Article

Maternal Exposure to Toxoplasmosis and Risk of Schizophrenia in Adult Offspring

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Objective: The authors examined the relationship between maternal antibody to toxoplasmosis and the risk of schizophrenia and other schizophrenia spectrum disorders in offspring. Toxoplasmosis is known to adversely affect fetal brain development.

Method: In a nested case-control design of a large birth cohort born between 1959 and 1967, the authors conducted serological assays for *Toxoplasma* antibody on maternal serum specimens from pregnancies giving rise to 63 cases of schizophrenia and other schizophrenia spectrum disorders and 123 matched comparison subjects. *Toxoplasma* immunoglobulin (Ig)G antibody was quantified by using the Sabin-Feldman dye test. The Ig titers were classified into three groups: negative (<1:16) (reference), moderate (1:16–1:64), and high (≥1:128).

Results: The adjusted odds ratio of schizophrenia/schizophrenia spectrum disorders for subjects with high maternal *Toxoplasma* IgG antibody titers was 2.61 (95% confidence interval=1.00–6.82). There was no association between moderate *Toxoplasma* Ig antibody titers and the risk of schizophrenia/spectrum disorders.

Conclusions: These findings suggest that maternal exposure to toxoplasmosis may be a risk factor for schizophrenia. The findings may be explained by reactivated infection or an effect of the antibody on the developing fetus. Given that toxoplasmosis is a preventable infection, the findings, if replicated, may have implications for reducing the incidence of schizophrenia.

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Several maternal infections have been associated with an elevated risk of schizophrenia in offspring (1–3). Evidence suggests that infections known to cause congenital CNS anomalies in humans, including rubella (4), herpes simplex (5), polio, and varicella-zoster virus (1), might be related to the risk of schizophrenia. Toxoplasmosis is also associated with maldevelopment of the CNS, and ecological data have led to the suggestion that this organism might be involved in the etiology of schizophrenia (6). Therefore, we used serological methods to investigate whether maternal exposure to toxoplasmosis is associated with an increased risk of schizophrenia in adult offspring.

Toxoplasma gondii, the cause of toxoplasmosis, is a ubiquitous intracellular parasite (7, 8). When primary infection occurs during pregnancy, the offspring have a markedly increased risk of CNS congenital abnormalities, including microcephaly, hydrocephalus, mental retardation, convulsions, cerebral calcifications, and chorioretinitis (7–9). Delayed neurologic sequelae, including lower IQ, retarded psychomotor development, and sensorineural deafness, have also been demonstrated in subjects who were exposed in utero, even among those with subclinical infection during the neonatal period (7, 8).

Serological methods for detection of *Toxoplasma* include direct detection of the parasite, immunoassays for serum immunoglobulin (Ig)M antibody, and elevation of maternal IgG antibody to *Toxoplasma*. Elevation of *Toxoplasma* IgG may reflect primary active or reactivated infection; however, unlike IgM antibody, which is a specific indicator of recent infection, increased IgG may persist for years in subjects with dormant infection (7). Increased IgG titers to *Toxoplasma* have been associated with both severe and subtle neuropsychiatric abnormalities (10).

In the present study, we conducted assays of archived prenatal serum specimens drawn prospectively in subjects with schizophrenia and matched comparison subjects from the Prenatal Determinants of Schizophrenia Study, a large birth cohort investigation (11), to examine the relationship between elevated *Toxoplasma* antibody and risk of adult schizophrenia.

Method

Description of the Cohort

The Prenatal Determinants of Schizophrenia Study has been described previously (11) and will be only briefly reviewed here. The cohort members were enrolled in the Child Health and Development Study (12), which took place from 1959 to 1967. The Child Health and Development Study recruited nearly every pregnant woman under obstetric care from the Kaiser Foundation Health Plan in Alameda County, Calif. The 19,044 live-born offspring of these women were automatically enrolled in the Kaiser Foundation Health Plan. The Child Health and Development Study collected data from maternal medical records, maternal interviews, and other sources.

