Research paper

Toxoplasma gondii infection and common mental disorders in the Finnish general population

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ABSTRACT

Objective: We investigated whether *T. gondii* seropositivity is associated with 12-month depressive, anxiety and alcohol use disorders and current depressive symptoms and whether inflammation, measured by C-reactive protein (CRP) level, explains these associations.
Method: Health 2000 study (BRIF8901), conducted in years 2000–2001, is based on a nationally representative sample of Finns aged 30 and above, with 7112 participants and 88.6% response rate. DSM-IV depressive, anxiety and alcohol use disorders were assessed with the Composite International Diagnostic Interview and depressive symptoms with the Beck Depressive Inventory (BDI-21). We used logistic regression to investigate the association of *T. gondii* seropositivity with mental disorders and linear regression with BDI-21 scores.
Results: *T. gondii* seroprevalence was significantly associated with 12-month generalized anxiety disorder but not with other anxiety, depressive or alcohol use disorders. *T. gondii* seropositivity was associated with higher BDI-21 scores (beta 0.56, 95% CI 0.12–1.00, P = 0.013) and with having a comorbid depressive and anxiety disorder (OR 1.86, 95% CI 1.16–2.97, P = 0.010). Higher CRP levels were associated with these outcomes and with *T. gondii* seropositivity, but adjusting for CRP did not change the effect of *T. gondii* seropositivity.
Limitations: Cross-sectional study design with no information on the timing of *T. gondii* infection.
Conclusion: *T. gondii* seropositivity is associated with generalized anxiety disorder, depressive symptoms and comorbid depressive and anxiety disorders, which is not mediated by inflammation.

1. Introduction

Toxoplasma gondii (*T. gondii*) is an intracellular parasite that usually causes an inapparent primary infection but remains then latent in the body and may become reactivated later in life (Saadatnia and Golkar, 2012). The most common sources of infection are ingestion of food or water that is contaminated with oocysts shed by cats or by eating undercooked or raw meat containing tissue cysts (Montoya and Liesenfeld, 2004; Saadatnia and Golkar, 2012).

T. gondii seropositivity has been associated with several mental disorders (Sutterland et al., 2015). A recent meta-analysis investigated its association with schizophrenia, bipolar disorder, major depressive disorder (MDD) and addiction (mainly opioid dependence), and found significant association with schizophrenia, bipolar disorder and addiction but not with MDD (Sutterland et al., 2015). In addition, previous reports have associated *T. gondii* seropositivity with depressive and anxiety symptoms (Groër et al., 2011; Duffy et al., 2015), generalized anxiety disorder (GAD) (Markovitz et al., 2015), obsessive-compulsive disorder (OCD) (Miman et al., 2010), suicidality (Zhang et al., 2012), mixed anxiety and depressive disorder (Alvarado-Esquivel et al., 2016) and aggression and impulsivity (Cook et al., 2015). However, negative findings have also been published (Gale et al., 2014; Sugden et al., 2016).

The prevalence of *T. gondii* seropositivity varies markedly by region, age, and ethnic group (Saadatnia and Golkar, 2012; Sutterland et al., 2015), complicating comparisons between studies. Finland is an ethnically homogeneous Nordic country with relatively low *T. gondii* seroprevalence (von Hertzen et al., 2006). Here, we investigated the association of *T. gondii* seroprevalence and serointensity with mental health in a large, population-based representative sample of adult

Finns.

We investigated the association of *T. gondii* seropositivity and seriointensity with 12-month DSM-IV anxiety, depressive and alcohol use disorders as well as current depressive symptoms, adjusting for other factors associated with these disorders or with *T. gondii* seroprevalence. Furthermore, we investigated whether the effect of *T. gondii* seropositivity/seriointensity could be explained by inflammation, which was measured by sensitive C-reactive protein (CRP) level.

2. Materials and methods

2.1. Participants

The Finnish Health 2000 Survey was based on a nationally representative sample of 8028 persons aged 30 years or over from Finland (Aromaa and Koskinen, 2004). A two-stage stratified cluster sampling design was used to ensure that the sample was representative of the whole country. The sampling frame comprised adults aged 30 years and over living in mainland Finland. The field work took place between September 2000 and June 2001, and consisted of a home interview and a health examination at the local health center, or a condensed interview and health examination of non-respondents at home. In addition, several questionnaires were used to assess symptoms, lifestyle, and exposures related to different health problems. Descriptive data on the participants is presented in Table 1. Plasma samples were collected as a part of the health examination. Stored samples were available from 6250 participants for the current study.

The Health 2000 survey was approved by the Ethical Committee of THL and the Coordinating Ethics Committee at the Hospital District of Helsinki and Uusimaa. Written informed consent was received from

Table 1
Descriptive information of the participants.

