excluding the other studies included one or more of the following: inclusion of patients with psychiatric diagnoses other than schizophrenia (eg, "psychiatric inpatients") (8 studies[28–35]), use of skin testing and other nonserological measures of *T. gondii* antibodies (5 studies[8,36–39]), failure to include a control group (3 studies[40–42]), missing data (2 studies[43,44]), and selection of

Table 1. Serological Studies of *Toxoplasma gondii* Antibodies in Individuals With Schizophrenia and Controls

Year	Authors and Country	Serological Test	Control Group	% Patients Antibody Positive	% Controls Antibody Positive	Odds Ratio
I. All schizophrenia patients						
1961	Cook & Derrick,[12] Australia	CF	"General population"	6/53 (11%)	99/760 (13%)	0.88
1962	Yegorov et al,[13] Russia	CF	Healthy hospital employees	12/37 (32%)	7/25 (28%)	1.23
1958	Caglieris,[14] Italy	dye test	Hospital employees, and blood donors	13/61 (21%)	12/81 (15%)	1.55
2003	Torrey & Yolken,[a] Ireland	ELISA	Hospital staff	31/52 (60%)	9/20 (45%)	1.79
1999	Li et al,[15] China	ELISA	Normal persons, from same region	22/152 (15%)	34/396 (9%)	1.81
1968	Garrido & Redondo,[16] Spain	CF	Medical clinic patients	17/39 (44%)	147/500 (29%)	1.86
1956	Wende,[17] East Germany	dye test	Inpatients with neurological disorders	3/38 (8%)	24/520 (5%)	1.88
1994	Zhang et al,[18] China	ELISA	Normal persons from same region	17/92 (18%)	118/1365 (9%)	2.42
1990	Lu et al,[19] China	ELISA	Normal persons from same city	35/418 (8%)	16/512 (3%)	2.81
1995	Wang et al,[20] China	ELISA	General population	11/104 (11%)	8/210 (4%)	2.96
2005	Dickerson et al,[b] United States	ELISA	Volunteers screened to rule out psychiatric disorders and matched to group	71/405 (18%)	10/170 (6%)	3.33
1966	Berengo et al,[21] Italy	dye test	Blood donors	76/560 (14%)	49/1200 (4%)	3.68
1996	Lian et al,[22] China	IHA	Hospital employees and their families	20/67 (30%)	5/60 (8%)	4.51
2002	Lu et al,[23] China	IHA	Healthy persons for routine physicals	17/222 (7%)	1/78 (1%)	5.19
1999	Miao & Ding,[24] China	ELISA	Clinic patients for routine physicals	56/146 (38%)	4/56 (7%)	7.66
1984	Cui,[10] China	IHA	Local population	133/257 (52%)	19/274 (7%)	14.22
Pooled estimate for all schizophrenia patients 2.79						
II. First-episode schizophrenia patients only						
2005	Tanyuksel et al,[c] Turkey	ELISA	Healthy individuals with no physical or psychiatric disease	23/64 (36%)	13/40 (33%)	1.16
2005	Schwarz et al,[d] Germany	ELISA	Volunteers screened to rule out psychiatric disorders	27/100 (27%)	16/87 (18%)	1.63
2005	Gallo et al,[e] Peru	ELISA	Individually matched controls, no psychiatric or neurological illness	64/120 (53%)	41/120 (34%)	2.19
2004	Leweke et al,[25] Germany	ELISA	Healthy volunteers from same area	38/113 (34%)	16/102 (16%)	2.70
2006	Wang et al,[26] China	ELISA	200 for routine physical exams and 200 hospitalized for nonpsychiatric illnesses	82/600 (14%)	15/400 (4%)	4.01
2001	Gu et al,[f] China	ELISA	Normal individuals matched to group	45/135 (33%)	4/43 (9%)	4.63
2001	Yolken et al,[27] Germany	ELISA	Healthy individuals matched by block design	16/38 (42%)	3/27 (11%)	5.45
Pooled estimate for first-episode schizophrenia patients only 2.54						
Pooled estimate for all 2.73						

