HHS Public Access

Author manuscript

Biol Psychiatry. Author manuscript; available in PMC 2016 February 11.

Published in final edited form as:

Biol Psychiatry. 2012 August 15; 72(4): 290–295. doi:10.1016/j.biopsych.2012.01.003.

The relationship between *Toxoplasma gondii* infection and mood disorders in the NHANES III

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Abstract

Background—*Toxoplasma gondii (T. gondii)* is a neurotropic protozoan parasite that causes persistent infection in humans. A substantial literature suggests that schizophrenia is associated with increased seroprevalence of *T. gondii*, but a possible link of the parasite with mood disorders has not been as thoroughly investigated.

Methods—We examined the association of Toxoplasma-specific IgG results with mood disorder outcomes in 7440 respondents from the third National Health and Nutrition Survey (NHANES III), which is a nationally representative sample of the U.S. noninstitutionalized civilian population. Regression models were adjusted for numerous potential confounders including tobacco smoking and C-reactive protein levels.

Results—No statistically significant associations were found between *T. gondii* seroprevalence and a history of major depression (n=574; adjusted odds ratio, 0.8; 95% CI 0.5–1.2), severe major depression (n=515; adjusted odds ratio, 0.8; 95% CI, 0.6– 1.2), dysthymia (n=548; adjusted odds ratio, 1.1; 95% CI 0.7–1.8), or dysthymia with co-morbid major depression (n=242, adjusted odds ratio, 1.2; 95% CI 0.6–2.4), all p-values were >0.05, including analysis stratified by gender. However, there was a significant relationship between *T. gondii* seroprevalence and bipolar disorder type I for respondents in which both manic and major depression symptoms were reported (n=41; adjusted odds ratio, 2.4; 95% CI, 1.2–4.8; $p<0.05$).

Conclusions—In a population-based sample, *T. gondii* seroprevalence is not elevated in unipolar mood disorders but is higher in a subset of respondents with a history of bipolar disorder type 1.

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Financial disclosures.

Dr. Pearce reports no financial or other conflicts of interest. Dr. Kruszon-Moran and Dr. Jones report no financial or other conflicts of interest.

Keywords

bipolar disorder; major depression; dysthymia; Toxoplasma; C-reactive protein; neuroimmunology

Introduction

Toxoplasma gondii (*T. gondii*) is a protozoan parasite that infects humans by exposure to the organism in contaminated soil, water, undercooked meat, or in cat feces (1). It has evolved a complex lifecycle to continue its existence, which includes unique mechanisms to evade immune-mediated destruction and modify host behavior (2, 3). *T. gondii* is neuroinvasive and causes a persistent brain infection in rodents (3, 4). *T. gondii* cysts are assumed to remain in the brains of infected humans for life, but this assumption is based on the permissibility of human neural cells and the common reactivation of latent *T. gondii* during immunosuppression, as well as incidental findings of *T. gondii* cysts in brain tissue on autopsy (2, 5, 6).

Studies in humans and rodents have yielded indirect evidence implicating *T. gondii* in neuropsychiatric disorders. *T. gondii* evolved to induce subtle behavioral dysfunction causing infected rodents to have reduced fear of cats, promoting the transmission of the parasite (3, 4, 7). Although infection of the human host is irrelevant to the life cycle of the parasite in modern times, there is no reason to think that the ability of *T. gondii* to influence neurotransmitter regulation and host behavior becomes disengaged upon infection of the human brain. Several neurotransmitters relevant to mood disorders and psychosis may be affected by *T. gondii* infection (4, 8). For example, there is evidence that infection with *T. gondii* can induce indoleamine 2,3-dioxygenase, which can then decrease serotonin and influence glutamatergic neurotransmission (4, 9). Studies in animal models suggest that *T. gondii* upregulates dopaminergic neurotransmission, and the *T. gondii* genome contains two genes that code for tyrosine hydroxylase, the rate-limiting enzyme for synthesis of dopamine (4, 10). Among psychiatric illnesses, *T. gondii* has been studied most extensively in schizophrenia, and a meta-analysis found the overall the odds of *T. gondii* seropositivity was 2.73 times higher in schizophrenic patients than the general population (2).

