Driving us mad: the association of *Toxoplasma gondii* with suicide attempts and traffic accidents – a systematic review and meta-analysis

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Abstract

Unnatural causes of death due to traffic accidents (TA) and suicide attempts (SA) constitute a major burden on global health, which remained stable in the last decade despite widespread efforts of prevention. Recently, latent infection with *Toxoplasma gondii* (*T. gondii*) has been suggested to be a biological risk factor for both TA and SA. Therefore, a systematic search concerning the relationship of *T. gondii* infection with TA and/or SA according to PRISMA guidelines in Medline, Pubmed and PsychInfo was conducted collecting papers up to 11 February 2019 (PROSPERO #CRD42018090206). The random-effect model was applied and sensitivity analyses were subsequently performed. Lastly, the population attributable fraction (PAF) was calculated. We found a significant association for antibodies against *T. gondii* with TA [odds ratio (OR) = 1.69; 95% confidence interval (CI) 1.20–2.38, $p = 0.003$] and SA (OR = 1.39; 95% CI 1.10–1.76, $p = 0006$). Indication of publication bias was found for TA, but statistical adjustment for this bias did not change the OR. Heterogeneity between studies on SA was partly explained by type of control population used ($OR_{healthy\ controls} = 1.9$, $p < 0.001$ $v.$ $OR_{psychiatric\ controls} = 1.06$, $p = 0.87$) and whether subjects with schizophrenia only were analysed ($OR_{schizophrenia} = 0.87$, $p = 0.62$ $v.$ $OR_{various} = 1.8$, $p < 0.001$). The association was significantly stronger with higher antibody titres in TA and in studies that did not focus on schizophrenia subjects concerning SA. PAF of a *T. gondii* infection was 17% for TA and 10% for SA. This indicates that preventing *T. gondii* infection may play a role in the prevention of TA or SA, although uncertainty remains whether infection and outcome are truly causally related.

Introduction

Unnatural causes of death due to traffic accidents (TA) or suicide attempt (SA) constitute a major burden on global health. According to the World Health Organisation (WHO) about 1.4 million people die each year as a result of road injuries, rendering it among the 10 leading causes of death globally for years (Naghavi *et al.*, 2017). Between 20 and 50 million more people suffer from non-fatal road accidents, with many incurring a disability as a result of their injury. According to the WHO, TA are among the most important problems with regard to social, economic and human health issues (Naghavi *et al.*, 2017). Likewise, suicide also has a huge impact on society, with 0.8 million people dying annually due to self-harm (Naghavi *et al.*, 2017). For every fatal SA, 10–20 persons are estimated to attempt suicide, with approximately 10 million people attempting suicide worldwide annually (Turecki and Brent, 2016).

Both these causes of unnatural death are considered to be multifactorial, with psychological, social and biological factors involved (Turecki and Brent, 2016; Lutz *et al.*, 2017). Resources are directed at addressing modifiable factors in policymaking (Perron *et al.*, 2013; Goniewicz *et al.*, 2016; Herbert *et al.*, 2017) (i.e. making more difficult to jump of bridges, increasing road safety, preventing drug abuse) and healthcare (Goniewicz *et al.*, 2016; Turecki and Brent, 2016; Gilissen *et al.*, 2017) (improved immediate care for people involved in a car crash, lowering barriers for people with suicidal ideation to receive help) in order to diminish health burden. These interventions showed regional successes although without affecting global mortality rates in the last decade (Naghavi *et al.*, 2017). Recently, a hitherto unsuspected, but potentially modifiable biological factor has received increasing attention with its association to both SA and TA: the latent infection with *Toxoplasma gondii* (*T. gondii*) (Flegr *et al.*, 2009; Pedersen *et al.*, 2012).