Variable	N with available data on the variable	Proportion (%) or mean with 95% CI
Age	7112	53.0 (52.6–53.4)
Sex:	7112	
Women		52.5% (51.3–53.7%)
Men		47.5% (46.3–48.7%)
Education:	7072	
Basic		40.8% (39.4–42.3%)
Secondary		31.8% (30.7–33.0%)
High		27.3% (26.2–28.5%)
Place of residence:	7112	
Urban		61.4% (55.1–67.6%)
Semi-urban		14.4% (8.4–20.4%)
Rural		24.2% (18.0–30.5%)
Region of residence:	7112	
North		13.4% (13.2–13.8%)
East		17.2% (16.9–17.5%)
West		23.0% (22.5–23.6%)
Southwest		13.5% (13.2–13.8%)
South		32.9% (32.3–33.5%)
Marital status:	7091	
Married or cohabiting		68.0% (66.8–69.2%)
Single, separated or widowed		32.0% (30.8–33.2%)
Cat ownership:	5227	
Current		20.1% (18.7–21.5%)
Previous		54.0% (52.6–55.4%)
Never		25.9% (24.5–27.3%)
12-month depressive disorder	5995	6.5% (5.8–7.2%)
12-month anxiety disorder	6004	4.1% (3.5–4.6%)
12-month alcohol use disorder	5957	4.5% (3.9–5.1%)
Antidepressant use	7112	5.8% (5.3–6.4%)
BDI-21	6311	7.1 (6.9–7.3)
C-reactive protein	6266	2.22 (2.08–2.37)

each participant.

2.2. Mental health assessment

Mental disorders were assessed using the Munich-Composite International Diagnostic Interview or M-CIDI (Wittchen et al., 1998), using the sections on mood, anxiety and substance use disorders. These sections covered eight DSM-IV diagnoses: MDD and dysthymia, combined as depressive disorders; panic disorder with or without agoraphobia, agoraphobia without panic disorder, social phobia and GAD, combined as anxiety disorders, and alcohol abuse and dependence, combined as alcohol use disorders (Pirkola et al., 2005). The presence of symptoms within the past 12 months (12-month prevalences) were assessed. Of the total sample, 6005 (74.8%) completed the CIDI interview, and blood samples were available for 5917 (98.5%) of them.

In addition, current depressive symptoms were enquired about using the 21-item version of the Beck Depression Inventory (BDI-21) (Beck et al., 1961).

2.3. Sociodemographic variables

We used the following sociodemographic variables in the analysis: age, sex, education and place and region of residence.

Information on general education and on higher and vocational education was combined into a variable describing level of education with three categories. Basic education meant compulsory education with no vocational training beyond a vocational course or on the job training, high meant a degree from higher vocational institutions, polytechnics or universities, and secondary was between these categories, e.g. completion of vocational school. (Aromaa and Koskinen, 2004)

Current place of residence was categorized based on Statistics Finland's classification as urban, semi-urban and rural. Region of residence was categorized based on the university hospital districts as Northern, Eastern, Western, Southwestern, and Southern Finland.

2.4. Other variables

The participants were asked about cat ownership in a questionnaire, categorized as current, previous and never. This variable was added in the models, because domestic cats are a potential source of infection.

A previous Nordic study has found that *T. gondii* seropositivity is associated with higher values of C-reactive protein (CRP) (Birgisdóttir et al., 2006), which in turn is associated with both depression (Young et al., 2014) and anxiety (Copeland et al., 2012). Therefore, we investigated whether associations between mental health and *T. gondii* seropositivity changed after adjusting for CRP level. Serum high-sensitivity CRP levels (mg/L) had been measured in the Health 2000 study using automated analyser (Optima, Thermo Electron Oy, Vantaa, Finland) and an immunoturbidimetric test (Ultrasensitive CRP, Orion Diagnostica, Espoo, Finland), as described in detail in Heikkilä et al. (2011).

We controlled for the effect of antidepressant use, because one previous study found suggestive evidence that they may be associated with seriointensity in patients with MDD (Hinze-Selch et al., 2007).

2.5. T. gondii IgG level measurement

Concentration of IgG antibodies to Toxoplasma gondii was measured by solid phase enzyme immunoassay employing whole tachyzoite lysate from Ross South Labs, Spanish Fork Utah, USA employing methods similar to those which have been previously described (Dickerson et al., 2007). Sample values were converted to international units by comparison to standards with known levels of antibody.

We used 50 IU/ml as the cut-off for seropositivity, as in Sugden et al. (2016). In addition, seriointensity, defined as the quantitative level of