The relationship of *T. gondii* infection and mood disorders is less clear. Two recent studies of *T. gondii* serology, which were focused on schizophrenia, also included individuals with major depressive disorder (MDD). These studies did not find a significant association between *T. gondii* seroprevalence and unipolar major depression. However, these were small case-control studies with 50 or fewer cases of MDD (11, 12). Another larger study (focused on suicide) examined *T. gondii* serology in 218 individuals classified as having major depression or bipolar disorder along with 39 healthy controls. While this study did not find a statistical association between *T. gondii* seropositivity and these mood disorders, the patients with mood disorders were a unique clinical sample with inclusion based on a prior suicide attempt or enrollment in a different study examining the relationship between depression and allergy (13). Thus, the results from this study may not be broadly applicable, though *T. gondii* antibody titers were higher in individuals who had attempted suicide versus those

without a history of suicide attempts. Another study examined *T. gondii* titers in inpatients being treated for depression, with the main analysis focused on 221 of these inpatients who were over age 45 years (9). While there was no significant difference in seroprevalence between the patients with depression and healthy controls, there were more individuals with high serointensity (i.e. high *T. gondii antibody titers*) in the major depression group compared to the control group.

Studies of *T. gondii* in bipolar disorder have also been inconclusive, in part because they have not clearly defined bipolar disorder and its subtypes, or they have collapsed multiple psychiatric illnesses into a single group. One large study using clinical samples from patients treated in a psychiatry department in China defined recent-onset affective disorders based on elevated scores on psychological tests of depression or mania (14). *T. gondii* seroprevalence did not differ between this affective disorders group and the control group. Another study of an inpatient population with various psychiatric disorders did not find evidence of heightened *T. gondii* seroprevalence in bipolar disorder or schizophrenia (15). However, this study mainly utilized patients with personality disorder co-morbidities. Other studies of *T. gondii* in affective psychosis have focused exclusively on prenatal or neonatal exposures (16–18).

Thus, the relationship between *T. gondii* exposure and major depression or bipolar disorder has not been studied in a population-based and racially diverse sample. A large sample is desirable because a number of potential confounder and mediator variables deserve consideration. For example, in addition to key demographic variables, several studies have shown an association between mood disorders and low-grade inflammation (19). In particular, major depression and bipolar mania are positively-associated with serum levels of C-reactive protein (CRP) (20–22). In the current study we examined the association between *T. gondii* exposure and several well-defined mood disorders in a sample of 7440 individuals age 15–39 years using the Third National Health and Nutrition Examination Survey (NHANES III). We controlled for demographic variables in addition to CRP and smoking.

Methods

To examine the relationship between prevalence of IgG antibodies to *T. gondii* and the diagnosis of selected mood disorders we used data from NHANES III, a cross-sectional survey conducted between 1988 and 1994 by the National Center for Health Statistics, Centers for Disease Control and Prevention. NHANES III was designed to obtain nationally representative statistics on health measures and conditions through household interviews, standardized physical examinations, and collection of biological specimens in mobile examination centers (23). NHANES III was based on a stratified, multistage, probability cluster design from which a sample representative of the civilian, noninstitutionalized U.S. population aged 2 months or older was drawn (23). Non-Hispanic Blacks, Mexican-Americans, children 2 months through 5 years, and persons ≥ 60 years of age were sampled at higher rates than other persons to assure an adequate sample size for these groups. Degree of urbanization was dichotomized as metro and non-metro with metro areas defined as central counties or fringe counties of metro areas with a population of 1 million or more and

non-metro as all others. Detailed descriptions of the design of the survey and the sample have been described elsewhere (23).

Surplus sera were tested for the prevalence of IgG antibodies to *T. gondii*. During the physical examination the Diagnostic Interview Schedule (DIS) (24), a structured psychiatric interview schedule, was administered in a private room. The Diagnostic and Statistical Manual of Mental Disorders - Edition 3 DSM-III version of the DIS was used in NHANES III. The DIS was administered only to respondents who were age 15–39 at the time of the interview, which limited the analysis to this relatively young subgroup. These data yielded lifetime prevalence for the seven mood disorder outcomes of interest. Specifically, respondents were coded dichotomously for ever having met the criteria for each mood disorder diagnosis (severe major depression, major depression, dysthymia with and without history of major depression, bipolar disorder type I with and without both manic and depressive episodes, and atypical bipolar disorder (bipolar type II) using the NHANES III reference source book)(25).