T. gondii is an intracellular and neurotropic parasite affecting most of the warm-blooded animals including humans. In humans, infection is acquired by ingestion of contaminated water or food that contains tissue cysts. It is estimated that approximately 30% of the global population is infected with the parasite, with large regional variances (Montoya and Liesenfeld, 2004). The parasite has a complex life cycle, whereby it needs to end up in the intestine of felines (cats) in order to complete its lifecycle (Montoya and Liesenfeld, 2004). Interestingly, non-feline mammals show cognitive and behavioural changes that increase their risk of being caught by felines (Berdoy *et al.*, 2000; Webster, 2007), which are considered evolutionary adaptations of the parasite facilitating its survival. There is evidence that the parasite accomplishes this behavioural change by influencing neurotransmitters in the brain (Flegr, 2013; Parlog *et al.*, 2015). Studies have shown that the parasite is able to increase dopamine release in infected neurons (Prandovszky *et al.*, 2011) and potentially influences the kynurenine pathway, which could influence glutamate signalling (Notarangelo *et al.*, 2014).

Since these findings emerged, research focussed increasingly on possible cognitive and behavioural changes by a latent *T. gondii* infection in humans. Indeed, neurocognitive changes have been reported in people with a latent *T. gondii* infection, whereby increased impulsiveness has been reported in people with *T. gondii* infection, although results so far are heterogeneous (Dickerson *et al.*, 2014; Gale *et al.*, 2015; Sugden *et al.*, 2016; Peng *et al.*, 2018). Nonetheless, meta-analyses did show overall a significant association of exposure to *T. gondii* with several psychiatric disorders, especially schizophrenia, suggesting that the infection could impact human behaviour as well (Sutterland *et al.*, 2015).

The objective of the study was to determine if *T. gondii* infection is indeed associated with SA and/or TA by conducting a systematic review and meta-analysis.

Methods

We followed the systematic review guidelines provided by the PRISMA statement (Moher *et al.*, 2009). We conducted a systematic search (see online Supplementary Appendix 1) throughout Medline, PsychInfo and EMBASE until 11 February 2019 (Prospero #CRD42018090206).

Inclusion criteria were: (i) original research papers with comparable quantitative data; (ii) any language; (iii) analysis of latent *T. gondii* infection by measuring IgG antibodies using one of the following diagnostic assays: Sabin–Feldman dye test, complement fixation, immune haemagglutination, immune fluorescence or enzyme-linked immunosorbent assay (ELISA); (iv) case–control or cohort studies with human subjects; (v) data on SA and/or TA. Exclusion criteria were: (i) studies without a control group, (ii) case reports or case series and (iii) studies with immunocompromised patients. Additional studies were sought in references to all reviews on this topic. Screening of search results by manuscript titles and abstracts were performed by three researchers (AS, BK, AK). Final screening by reading the whole manuscript was performed to validate inclusion (AS, AK). The corresponding authors were asked to provide additional data if not included in the original publications and for unpublished results.

All selected articles were screened on study quality independently by two researchers (AS, GF) following Cochrane criteria of quality on case–control or cohort studies (Higgins *et al.*, 2011). If there was a difference in quality score, the difference was discussed. If consensus could not be reached, a third opinion was asked (LdH) for a final decision.

Some studies included only subjects which had committed SA as cases (e.g. cases presented at the emergency department due to a SA) and collected healthy controls as a control population in order to compare antibody levels against *T. gondii*. In contrast, other studies included subjects with certain psychiatric disorder (s) cross-sectionally and defined caseness as having a history of SA(s) and control population as subjects not having this history. In order to evaluate whether this difference in sampling method mattered, we stratified studies based on the type of control population used.

Meta-analysis of eligible studies

For all studies an odds ratio (OR) was calculated. ORs adjusted for confounders were used if available. The random-effects model was applied for all analyses. Heterogeneity was assessed by eyeballing and calculating I^2. Meta-analytical calculations were carried out with Comprehensive Meta-analysis Software 3.0 (Borenstein *et al.*, 2013).

Effect of potential moderators on heterogeneity was assessed if possible (study quality, mean age, sex, seroprevalence of the control population, fatality, type of control population, diagnosis of cases and timing of outcome measurement: prospective or retrospective). Whether studies had a prospective design was determined based on the fulfilment of one of the following two criteria: (a) the study was designed as a longitudinal cohort study in which the assessment of seropositivity to *T. gondii* preceded the outcome (TA or SA) or (b) in a cross-sectional study the outcome (TA or SA) had occurred at or shortly before the measurement of IgG antibodies against *T. gondii* (since these antibodies are indicative of a latent infection and emerge months after primary infection). Considering the diagnosis of cases, specifically for SA, studies were grouped in studies that had included only cases with schizophrenia (schizophrenia only) compared with studies that had included other or any psychiatric disorder (various psychiatric disorders).