Note: CF, complement fixation; ELISA, enzyme-linked immunosorbent assay; IHA, immune hemagglutination.
[a] E. F. Torrey, MD, and R. H. Yolken, MD, unpublished data, 2003.
[b] F. Dickerson, PhD, et al, unpublished data, 2005.
[c] M. Tanyuksel, MD, et al, unpublished data, 2005.
[d] M. J. Schwarz, MD, and N. Mueller, MD, PhD, unpublished data, 2005.
[e] C. Gallo, MSc, et al, unpublished data, 2005.
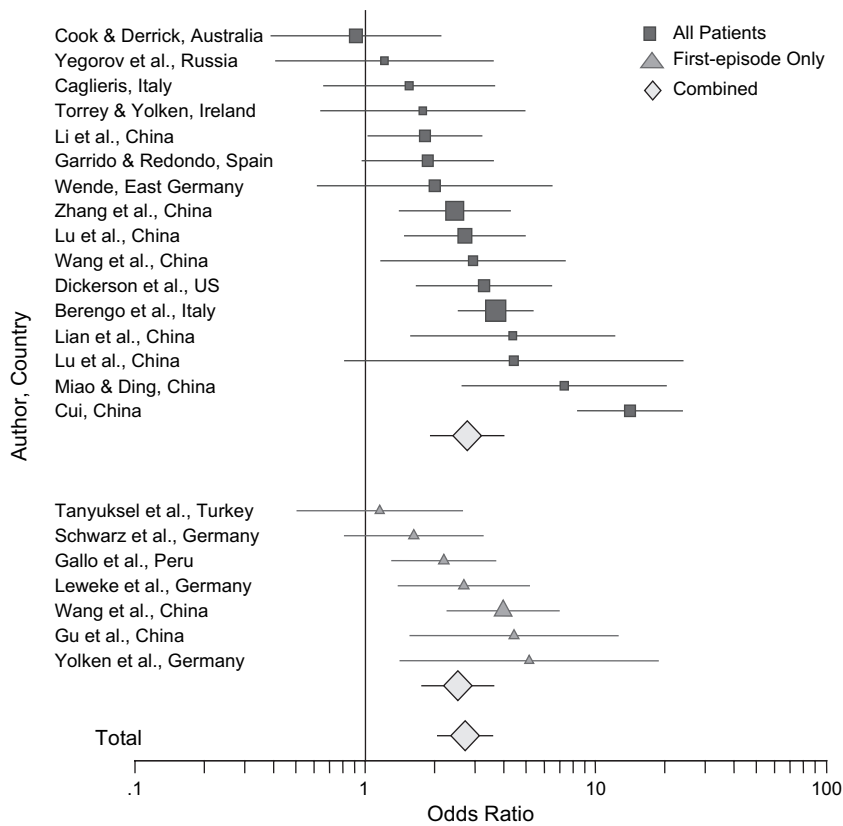[f] H. Gu, PhD, et al, unpublished data, 2001.

Figure 1. Forest Plot of Odds Ratio for the 23 Studies in Table 1.

patients because of possible exposure to *T. gondii* (1 study[45]).

Seven of the studies involved the analysis of outpatients; the remainder were directed largely at hospitalized populations. Eight studies included individuals who were undergoing their first episode of schizophrenia, with 7 of these meeting the criteria for inclusion in the meta-analysis; the remainder of the studies included patients with varying lengths of illness duration.

Table 1 lists the 23 studies, divided by first episode, and other studies, with ORs. The chi-square test for heterogeneity across the 23 studies is 25.3, 3 *df* and $P < .000001$, strongly supporting the use of the random model, which thus was used throughout the statistical analyses. Figure 1 is a forest plot of these studies. The overall combined OR is 2.73 (95% CI, 2.10 to 3.60; chi-square with 1 *df* 263; $P < .000001$). The OR for the combined first-episode studies is 2.54 and for the other combined studies 2.79 (Mentel-Haenszel chi-square with 1 *df* 0.81; $P < .36$); thus, there is no significant difference between the two ORs 2.54 and 2.79 and consequently the two studies. Dividing the studies by the serological test yields ORs of 1.38 for CF (3 studies), 2.61 for ELISA (14 studies), 2.54 for the dye test (3 studies), and 8.27 for IHA (3 studies) (Mantel-Haenszel chi-square with 3 *df* 25.3, $P < .0001$).