For depression, the primary analysis focused on individuals meeting lifetime criteria for severe major depression without bereavement (coded as MQPDEP=3). The criteria for severity of depression in this group were seeking professional help or medication, or affirming that the symptoms of depression interfered a lot with the respondent's life or activities. Additional analysis used a broader category that did not consider severity and included all eligible respondents with a lifetime history of major depression, including severe and non-severe subtypes without bereavement (MQPDEP=2 or 3). Dysthymia was classified as a broad category that included dysthymia with or without a history of major depression (MQPDYSTH= 2 or 3). Respondents were classified as having double depression if they met lifetime criteria for dysthymia and major depressive episode as well (MQPDYSTH= 3)(25)

For bipolar disorder, the main analysis focused on bipolar disorder type I in which respondents met severity and exclusion criteria for both a manic and a depressive episode (MQPBIPOL=2). In addition, a more inclusive group included respondents that met criteria for a manic episode but for whom a depressive episode diagnosis was coded as either absent or missing (MQPBIPOL=2 or 3). Atypical bipolar disorder (bipolar type II) was defined by hypomanic episodes in addition to major depression, and this diagnosis was only made in respondents who had not met criteria for a manic episode or bipolar I (MQPBIPII= 2 or 3) (25).

Socio-demographic factors related to mood disorders and *T. gondii* seropositivity were also assessed. Age was grouped as 15–19, 20–29, and 30–39 years. Race/ethnicity was based on self-reported information and categorized as non-Hispanic White, non-Hispanic Black, or Mexican American. Those who did not self-select as non-Hispanic white, non-Hispanic black, or Mexican American were placed in the "other" racial/ethnic group, which is included in the calculations for the total population but not in the models because the sampling frame was not designed to create national estimates representative of this group. Poverty index was calculated by dividing the total family income by the U.S. poverty threshold, adjusted for family size and categorized as below poverty (<1.0) and at or above

poverty (>=1.0). Education was measured as the last year of schooling completed by the individual (for sample persons age 20–39 years) or the head of household (for sample persons age 15–19 years) and grouped into three levels (less than high school, high school completed, and some college or college graduate). Place of birth was coded as U.S. versus non-U.S. Smoking was assessed by questionnaire and coded as current smoker versus past or never smoked.

Laboratory testing

Surplus sera specimens were tested for *T. gondii* IgG antibodies using the Patelia Toxo-G immunoglobulin G enzyme immunoassay (Sanofi Diagnostics Pasteur, BioRad, Hercules, California), according to the manufacturer's instructions. Prior to the study the Patelia Toxo-G kit was evaluated by comparison with the Centers for Disease Control and Prevention's *Toxoplasma* immunofluorescence assay-immunogloblin G test and Sabin-Feldman dye test (Dr. Jack Remington, Palo Alto, California) and found to have a sensitivity and specificity of 100% (1). For most analysis, *T. gondii* antibody titers were categorized as negative (< 6 IU) or positive (>=6 IU)), according to the manufacturer's instructions. We also performed a sub-analysis of serointensity that further distinguished between seropositive respondents with high Toxoplasma titers (>=240 IU) compared to intermediate titers (6-239 IU)(26).

In addition, C-reactive protein (CRP) levels were measured and used as a cofactor when examining the relationship between *T. gondii* infection and prevalence of a mood disorder. CRP levels were measured using a latex-enhanced Behring Nephelometer (26). The coefficient of variation for CRP throughout the period of data collection was 3.2% to 16.1% (26). Consistent with previous studies of depression in this cohort, CRP was dichotomized as undetectable (<2.2mg/L) versus elevated (>=2.2 mg/L)(20, 21).

Statistical analysis

Prevalence estimates were weighted to represent the total U.S. population and to account for oversampling and nonresponse to the household interview and physical examination (27, 28). Statistical analyses were conducted with SUDAAN (version 10.0.1), a family of statistical procedures for analysis of data from complex sample surveys (Research Triangle Park, NC: Research Triangle Institute). Standard error estimates were calculated using the Taylor Series Linearization method. Ninety-five percent confidence limits were estimated by using the exact binomial method (29). Estimates with relative standard errors (RSEs) greater than or equal to 40 were not reported because they are considered highly unstable. Multivariate logistic regression was used to examine the association between *T. gondii* infection and prevalence of each mood disorder. Multiple models for each mood disorder outcome were examined (each included a variable for *T. gondii* infection): a univariate model with only *T. gondii* infection, a model adjusting for age, race/ethnicity and gender, and a fully adjusted model with all potential cofactors under consideration, including a variable for CRP level. Additional analysis explored the relationship between CRP and unipolar mood disorders in logistic models stratified by *T. gondii* seropositivity. A P-value of <0.05 from a Satterthwaite adjusted F-statistic was considered significant.