Where applicable meta-regression analysis (for continuous data) or subgroup analysis (for categorical data) were performed with the methods of moments and the mixed-effects model, respectively (Borenstein *et al.*, 2009).

To assess by which proportion moderators influenced the variance of the true effect, regression analyses were performed investigating the moderator as a covariate. The amount of variance was expressed by R^2. Due to the number of included studies, moderator effects were analysed individually (Borenstein *et al.*, 2009).

For seropositivity definition, cut-off scores used for the assays in the respective studies were used. If multiple assays were used in a study, we utilized the results of the assay that showed the smallest effect size.

Higher average antibody titres (compared with controls) have been called serointensity, whereby preferably numbers on high *v.* low, but still positive, antibody titres were used to see if this influenced the magnitude of the OR. If these were not available, average titres in groups were used and converted into an OR.

The potential for publication bias was assessed by examination of funnel plots and by the Egger's test (which was considered significant if the one-sided *p* value was <0.10). If applicable, Duval and Tweedie's trim and fill method was used for a better estimation of the true OR.

Since the global incidence of TA and SA are both low (0.3–0.7% per year and 0.14% per year, respectively), OR becomes identical to the risk ratio (RR) (Zhang and Yu, 1998). As the
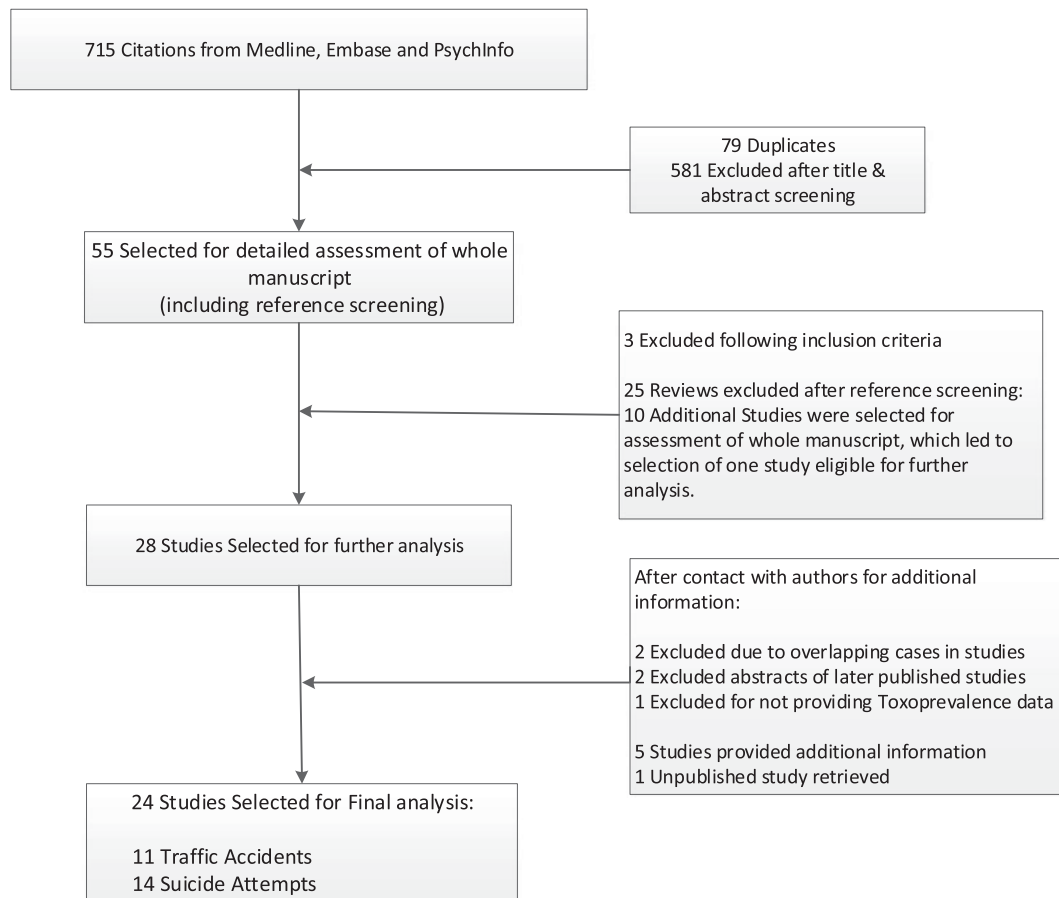
Fig. 1. Flowchart of the study selection process.