Among the 23 studies used in the meta-analysis, 17 have been published and 6 are unpublished. The OR for published studies is 2.97 and for unpublished studies 2.16. The chi-square of equality with 1 *df* is 4.8, $P < .03$. Thus, there appears to be some evidence that studies with a higher OR are more likely to have been published. In addition, further sensitivity analysis for the 23 studies was explored using the Pearson product moment correlation between the size of the study and the size of the OR. For all 23 studies, it was -0.01, $P < .96$; for the 17 published studies, it was -0.06, $P < .81$; and for the 6 unpublished studies, it was 0.17, $P < .71$, all statistically nonsignificant, indicating no association between the size of the study and the size of the OR in any of the comparisons.

Among the 19 studies not meeting the criteria used for this meta-analysis, 11 had analyzable data for cases and controls.[8,28–34,36,37,39] Because they included some psychiatric patients with diagnoses other than schizophrenia in their sample and/or used nonserological measures of *T. gondii* antibodies, one would predict greater variability in the results. These studies are listed in table 2 with ORs; figure 2 is a forest plot of these studies. The combined OR is 1.60 (95% CI, 0.98 to 2.69; chi-square with 1 *df* 158, $P < .000001$). A chi-square test with 10 *df* for variability among the 11 studies is 73.06, $P < .000001$. Thus, in these 11 studies not used in the meta-analysis, the individuals

Table 2. Studies Not Used

Year	Author and Country	Reason for Nonuse	Cases	Controls	Odds Ratio
1995	Lu et al,[28] China	Inpatients with mental disease	182/754 (24%)	17/29 (59%)	0.23
1995	Tan et al,[29] China	Inpatients with nervous system disease	43/674 (6%)	4/26 (15%)	0.36
2003	Tang et al,[30] China	Inpatients with psychosis	64/455 (14%)	9/50 (18%)	0.73
1983	Choi et al,[31] Korea	Inpatients	11/573 (1.9%)	1/76 (1.3%)	1.20
1957	Jirovec et al,[36] Czech	Skin test	238/501 (48%)	296/970 (29%)	2.06
2005	Luo et al,[32] China	Inpatients	38/413 (9%)	5/117 (4%)	2.18
1962	Avlavidov,[33] Bulgaria	Inpatients	3/14 (21%)	3/34 (9%)	2.78
1953	Kozar,[8] Poland	Skin test, inpatients	495/961 (52%)	170/681 (25%)	3.19
1979	Garcia,[37] Cuba	Skin test, psychiatric patients	60/100 (60%)	30/100 (30%)	3.48
2004	Liu et al,[34] China	Inpatients with nervous system disease	37/93 (40%)	9/87 (10%)	5.60
1966	Destounis,[39] United States	Skin test	5/45 (12%)	0/45 (0%)	23.61

Pooled estimate for 11 studies 2.29

with mixed psychiatric diagnoses had significantly more antibodies to *T. gondii* than the controls although, as expected, there was much greater variability among the studies.