The Prenatal Determinants of Schizophrenia Study cohort consisted of the 12,094 live births who belonged to the Kaiser Perma-

TABLE 1. Distribution of Immunoglobulin G Toxoplasmosis Antibody Titers With the Sabin-Feldman Dye Test in Subjects With Schizophrenia Spectrum Disorders and Comparison Subjects

	Subjects With Schizophrenia Spectrum Disorders		Comparison Subjects	
Antibody Titer[a]	N	%	N	%
Reference (<1:16)	45	71.4	101	82.1
Moderate (1:16–1:64)	5	7.9	9	7.3
High (1:128–1:1024)	13	20.6	13	10.6

[a] Antibody titers are presented only for subjects who were seropositive; titers <1:16 are considered seronegative by definition.

nente Medical Care Plan between January 1, 1981 (the year in which computerized registries became available) and December 31, 1997. The subjects who remained in the Kaiser Permanente Medical Care Plan and the subjects lost to follow-up were similar to one another on most maternal and paternal characteristics (11), and the vast majority of individuals who left Kaiser Permanente Medical Care Plan did so before age 10 (11).

Collection of Maternal Sera

Maternal serum samples were obtained during pregnancy for virtually all subjects, were frozen immediately, and were archived at –20°C in a single repository. All specimens were uniformly handled and stored in accordance with a strict protocol.

Diagnosis of Schizophrenia Spectrum Disorders

The outcome was schizophrenia and other schizophrenia spectrum disorders, defined from previous studies (13) as any of the following: schizophrenia, schizoaffective disorder, delusional disorder, psychotic disorder not otherwise specified, and schizotypal personality disorder. Case ascertainment involved three steps: 1) ascertainment of potential cases from computerized records, 2) chart review of potential cases to confirm eligibility for assessment, and 3) diagnostic interview (or chart review) and consensus diagnosis. Case ascertainment was conducted by a computerized record linkage between the Child Health and Development Study and Kaiser Permanente Medical Care Plan identifiers by using inpatient, outpatient, and pharmacy registries. Subjects from the hospital registry were screened for potential schizophrenia spectrum disorders based on diagnoses of ICD-9 295–299 and psychiatrist review of all psychiatric and medical records. Patients from the outpatient registry screened positive if they were assigned ICD-9 diagnoses of 295, 297, 298, or 299. Subjects from the pharmacy registry screened positive based on a history of antipsychotic treatment.

There were 13 deceased subjects among those who screened positive for potential schizophrenia spectrum disorders (N=183). Among the 170 remaining potential subjects with schizophrenia spectrum disorders, 146 (86%) were contacted to schedule a diagnostic interview.

Clinicians with at least a master's degree in a mental health field who were trained to reliability administered the Diagnostic Interview for Genetic Studies to potential subjects with schizophrenia spectrum disorders (14). Consensus of three experienced research psychiatrists was used to obtain DSM-IV diagnoses based on a review of the Diagnostic Interview for Genetic Studies narrative and medical records and discussions with the interviewer. The Diagnostic Interview for Genetic Studies was completed by 107 (73%) of the 146 contacted potential subjects with schizophrenia or schizophrenia spectrum disorders. For the 76 potential subjects who were not interviewed, chart reviews by experienced clinicians were conducted; all diagnoses were confirmed by a research psychiatrist. These procedures yielded a total of 71 subjects with schizophrenia spectrum disorders, 44 of whom received the Diagnostic Interview for Genetic Studies and 27 of whom were diagnosed by chart review. Among these 71 subjects with schizophrenia spectrum disorders, 64 had available prenatal sera. The diagnoses of these subjects were schizophrenia (N=38), schizoaffective disorder (N=15), delusional disorder (N=1), schizotypal personality disorder (N=5), and other schizophrenia spectrum psychosis (N=5).

All subjects in the Prenatal Determinants of Schizophrenia Study provided written informed consent for human investigation. The study protocol was approved by the institutional review boards of the New York State Psychiatric Institute and the Kaiser Foundation Research Institute.

Laboratory Assay

All of the assays were performed with researchers blind to case/comparison status in the Toxoplasma Serology Laboratory at the Palo Alto Medical Foundation Research Institute, the *Toxoplasma* reference laboratory for the United States (15), under the direction of Dr. Jack Remington.

Three assays were used in the present study (15). The first two concern the assessment of *Toxoplasma* IgG antibody titer. In accordance with established practice, samples were first screened for the IgG antibody titer by using the screen agglutination test. Then, to definitively establish the presence of *Toxoplasma* IgG antibody, the Sabin-Feldman dye test (16), the reference standard for the serological detection of *Toxoplasma* antibody (7), was performed in the samples that screened positive on the agglutination test.