Our sample consisted of individuals with complete data on all mood disorder diagnoses who were tested for *T. gondii* antibody. Specifically, 9473 individuals age 15–39 years were interviewed and 8773 (93% of those interviewed) were examined. Of the 8773 individuals examined, 8433 (96%) had complete mood disorder data, 7715 (88%) were tested for *T. gondii* antibodies, and 7440 (85% of those examined) had complete data for both. Although differences in response to completing both the *T. gondii* serologic testing and the DIS III varied significantly by levels of age, race/ethnicity, education, and foreign birth ($p<0.05$ from a chi-square analysis) response varied by <=3% among levels of each of these variables except with respect to foreign birth (81% among those foreign born versus 86% among those U.S. born).

Results

Characteristics of the study population are shown in Table 1. All percentages reported are weighted; the actual number of respondents is reported only to indicate sample size in each subgroup. Of the 7440 respondents included in this study, 1211 were seropositive for *Toxoplasma gondii* with a weighted percent of 14.5 (95% CI, 13.0–16.0).

As shown in table 2, there was no statistically significant association between *T. gondii* seroprevalence and severe major depression (unadjusted OR, 0.8; 95% CI, 0.5 –1.1). In addition, there was no statistically significant association between *T. gondii* serology and a history of major depression inclusive of severe and non-severe subtypes (unadjusted OR, 0.7; 95% CI, 0.5–1.1) as well as dysthymia (unadjusted OR, 1.3; 95% CI, 0.8 –1.9) or dysthymia combined with major depression (unadjusted OR, 1.3; 95% CI, 0.7–2.3). Since each of these logistic models in this population-based analysis included some respondents in the comparison group with a positive history of one or more mood disorders, which might bias our results toward the null, additional analysis were performed that limited the comparison group to only those individuals who never met criteria for any mood disorder. These results also indicated no association between *T. gondii* seropositivity and any combination of major depression or dysthymia ($P>0.05$, data not shown). Based on the emerging concept that the robustness of the antibody response (i.e. serointensity or *T. gondii* titer) rather than seroprevalence is an important factor linking *T. gondii* with psychiatric illnesses (9, 13) additional analyses were performed categorizing *T. gondii* serology results as a three level variable, < 6 IU (negative), 6-239 IU (intermediate titer), >=240 (high titer). For major depression, and dysthymia with major depression, the relative standard errors were too high for reliable estimates (RSE > 40%). For dysthymia there was no significant relationship with *T. gondii* serointensity ($P>0.10$, data not shown).

Several potential confounding variables were considered in adjusted models (Table 2). Adjustment for age, race/ethnicity, and gender resulted in similar ORs as the unadjusted findings. There was also no statistically-significant relationship between *T. gondii* seropositivity and any of these unipolar mood disorders in the full model, which controlled for age, race/ethnicity, gender, poverty level, education level, foreign birth, smoking and CRP level (Table 2). Elimination of CRP from these models did not reveal any significant associations ($P>0.05$). However, since these mood disorders were more common in women, and prior studies have shown an association between CRP and depression only in men, the

fully adjusted models were rerun stratified by gender. Again, no significant association between *T. gondii* seropositivity and any of these mood disorders was found (p>0.05, data not shown). As expected, in men but not women these models revealed a significant association between high CRP and each of these unipolar mood disorders (P<0.05, data not shown). The largest effect of CRP was observed in men with a history of dysthymia and depression, “double depression” (OR 5.1, 95% CI 1.9–13.6, p<0.01).