current meta-analysis provides an estimation of ORs and the global prevalence (Pglob) of a latent *T. gondii* is estimated to be 30% (Montoya and Liesenfeld, 2004), the population attributable fraction (PAF) can be calculated. The formula PAF = [Pglob × (RR − 1)]/[Pglob × (RR − 1) + 1] was applied (Levin, 1953).

Results

The systematic search rendered in a total of 715 studies. After duplicate removal, 636 studies remained. After title and abstract screening for inclusion criteria, 51 studies were selected for full-text screening. Ten studies were added after reference screening of reviews. After full-text screening, 24 studies were finally selected for quantitative synthesis, with a total of 4229 cases and 12 234 controls in TA and 2259 cases and 9400 controls in SA (see Fig. 1 for flowchart and Table 1 for study characteristics).

Traffic accidents

In total, 11 studies comparing seropositivity to *T. gondii* with the risk of being involved in a TA were identified (Flegr *et al.*, 2002; Yereli *et al.*, 2006; Flegr *et al.*, 2009; Kocazeybek *et al.*, 2009; Galvan-Ramirez *et al.*, 2013; Samojlowicz *et al.*, 2013; Alvarado-Esquivel *et al.*, 2015; Shotar *et al.*, 2016; Sugden *et al.*, 2016; Stepanova *et al.*, 2017; Burgdorf *et al.*, 2019), showing an overall OR of 1.69 (95% CI 1.20–2.38, *p* = 0.003), see Fig. 2. The Egger's test did indicate the presence of publication bias (*p* = 0.06), however the Duval and Tweedie's trim and fill rendered

the same OR using the random-effects model if missing studies were searched left from the mean. Also, the funnel plot using the random-effects model did not indicate publication bias (online Supplementary Appendix 2). Heterogeneity was considerable and significant (I^2 = 86%, *p* < 0.0001, τ^2 = 0.247).

To explore heterogeneity, moderators were assessed for their impact on the between-study variance. No effect of overall study quality on OR was found. Noteworthy, when quality of the definition of cases in TA was considered separately, the OR was significant in studies using a more concise description of TA (excluding alcohol use, making sure the driver was responsible for the accident), as opposed to those with broader inclusion criteria. Importantly, studies selectively assessing fatal TA as well as studies measuring antibodies against *T. gondii* occurring directly after or before the occurrence of TA (representing prospective study designs, as IgG antibodies against *T. gondii* represents a latent infection) both showed significant associations (Table 2a).

None of the moderators had a significant impact on the variance of the overall effect.

Serointensity and TA

In total, five studies reported serointensity (Flegr *et al.*, 2002; Flegr *et al.*, 2009; Kocazeybek *et al.*, 2009; Galvan-Ramirez *et al.*, 2013; Shotar *et al.*, 2016). Overall, the odds for TA were increased in cases with high titres compared with low titres; OR 1.75 (95% CI 1.28–2.38; *p* < 0.001). Significant heterogeneity was present

Table 1a. (a) Study characteristics of studies reporting *T. gondii* infection and traffic accidents