To examine whether recent infection with toxoplasmosis occurred in our samples, we assayed for *Toxoplasma* IgM antibody using the double-sandwich enzyme-linked immunosorbent assay (IgM ELISA) (17). Given the extremely low likelihood that positive IgM antibody would be found in a sample with a negative antibody result on the IgG screening agglutination test, the IgM ELISA was performed only on subjects who screened positive in the agglutination test.

Categorization of Exposures

Following established practice, the screen agglutination test results for *Toxoplasma* IgG were categorized as a dichotomy (positive/negative).

The Sabin-Feldman dye test (16) yields IgG antibody titer results in serial twofold dilutions. All dye test IgG titers <1:16 are considered negative. Given the lack of clear precedents in the literature for the classification of *Toxoplasma* IgG antibody titers, we categorized the subjects with positive IgG titers based on the distribution of the titers in our sample. "High" titer was defined as a *Toxoplasma* IgG antibody titer of ≥1:128; this category represented approximately the highest 10th percentile (10.5%) of IgG titers for comparison subjects in our study group. The moderate titer group was defined as an IgG antibody titer of 1:16–1:64 and consisted of the remaining subjects with positive IgG antibody titers. This classification strategy provided sufficient subject numbers in each of the exposure groups to permit a meaningful analysis of the data, while also allowing us to examine the effect of different magnitudes of antibody titer on the risk of schizophrenia spectrum disorders. The reference category consisted of subjects with negative IgG antibody titers.

In accordance with the methods used by the Toxoplasma Serology Laboratory at the Palo Alto Medical Foundation Research Institute (17), IgM ELISA antibody titer values >1.9 were considered positive, values from 1.7 to 1.9 were equivocal, and values ≤1.6 were negative.

Analytic Strategy

The analysis was based on a nested case-control design (18) in which the comparison subjects for each case are selected to represent the population at risk when the case was ascertained. In the Prenatal Determinants of Schizophrenia Study, cases were ascertained on the first date of medical attention for schizophrenia spectrum disorders.

Eligible Subjects With Schizophrenia Spectrum Disorders

Among the 71 subjects with schizophrenia spectrum disorders, 64 had at least one available prenatal serum sample; 58 (90.6%) of these 64 subjects had either schizophrenia or schizoaffective disorder. The last serum sample available for each pregnancy (late third trimester or perinatal) was used. This provided the greatest opportunity to detect *Toxoplasma* infection if it occurred at all during pregnancy. Even if exposure occurred in early pregnancy, it was unlikely to have been missed by our assay method because *Toxoplasma* IgG antibodies generally remain elevated for many months or years after infection (7).

Eligible Comparison Subjects

Eligible comparison subjects (N=10,768) were selected from offspring without schizophrenia spectrum disorders in the Prenatal Determinants of Schizophrenia Study cohort after excluding siblings of subjects with schizophrenia spectrum disorders, subjects with major affective disorders, and subjects without prenatal sera.

Matching Procedure

Matching by a nested case-control design ensured that each case and its corresponding comparison subject were followed for equal lengths of time from birth until first treatment of the case. Comparison subjects were matched to subjects with schizophrenia spectrum disorders on membership in the Kaiser Permanente Medical Care Plan at the time the case was ascertained, date of birth (±28 days), gender, and number and timing (±28 days) of the first maternal blood sample taken during the index pregnancy (2, 11).

To conserve the sera, two comparison subjects were selected at random from the pool of potential matched comparison subjects for each case and were further matched on gestational age by requiring that they were drawn within 42 days of the serum sample of the case. This selection process resulted in 124 matched comparison samples (60 sets with 1:2 matching and four sets with 1:1 matching). A comparison in a 1:1 matched set was eliminated from the analysis because of an insufficient quantity of serum, resulting in 63 subjects with schizophrenia spectrum disorders and 123 comparison subjects (60 sets matched at 1:2 and three sets matched at 1:1). Gestational ages (in days) of sera from subjects with schizophrenia spectrum disorders (mean=271.7, SD=24.8) and comparison subjects (mean=275.3, SD=26.3) did not differ significantly from one another (t=–0.67, df=184, p=0.51).

Appropriate to the nested case-control study design, point and interval estimates of odds ratios were obtained by fitting conditional logistic regression models for matched sets (19). We first tested the relationship between high maternal *Toxoplasma* IgG and risk of schizophrenia spectrum disorders. We then examined whether moderate *Toxoplasma* IgG was associated with schizophrenia spectrum disorders. Statistical significance was judged at α=0.05.