Because *T. gondii* infection could be contributing to some of the reported differences between men and women in the correlation between elevated CRP and mood disorder risk, we further explored the relationship between CRP and these mood disorders in logistic models stratified by *T. gondii* seropositivity and adjusted for age, race/ethnicity, poverty level, education, foreign birth, and smoking. In women, there was still no significant association between CRP and any of these unipolar mood disorders regardless of *T. gondii* serologic status (P>0.05, data not shown). In seronegative men, CRP remained a risk factor for severe major depression (OR 2.4; 95 % CI, 1.1–5.3), dysthymia (OR, 2.8: 95% CI 1.4–5.8), and double depression (OR, 4.8; 95% CI 1.7–13.7) and was marginally significant for broadly-defined major depression (OR, 2.0; 95% CI 1.0–4.3). Our sample contained too few *T. gondii* seropositive men with these mood disorders for reliable estimates, but ORs were of similar or greater magnitude as observed in the seronegative men (data not shown). Thus, consideration of *T. gondii* serologic status did not attenuate sex differences in the relationship between CRP and mood disorders.

Additional analysis considered potential confounding by rural versus urban residence. In this sample, residents of metro areas were less likely to be seropositive for *T. gondii* than residents of non-metro areas (OR 0.7; 95% CI 0.6 –1.0; p<0.05). However, there was still no significant association between T. *gondii* and any of these mood disorders after inclusion of urbanization as an independent variable (p>0.05 for fully adjusted models).

The ORs for logistic regression analysis of *T. gondii* serology and bipolar disorder are shown in table 3. There was a significant association between Toxoplasma seropositivity and lifetime history of bipolar disorder with mania and depressive episodes (unadjusted OR, 2.2; 95% CI, 1.2–4.1; p<0.01). This association remained significant after adjusting for age, race/ethnicity and gender (p<0.01), as well as the full model which also controlled for poverty level, education level, foreign birth, smoking and CRP (p<0.05). The odds ratio was similar after urbanization was stepped into the fully adjusted model (adjusted OR 2.3; 95% CI 1.1–4.7; p<0.05). Note, the number of persons with bipolar disorder that included mania and depressive episodes was small, only 8 in the *T. gondii* seropositive subgroup. When bipolar disorder type I was considered more broadly to include individuals who met criteria for a manic episode but not major depression, the OR was not significant (Table 3). Thus, inclusion of respondents who met lifetime criteria for mania but not major depression reduced the effect size of *T. gondii* seropositivity. Specifically, of the 68 respondents in this broad bipolar I group (Table 3), 27 met criteria for a manic episode but not major depression, and only 1 of these 27 was seropositive for *T. gondii*. Conversely, of the 41 respondents meeting criteria for both manic and depressive episodes, 8 were seropositive for *T. gondii*. The association between *T. gondii* seroprevalence and bipolar disorder II could

not be assessed because the estimate among *T. gondii* positives was highly unstable (RSE > 50%).

Discussion

The main finding in the group studied is that *T. gondii* antibody is not associated with major depression but is associated with bipolar disorder type I in which both manic and depressive features were reported. Strengths of the study include a large sample size with clearly defined racial and ethnic composition, and appropriate adjustment for confounding demographic and other variables including tobacco smoking. Moreover, the sample is community-based and not biased by selection of only inpatients for the psychiatric illness group (e.g who could have particular nosocomial exposures).

The lack of an association between *T. gondii* and MDD confirms prior smaller studies (11–13). In addition, we considered depression as a symptom spectrum to include dysthymia and "double depression", but we still found no relationship between *T. gondii* and these unipolar mood disorders. We also found no relationship between *T. gondii* antibody serointensity (titer) and dysthymia, but we had inadequate statistical power to examine this relationship in the other mood disorder outcomes.

Prior studies in this cohort have reported a positive association between CRP and depression in men but not women (20, 21). Our studies expanded these findings to include respondents with a history of dysthymia superimposed on major depression (double depression), and likewise found a strong association between CRP and this mood disorder in men. We considered that this sex difference could involve enhanced or prolonged inflammatory responses to *T. gondii* infection in men. However, we found no evidence to support this hypothesis since high CRP was associated with unipolar mood disorders even in *T. gondii* seronegative men. Thus, we found no evidence for a role for *T. gondii* in unipolar depression.

In contrast, *T. gondii* antibody was associated with bipolar disorder type I. Respondents with a prior *T. gondii* infection (as measured by *T. gondii* antibody) were approximately 2.3 fold more likely to have a history of bipolar disorder type I with manic and depressive symptoms than respondents who tested negative for *T. gondii* antibody. However, this association was attenuated when we broadened our definition of bipolar disorder type I to include respondents with a history of mania but not major depression. One possible explanation for this is that, in individuals predisposed to bipolar disorder type I, infection with *T. gondii* precipitates or accelerates the switch to depression.