Study (year)	Country	Case population	Control population	Outcome measure	Analysis method	Findings (*n*, % in cases and controls respectively)[a]
Alvarado-Esquivel et al. (2015)	Mexico	Interstate truck drivers with toxoplasmosis (*n* = 62) Age: unclear Gender: unclear	Interstate truck drivers without toxoplasmosis (*n* = 130) Total group (*n* = 192) Age(±s.ᴅ.): 43.4(10.2) years Gender: 97% male	History of traffic accidents	ELISA	Seropositivity: 10/62 (16.1%) *v.* 13/130 (10%) Serointensity: not available
Burgdorf et al. (2019)	Denmark	Blood donors who had a registered traffic accident (*n* = 2724) Age: 37.4 years (overall population) Gender: 55% male	Blood donors without registered traffic accident, matched on age, sex and parental history of psychiatric disorder with cases on time of blood sampling (*n* = 6294). Cases with a psychiatric disorder without traffic accident were included as controls	Registered as being involved in a traffic accident in Danish national patient register or Danish register of causes of death. Cases registered as pedestrian or passenger were excluded	Solid phase ELISA	Seropositivity: 723/2724 (27%) *v.* 1579/ 6294 (25%) Prospective subgroup; outcome after blood sampling: 206/751 (27%) *v.* 1309/ 5228 (25%) Serointensity: not available
Flegr et al. (2002)	Czech Republic	Outpatients at the surgery unit of the Kralovske Vinohrady Hospital, Prague (*n* = 146) Age: 15–70 years Gender: 58% male	Residents of central Prague, selected by quota sampling in a survey (*n* = 446)	History of traffic accidents. Only those who had negative alcohol laboratory test and actively influenced probability of their TA were included (judged by three independent persons)	CFT ELISA	Seropositivity: 58/146 (40%) *v.* 84/446 (19%) ORs stratified by age confirmed overall finding Serointensity: grouping according to low (8–16), moderate (32–64) and high antibody titres(>64): OR 1.86 (95% CI 1.1–3.0), 4.78 (95% CI 2.4–9.6) and 16.03 (95% CI1.9–135.7) respectively Moderate or high *v.* low seropositive titres: 25/84 (30%) *v.* 18/84(21%)
Flegr et al. (2009)	Czech Republic	Male draftees who were involved in traffic accidents during follow-up of 1.5 years, while fulfilling compulsory military service (*n* = 111) Age: 20.4 Gender: 100% male	Male draftees who attended the Central Military Hospital in Prague for regular examinations for compulsory military service (*n* = 3890) Age(±s.ᴅ.): 20.1(±1.55) Gender: 100% male	Draftees who were involved in traffic accidents during follow-up of 1.5 years, while fulfilling compulsory military service (prospective cohort study)	CFT ELISA	Seropositivity: 28/111 (25.2%) *v.* 862/ 3779 (22.8%) When corrected for age, starting year of service and RhD: OR 2.56 (95% CI 1.1–5.7) Serointensity: increasing titre – interacting with RhD (χ^2 = 7.85, *p* = 0.02)

(*Continued*)

Table 1a. (*Continued.*)