Discussion

We found that the prevalence of antibodies to *T. gondii* in individuals with schizophrenia is significantly higher than the prevalence of antibodies in control populations, with an OR of 2.73. This difference was found in studies carried out over 5 decades in 17 countries employing several different methods of antibody measurement.
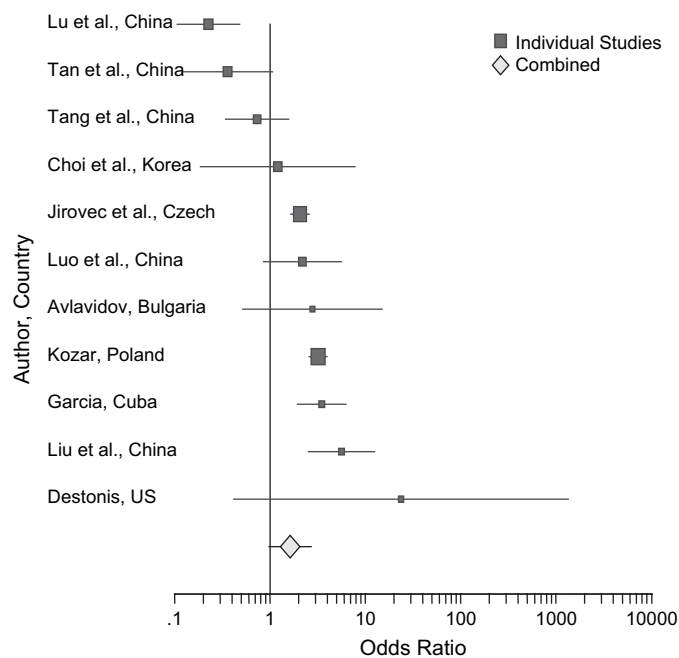
Figure 2. Forest Plot of Odds Ratio for the 11 Studies in Table 2.

The findings in the present study are consistent with other studies linking *T. gondii* to schizophrenia. A study of maternal sera of women who gave birth to offspring who later developed schizophrenia spectrum disorders[46] and a study of newborn sera of individuals who later developed schizophrenia[47] both reported increased antibodies to *T. gondii* in cases versus controls. Two other studies reported that children who were later diagnosed with schizophrenia or other psychoses had had more childhood exposure to cats, but not dogs.[48,49] It has also been observed that some individuals who develop adult-onset toxoplasmosis exhibit delusions and hallucinations.[50]

It is noteworthy that the largest number of studies have been done in China, where, until recently, the keeping of cats as pets has been uncommon and where the prevalence of *T. gondii* antibodies in the general population has been low.[7] In such instances, the higher prevalence of antibodies in patients with schizophrenia may be more apparent. By contrast, in a country like Ireland, where cats are ubiquitous and where the prevalence of *T. gondii* antibodies in the general population is known to be high,[51] a modest increase in patients with schizophrenia may be less apparent.

Given what is known about the causes of schizophrenia, is it plausible that *T. gondii* could play a role in its etiology? There are four major considerations. First, schizophrenia is known to have a genetic component, with concordance among monozygotic twins of 35%–50%. Genes are also known to influence the susceptibility of animals to *T. gondii*,[52,53] and in mice, *T. gondii* has also been shown to be transplacentally transmitted for as many as 5 successive generations in a pseudogenetic pattern.[54] Second, schizophrenia is known to include abnormalities of neurotransmitters; animal studies have demonstrated an effect of *T. gondii* on dopamine and serotonin.[55] Third, schizophrenia is widely believed to be a disease of neurodevelopment; this is consistent with

T. gondii's known ability to cause prenatal infections and then remain latent for many years before becoming reactivated. Fourth, an association between *Toxoplasma* infections and schizophrenia is consistent with animal models indicating persistent behavioral changes in *Toxoplasma*-infected animals.[56]

In other aspects of plausibility, *T. gondii* is neurotrophic, with a special affinity for glia,[57,58] now thought to be centrally involved in the schizophrenia disease process. It is also of interest that some antipsychotic drugs used to treat schizophrenia have been shown to inhibit the growth of *T. gondii* in cell culture.[59] Finally, individuals who develop schizophrenia are known to have had an excess number of winter and spring births[60]; toxoplasmosis, like many infectious diseases, also occurs more commonly in the winter and spring months.[61–63]

Despite many attractive aspects, there are three major problems with the plausibility of *T. gondii* being etiologically linked to schizophrenia. One is the fact that these studies are serological in nature and are not based on the direct detection of *Toxoplasma* organisms or DNA in infected body fluids. This is an inherent limitation of studies in *Toxoplasma* biology because the organism is difficult to detect in non–immune-compromised individuals. However, numerous studies have indicated that properly performed serological assays are accurate indicators of prior *Toxoplasma* infection.[64,65] The second is epidemiological; the seropositivity rate of *T. gondii* is very high in countries such as France and Ethiopia, where undercooked or raw meat is regularly consumed, yet schizophrenia has not been found to be unusually prevalent in these countries. Possible explanations include the fact that transmission by eating tissue cysts in undercooked meat is a more benign mode of infection, and there is some evidence to support this[66]; thus, it may pose less of a risk for the development of schizophrenia than the consumption of oocysts shed by cat feces. There may also be differences in terms of the neuropathogenicity of strains of *Toxoplasma* prevalent in different areas of the world[67] as well as differences in the genetic susceptibility of different human populations.