There are several limitations to this study. A positive serology result for *T. gondii* IgG indicates that the infection occurred in the past, which could be weeks, months or decades prior to the NHANES examination. Thus this study, like prior studies of T. *gondii* in mood disorders, did not examine seroconversion prospectively, though a positive IgG serology is thought to be indicative of chronic infection (2). The apparent positive association with *T. gondii* and bipolar disorder type I could be due to greater exposure to the parasite as result of behavioral factors that could be more common among individuals with this mood disorder.

Conversely, infection could have been congenital in some cases, and a prior study reported indirect evidence for a connection between congenital toxoplasmosis and affective psychosis (17). Persons in this sample are young (<=39 years), and the negative findings for unipolar mood disorders from this sample cannot rule out a connection between *T. gondii* and MDD that is manifested after a long latency or that selectively affects older adults. It is also possible that preexisting MDD decreased behaviors related to *T. gondii* exposure (i.e. consumption of raw meat or outdoor exposure to soil) in some individuals, and that this outweighed any positive association between *T. gondii* and MDD in other individuals.

Although the total sample size in this study is large, the connection between *T. gondii* and bipolar disorder type I should be judged cautiously given the small number of respondents with both bipolar disorder type I and positive serology for *T. gondii*. Besides congenital infection, there are several mechanisms by which *T. gondii* could be related to bipolar disorder type I. *T. gondii* evolved to manipulate rodent behavior, and this infection can modulate the function of neurotransmitters including serotonin, dopamine and glutamate, all of which are involved in bipolar disorders (4, 7, 30). Interestingly, the mood stabilizer valproate inhibits replication of *T. gondii* (31), and treatment of rats with valproate or haloperidol reduces some behavioral traits associated with infection, possibly through decreasing *T. gondii* replication or neuroinvasiveness (32). Infection with *T. gondii* could also exacerbate neurocircuitry changes caused by genetic susceptibility to bipolar disorder. For example, during neuroinvasion or reactivation *T. gondii* could disrupt neural cell adhesion, which could be vulnerable to perturbation due to host genetic variants (33, 34). Genetic variants causing a predisposition to bipolar disorder could also interact with *T. gondii* infection by modifying the neurodistribution, neuroinvasiveness, or transition to tissue cysts of the parasite, and therefore confer adverse effects of infection on only a subset of individuals. For example, the major histocompatability region (MHC) on chromosome 6 harbors risk alleles for both bipolar disorder and schizophrenia (35), and MHC II (HLA-DQ allele) is linked with parasite burden in the brain and neurological outcome in congenitally *T. gondii*-infected infants and immunosuppressed adults (36, 37).

In conclusion, given that most studies have found a connection between *T. gondii* and schizophrenia, our finding that *T. gondii* is not associated with unipolar depression but might be associated with a subtype of bipolar disorder is indirect evidence that bipolar disorder and schizophrenia may share at least some etiological pathways.

Acknowledgments

We thank Sydney Hubbard M.P.H., and Drs. Erica Duncan, Bruce Jonas, and Patty Wilkins for helpful discussions.

Dr. Pearce reports grant support from the National Institutes of Health (NIMH, NICHD), The March of Dimes, and the Emory Neuroscience Initiative.

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Table 1

Sociodemographic and health-related variables in the NHANES III in our analytic sample[a]

Variable	Category	Number of respondents[b]	Percent (95% CI)[c]
Gender	Male Female	3402 4038	50.0 (48.7–51.4) 50.0 (48.6–51.3)
Age (years)	15–19 20–29 30–39	1600 3003 2837	16.7 (15.0–18.6) 40.3 (37.8–42.8) 43.0 (40.3–45.6)
Ethnicity	non-Hispanic white non-Hispanic black Mexican American All other	2134 2470 2519 317	71.5 (68.3–74.6) 12.6 (11.1–14.3) 7.2 (5.9–8.6) 8.7 (6.9–10.8)
SES (poverty level)	Below At or above	2047 4787	16.3 (14.2–16.5) 83.7 (81.5–85.8)
Education	<High School High School >High School	2486 2538 2377	20.3 (18.2–22.4) 34.7 (32.4–37.1) 45.0 (42.3–47.8)
Foreign birth	Outside US Inside US	1780 5645	13.7 (11.2–16.4) 86.3 (83.6–88.8)
Smoking status	Current smoker Past/Never smoker	2094 4623	37.3 (34.9–39.8) 62.7 (60.3–65.1)
T. gondii antibody titers (T. gondii serology)	Negative (< 6 IU) Positive (>=6 IU) High titer (>=240 IU) Intermediate titer (6-239 IU)	6229 1211 291 920	85.5 (84.0–87.0) 14.5 (13.0–16.0) 3.0 (2.4–3.7) 11.5 (10.2–12.8)
CRP level	<2.2 mg/L >2.2 mg/L	5589 1812	79.5 (77.4–81.5) 20.5 (18.5–22.6)