After first obtaining unadjusted estimates of the association between *Toxoplasma* IgG and schizophrenia spectrum disorders, we then assessed the following covariates as potential confounders: maternal age (<35 [reference], ≥35), maternal ethnicity (Caucasian [reference], African American, other), maternal socioeconomic status, defined as maternal education (<high school, high school only [reference], some college/college graduate), and gestational age of the serum sample (in days after last menstrual period).

Results

Demographic Characteristics

The mean ages of the subjects with schizophrenia spectrum disorders and the comparison subjects, respectively, were 24.2 years (SD=4.8) and 25.2 years (SD=4.9) (t=0.09, df=184, p=0.93). The proportion of male subjects was 50% (21 of 42) of the subjects with schizophrenia spectrum disorders and 66.7% (82 of 123) of the comparison subjects. Maternal age did not differ significantly between the subjects with schizophrenia spectrum disorders (mean=30.0, SD=6.2) and the comparison subjects (mean=28.6, SD=6.1) (t=–1.06, df=184, p=0.29).

Screen Agglutination Test

Of the 186 samples tested, 55 were positive on the screen agglutination test. For the subjects with schizophrenia spectrum disorders, 25 of 63 (39.7%) were positive; for the comparison subjects, 30 of 123 (24.4%) were positive.

IgG With Dye Test

The seroprevalence of IgG antibody by the Sabin-Feldman dye test among the 55 subjects who screened positive on the screen agglutination test was 18 of 63 (28.5%) of the subjects with schizophrenia spectrum disorders and 22 of 123 (17.9%) of the 123 comparison subjects. The prevalence of high *Toxoplasma* IgG antibody titers was greater for subjects with schizophrenia spectrum disorders than for comparison subjects (Table 1).

In the conditional logistic regression analysis, the odds ratio of schizophrenia spectrum disorders for the subjects with a high *Toxoplasma* IgG antibody titer was 2.42 (95% confidence interval [CI]=0.94–6.25, p<0.07) (Table 2). There was no increase in the risk of schizophrenia spectrum disorders for the group with moderate IgG antibody titers (odds ratio=1.37, 95% CI=0.40–4.73, p=0.62). The global test of association (df=2) yielded a p value of 0.19.

Testing of Covariates in Relation to Toxoplasma IgG

Of the four covariates examined in relation to the *Toxoplasma* IgG antibody among comparison subjects, an appreciable association was found only for maternal age: older mothers had higher IgG antibody titers than younger mothers (χ^2=4.07, df=1, p<0.05). No associations were observed between *Toxoplasma* IgG and maternal ethnicity, education, and gestational age of the serum samples.

Given the association between toxoplasmosis and maternal age, we adjusted for this covariate (Table 2). The adjusted odds ratio of schizophrenia spectrum disorders for subjects with high IgG antibody titers was 2.61 (95% CI= 1.00–6.82, p=0.051). There was no association between moderate IgG antibody titer and risk of schizophrenia

TABLE 2. Conditional Logistic Regression of Antibody to Toxoplasmosis and Risk of Schizophrenia and Other Schizophrenia Spectrum Disorders in Subjects With Schizophrenia Spectrum Disorders and Comparison Subjects

	Unadjusted				Adjusted for Maternal Age			
Immunoglobulin G Titer	χ^2	Odds Ratio	95% CI	p	χ^2	Odds Ratio	95% CI	p
Reference (<1:16)	—	1.00	—	—	—	1.00	—	—
Moderate (1:16–1:64)	0.25	1.37	0.40–4.73	0.62	0.02	1.11	0.30–4.05	0.88
High (1:128–1:1024)	0.88	2.42	0.94–6.25	<0.07	3.81	2.61	1.00–6.82	0.051

spectrum disorders after adjustment for maternal age. The global test of association (df=2) yielded a p value of 0.15.

Although maternal ethnicity and education were not associated with *Toxoplasma* IgG antibody titers, for further assurance, we also adjusted for these variables. The results were not appreciably altered from those of the analysis adjusting for maternal age alone (data available upon request).

IgM With ELISA

None of the case and comparison serum samples tested with ELISA were positive for the *Toxoplasma* IgM antibody. Thus, no statistical comparison could be conducted.

Discussion

To our knowledge, this is the first report of an association between elevated maternal IgG antibody to *Toxoplasma* and the risk of schizophrenia. This finding was revealed by using prospectively collected and archived prenatal serum specimens in a well-characterized birth cohort. Although the finding fell slightly short of statistical significance, these facts lend credence to the result.