The third problem with plausibility is that the majority of individuals with schizophrenia do not have measurable antibodies to *T. gondii*. This fact may be related to the relative insensitivity of available serological assays or to the heterogeneity of disease pathogenesis. It is also possible that other environmental factors may initiate neuropathogenic pathways similar to those employed by *T. gondii*, such as the ones involving the activation of interferon gamma.[68] The identification of pathways initiated by *T. gondii* within the central nervous system might thus lead to an increased understanding of schizophrenia pathogenesis in individuals without specific evidence of *Toxoplasma* infection.

A question for future research is the specificity of the finding. To date, only one study of *T. gondii* and schizophrenia has also included a large number of individuals with another psychiatric diagnosis; Wang et al[26] in China reported that 40/600 (7%) of patients with first-episode affective disorder had antibodies to *T. gondii* compared with 82/600 (14%) of those with first-episode schizophrenia and 15/400 (4%) of controls.

Future research should also focus on the timing of the infection. Individuals with schizophrenia may behave in ways that increase the likelihood of becoming infected with *T. gondii* either prior to or after the onset of the disease. An example of the latter was speculation by the authors of a Spanish study that the patients with schizophrenia had a high rate of seropositivity to *T. gondii* because they regularly worked in the hospital gardens that had been fecally contaminated by the hospital's cats.[16] Alternatively, institutionalized psychiatric patients may be fed undercooked meat, thereby increasing their exposure to *T. gondii*. Such post-onset explanations seem unlikely in view of the similar findings in first-episode schizophrenia patients who had not had a previous hospitalization and were unlikely to have undergone unusual environmental exposures after illness onset. The likelihood of infection occurring as an artifact of behavioral effects of the disease or its treatment is also not consistent with studies indicating an increased risk of schizophrenia in the offspring following maternal infection.[46,47]

Another alternate explanation of the association is that the increased *T. gondii* antibodies in individuals with schizophrenia are secondary to immune system abnormalities, such as are seen in individuals infected with HIV. In such a scenario, another infectious agent could be a primary cause of schizophrenia, with the reactivation of *T. gondii* tissue cysts and generation of antibody being merely a secondary manifestation. Although immune, and specifically lymphocyte, abnormalities have been described in schizophrenia, their magnitude is not impressive and seems unlikely to account for the increase in *T. gondii* antibodies. In addition, increases in antibodies to other infections associated with immunodeficiency, such as Epstein-Barr virus, have generally not been found in individuals with schizophrenia.[25] Finally, the possible effects of antipsychotic medication must be considered; however, antipsychotics have been shown to inhibit *T. gondii* in vitro,[59] and the one study of never-treated individuals with schizophrenia had an OR of 2.70.[25]

The schizophrenia-associated OR of *Toxoplasma* found in this meta-analysis, 2.73, while modest in extent, is greater than the ORs associated with individual genes (1.6–1.8)[69] and with other environmental factors such as obstetrical complications (~2).[70] Given the high prevalence of *Toxoplasma* infection in healthy individuals, *Toxoplasma* seropositivity has a relatively low predictive value for the development of schizophrenia, and most individuals who are *Toxoplasma* seropositive do not have manifestations of this disorder.

If the association between *T. gondii* infection and schizophrenia is, in fact, etiological, why should only

some individuals who are exposed to the infectious agent develop schizophrenia? Possible reasons include differences in genetic susceptibility, organism strain differences, route of infection (eg, ingestion of oocysts from infected cats versus tissue cysts from meat), and timing of the infection (eg, in utero, early postnatal, childhood, adulthood). Each of these factors is known to lead to different disease outcomes for other infectious agents. The study of these factors will be important in further defining the relationship between *T. gondii* and schizophrenia.

Acknowledgments

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