[a] Analytic sample consisted of individuals age 15–39 years who were interviewed, examined, had serologic testing to *T. gondii* and complete mood disorder data (N=7440).

[b] Number of respondents may not add to the total sample due to missing data for some variables.

[c] - Weighted percent of U.S. population as described in methods.

Table 2

Association between major depression or dysthymia outcomes and Toxoplasma serology in logistic regression models.

Type of mood disorder	T. gondii serology[a]	No. with mood disorder	Percent[b] [95% CI]	Crude		Model 1		Model 2		Model 2 Males		Model 2 Females	
				OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Major depression (severe subtype)	Negative N=6229 Positive N=1211	450 65	7.9 6.7–9.2 6.4 4.3–9.1	Ref 0.8	0.5 –1.1 p>0.05	Ref 0.8	0.6–1.2 p>0.05	Ref 0.8	0.6– 1.2 p>0.05	Ref 0.6	0.2–1.5 p>0.05	Ref 1.0	0.6–1.7 p>0.05
Major depression	Negative N=6229 Positive N=1211	498 76	8.9 7.6–10.3 7.0 4.8–9.8	Ref 0.7	0.5– 1.1 p>0.05	Ref 0.8	0.5–1.1 p>0.05	Ref 0.8	0.5–1.2 p>0.05	Ref 0.5	0.2–1.4 p>0.05	Ref 1.0	0.6–1.6 p>0.05
Dysthymia	Negative N=6229 Positive N=1211	440 108	5.8 4.7–7.0 7.8 5.4–10.9	Ref 1.3	0.8 –1.9 p>0.05	Ref 1.2	0.8–1.9 p>0.05	Ref 1.1	0.7–1.8 p>0.05	Ref 0.8	0.3–1.7 p>0.05	Ref 1.4	0.7–2.7 p>0.05
Double depression	Negative N=6229 Positive N=1211	206 36	3.2 2.4–4.2 4.2 2.3–6.9	Ref 1.3	0.7–2.3 p>0.05	Ref 1.3	0.7 –2.4 p>0.05	Ref 1.2	0.6–2.4 p>0.05	Ref 0.4	0.1–1.5 p>0.05	Ref 2.1	1.0–4.5 p>0.05

Model 1 was adjusted for age, race/ethnicity, and sex. Model 2 was adjusted for age, race/ethnicity, sex, poverty level, education level, foreign birth, current smoking and CRP level.

[a]-Negative, < 6 IU; Positive >=6 IU.

[b]-Weighted percent of U.S. population meeting mood disorder criteria.

Table 3

Association between bipolar disorder and Toxoplasma serology in logistic regression models

Type of mood disorder	T. gondii serology[a]	No. with mood disorder	Percent[b] [95% CI]	Crude		Model 1		Model 2	
				OR	95% CI	OR	95% CI	OR	95% CI
Bipolar I with manic and depressive episodes	Negative N=6229 Positive N=1211	33 8	0.4 0.2–0.8 0.8 0.5–1.3	Ref 2.2	1.2–4.1 P<0.01	Ref 2.3	1.4–4.1 P<0.01	Ref 2.4	1.2–4.8 P<0.05
Bipolar I (broadly defined)	Negative N=6229 Positive N=1211	59 9	0.8 0.5–1.2 0.9 0.6–1.3	Ref 1.3	0.7–2.3 p>0.05	Ref 1.4	0.8–2.3 p>0.05	Ref 1.3	0.6–2.8 p>0.05

Model 1 was adjusted for age, race/ethnicity, and sex. Model 2 was adjusted for age, race/ethnicity, sex, poverty level, education level, foreign birth, current smoking and CRP level.

[a]-Negative, < 6 IU; Positive >=6 IU.

[b]- Weighted percent of US population meeting mood disorder criteria.