The relationship was observed only for the high category of IgG antibody titer. It should be noted, however, that our definition of "high" titer was based on the maternal titers relative to our sample, rather than those found in the mothers of infants with congenital toxoplasmosis, in which elevated maternal IgM titers and/or very high IgG titers are typically observed. In the present study, no subjects had elevated maternal IgM titers, and very high IgG titers were rare. Thus, antibody titers in the "high" exposure group in our cohort may be consistent with subtle adverse developmental effects on the brain, such as those that could influence the pathogenesis of schizophrenia.

As reviewed in our introduction, toxoplasmosis during pregnancy is a known cause of congenital abnormalities in offspring (10, 11, 20, 21). Although most of these studies are based on direct observation of the parasite, elevated maternal IgM, or persistently elevated IgG in infant serum along with elevated IgG in maternal serum (9), some studies have examined whether a single elevated maternal *Toxoplasma* IgG antibody titer is associated with harm to the offspring. Sever et al. (10) showed that the 7-year-old offspring of mothers with elevated IgG *Toxoplasma* antibody titers had substantial increases in microcephaly, low IQ, and bilateral deafness. Effects were also observed, although at smaller magnitudes, for coordination problems, visual impairment, and extraocular movement abnormalities.

Prenatal exposure to toxoplasmosis is a plausible risk factor for schizophrenia. The parasite has a predilection for the developing fetal brain (7, 8) and results in a similar array of congenital abnormalities as rubella and other pathogens that have been implicated in schizophrenia (1, 4, 5). Postmortem and neuroimaging studies in newborns with congenital toxoplasmosis have revealed several CNS abnormalities, including enlargement of the third and lateral ventricles secondary to hydrocephalus, and intracranial calcifications, frequently of the basal ganglia, choroid plexus, and meninges. Although these findings differ in severity, and to some degree in type, from those in schizophrenia, radiological studies have not been conducted on children who were exposed in utero to toxoplasmosis but who did not have the stigmata of congenital toxoplasmosis at the time of birth. It has been shown, however, that 40%–70% of these asymptomatic newborns later developed neurocognitive and neuromotor abnormalities that resemble those found in children who were later diagnosed with schizophrenia (8). These sequelae include retarded mental and psychomotor development, mildly decreased IQ, coordination problems, neurologic soft signs, and stereotypies (7, 10).

Because antibody titers to *Toxoplasma* IgG may remain elevated for significant periods of time, an increase in IgG antibody may reflect an active primary infection, reactivation of infection, or a persistent immune response to a dormant infection. First, we discuss active primary infection. In the present study, none of the serum samples in our cohort tested positive for IgM-specific *Toxoplasma* antibody, the most robust indicator of recently acquired infection (7). In a previous birth cohort study conducted during the same years as the Child Health and Development Study, the prevalence of primary *Toxoplasma* infection during pregnancy was low (10), consistent with subsequent studies (7). These results indicate that primary infection is unlikely to account for the observed finding.

Second, we consider reactivation of a previous infection. Following acute *Toxoplasma* infection, the parasites are not completely eliminated by the immune system; rather, they become sequestered as bradyzoites in dormant cysts in affected organs, most commonly the brain, eye, heart, and skeletal muscle (7, 8). However, the cysts have been known to spontaneously rupture as a result of host immunosuppression or other factors. When this occurs, reactivation of infection is produced by conversion of bradyzoites into tachyzoites, which are released from the cyst, proliferate, and invade cells (7, 22). The resulting anamnestic re-

sponse produces elevations of IgG antibody titers. An effect of activated dormant *Toxoplasma* microcysts on brain function is suggested by studies demonstrating associations between increased *Toxoplasma* IgG antibody and first-episode schizophrenia (23), personality changes (24), and cryptogenic epilepsy (25) in adult patients. The prevalence of reactivated infection is not known.

Toxoplasma is transmitted to the fetus through the placenta (26). Infection is most often transmitted to the offspring when *Toxoplasma* is acquired later in pregnancy, with the highest risk in the third trimester (26). The proliferating tachyzoites in the fetal CNS and other organs destroy parasitized cells and result in an inflammatory response, leading to anoxia, cell death, and tissue necrosis (8). *Toxoplasma* also increases levels of homovanillic acid and dopamine, which are implicated in the pathogenesis of schizophrenia (27).

It has also been suggested that *Toxoplasma gondii* may result in congenital CNS abnormalities without direct transmission of the parasite to the fetus. This mechanism is proposed to involve toxofactor, a toxin released by *Toxoplasma* (28). When administered during pregnancy, toxofactor causes congenital abnormalities, particularly CNS defects, in exposed animals.

It is also possible that the risk of schizophrenia may be increased in the offspring of mothers with dormant *Toxoplasma* infection and elevated IgG antibody. Individuals with dormant *Toxoplasma* may have elevations of IgG antibody for months or years following the infection (7). Under this scenario, *Toxoplasma* IgG antibody, rather than the organism or a toxic product, may cross the placenta and cause damage to the developing fetal brain. IgG antibodies from women with spontaneous abortion (29) and from subjects with systematic lupus erythematosus (30) are known to cause teratogenic effects.

Our findings may help to distinguish between these possible explanations. The level of IgG antibody titer is generally correlated with both the severity and recency of infection. Thus, antibody titers in the "high" category are more likely to be associated with a current or recent reactivated infection than titers in the "moderate" category, which have a greater probability of reflecting dormant infection.

Given associations between prenatal exposure to other infectious agents and the risk of schizophrenia (1, 2), it also possible that an alteration of maternal immune status may have accounted for the findings. We aim to test this hypothesis in future work.

In a previous study from the Collaborative Perinatal Project, no association was found between antibody to *Toxoplasma* and the risk of adult psychosis (5). The group size of this study was small, however, and there was greater heterogeneity of psychotic disorders than the present study. Furthermore, the previous study quantified IgG antibody by solid-phase enzyme immunoassay rather than by the Sabin-Feldman dye test, the reference standard because of its high sensitivity and specificity (7).

Limitations

The sera in the present study had been frozen for over 30 years, raising the possibility that storage for this period of time may have altered the *Toxoplasma* antibody levels. However, this factor appears unlikely to have had an appreciable impact on our results for several reasons. First, *Toxoplasma* antibody levels are generally stable in frozen stored sera. Second, the seroprevalence of toxoplasmosis in comparison subjects was 17.9%, similar to the 17.5% seroprevalence found in a large previous study of toxoplasmosis in reproductive-age women in the United States (31). Third, we matched the comparison subjects to subjects with schizophrenia spectrum disorders on the date of birth and gestational timing, and the samples were uniformly handled and stored, indicating that storage time should not have biased the associations.

Second, we should consider the potential impact on our findings of associations between determinants of toxoplasmosis and factors related to maternal lifestyle or health. Toxoplasmosis is generally acquired by eating raw or undercooked meat containing *Toxoplasma gondii* tissue cysts, by ingesting oocysts from soil through activities such as gardening or eating unwashed vegetables or fruits, or possibly by exposure secondary to changing cat litter boxes (31). It is conceivable that mothers of future patients with schizophrenia, in relation to mothers of comparison subjects, were more likely to engage in these activities. It is also possible that factors related to determinants of toxoplasmosis and to maternal lifestyle and health in mothers of schizophrenia patients may have confounded the observed association. Maternal or family history of schizophrenia might be considered such a factor. We have not yet acquired sufficient data on family history of schizophrenia spectrum disorders to examine potential confounding by family history. There is no clear reason, however, to postulate that maternal toxoplasmosis should be related to maternal or other family history of schizophrenia after adjustment for potential demographic risk factors. Even if such a relation exists, the effect of these factors would need to be very substantial to account for the observed associations, and we did adjust for the potential confounders available in our data set (age, social class, or ethnicity); nonetheless, we cannot entirely rule out this possibility.

Third, the finding was marginally significant, and the group size was modest. Thus, independent replication of this result is essential.

Conclusions

In a birth cohort with archived prenatal sera, we demonstrated that elevated maternal IgG antibody to *Toxoplasma* is associated with an increased risk of schizophrenia and

other schizophrenia spectrum disorders. Toxoplasmosis is a potentially preventable infection. Indeed, standard obstetric practice has included recommendations to pregnant women aimed at minimizing exposure to *Toxoplasma*, including the avoidance of cat feces and the ingestion of undercooked meat, which may contain *Toxoplasma gondii* oocysts (32). Toxoplasmosis has also been effectively treated in infants with antibiotics, such as pyrimethamine and sulfadiazine, which appear to reduce neurologic and other sequelae of the infection (7).

These findings add to a growing literature suggesting a relationship between in utero exposure to infectious agents that are known to disrupt fetal brain development and the risk of adult schizophrenia (1). Although replication will be necessary, these results may have implications for the prevention of schizophrenia.

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