Study (year)	Country	Case population	Control population	Outcome measure	Analysis method	Findings (*n*, % in cases and controls respectively)[a]
Galvan-Ramirez *et al.* (2013)	Mexico	Drivers with traffic accidents (*n* = 159) Age(±s.d.): 37.1(±11.8) years Gender: 76% male	Drivers without history of traffic accidents, randomly selected from same region (*n* = 164) Age(±s.d.): 39.7(±11.8) years Gender: 76% male	Drivers sent for medical attention to hospital due to injuries caused by traffic accidents. People with positive alcohol tests were excluded	ELISA	Seropositivity: 54/159 (34%) *v.* 59/164 (36%) Multivariate analysis corrected for age: OR 1.002 (95% CI 1.000–1.004) Detection of *T. gondii* DNA: 2/33 *v.* 1/38 Serointensity; average titres(±s.d.): 237.9(±308.5) *v.* 122.9 (±112.7)
Kocazeybek *et al.* (2009)	Turkey	Group 1. Drivers presented at the emergency departments with traffic accidents (*n* = 67 non-fatal and *n* = 25 fatal) Group 2. Subjects who presented at emergency departments in Istanbul before study started (*n* = 151) Age group 1: 33.8 (non-fatal) and 37.4 (fatal) years Age group 2: 37.8 years Gender group 1: 71.4% (non-fatal) and 96% (fatal) male Gender group 2: 100% male Mean age overall: 36.7 Gender overall: 95.5% male	Drivers without history of traffic accidents matched to study groups for living area, gender and age, who had no complaints related to toxoplasmosis and had not been tested before for toxoplasmosis and visited the hospital for blood donation (*n* = 200) Age: 36.7 years Gender: 95.5% male	Group 1. Drivers acutely presented at the emergency departments who were involved in causing traffic accidents, had negative alcohol tests and had no neurological disorders (fatal and non-fatal) Group 2. Subjects with history of non-fatal traffic accidents who presented at emergency departments in Istanbul before study started. Negative alcohol tests, involved in traffic accidents and no neurological disorders	ELISA	Seropositivity: 130/243 (53.5%) *v.* 56/200 (28%) Group 1: 49/92 (53.3%) Group 2: 81/151 (53.6%) Serointensity; average titres per group(±s.d.): Overall: 154.3(±187) *v.* 102.5(±213) Group 1: 205.8(±252) Group 2: 122.2(±182) Analysis with logistic regression analysis correcting for age: OR 1.72 (95% CI 1.4–2.1)
Samojlowicz *et al.* (2013)	Poland	People who died suddenly due to traffic accidents (*n* = 42) Age: 19–88, median = 40 Gender: 93% male	People who died suddenly due to disease, hypothermia, alcohol intoxication, injuries as passenger or being murdered (*n* = 83) Age: 20–89, median = 51 Gender: 92% male	Died due to traffic accidents, who were driving the vehicle. Analysis of alcohol available, not excluded	IF	Seropositivity: 25/42 (60%) *v.* 41/83 (49%) Excluding alcohol use: 18/33 (54.5%) *v.* 16/40 (40%) Average titres not available Unadjusted for age and gender
Shotar *et al.* (2016)	Jordan	Drivers arrested and imprisoned for causing road TA (*n* = 13) Age(±s.d.): 32.9±7.5 Gender: 100% male	Healthy control population (*n* = 200) Age(±s.d.): unknown Gender: unknown	Drivers arrested and imprisoned for causing road accidents	ELISA	Seropositivity: 2/13(15.4%) *v.* 24/200 (12%) Mean IgG titres(s.d.): 3.19(5.85) *v.* 1.98(1.14)

Study	Country	Case population[a]	Control population	Method	Results
Stepanova et al. (2017)	Russia	Persons with driver's license hospitalized for causing road TA while driving, excluding alcohol/drug intoxication (n = 100). Age: 18–45, average unknown. Gender: 65% male	Healthy persons undergoing routine medical check-up (n = 152). Age: 18–45, average unknown. Gender: 53.9% male	ELISA	Seropositivity: 45/100(45%) v. 39/152 (25.6%). OR adjusted for gender: 2.35 (95% CI 1.4–4.0)
Sugden et al. (2016)	New Zealand	Dunedin birth cohort who were T. gondii positive (n = 236). Age: 38 (all). Gender: 58% male	Dunedin birth cohort who were T. gondii negative (n = 601). Age: 38 (all). Gender: 47% male	ELISA	Seropositivity: 51/236(21.6%) v. 89/601 (14.9%). Serointensity data not available
Yereli et al. (2006)	Turkey	People with TA from Izmir and Manisa in Turkey (n = 185). Mean age: unknown. Gender: 54% male	People without history of TA, recruited from same region and in same age range. No clinical signs or symptoms of toxoplasmosis (n = 185). Mean age: unknown. Gender: 51% male	ELISA	Seropositivity: 55/185 (29.7%) v. 14/185 (7.6%). Serointensity: Not available. Age group-specific rates available

ELISA, enzyme linked immunoassays; CFT, complement fixation test; IF, indirect fluorescence test.
[a]Data of cases are presented first, control population second.

($I^2 = 65\%$, τ 0.299), for which no explanation was found with available moderators (seroprevalence, age, quality, study design).

SA or suicide

Thirteen studies studying the association between SA and latent *T. gondii* infection and one unpublished study were identified (Arling et al., 2009; Yagmur et al., 2010; Okusaga et al., 2011; Pedersen et al., 2012; Zhang et al., 2012; Alvarado-Esquivel et al., 2013; Samojlowicz et al., 2013; Fond et al., 2015; Coryell et al., 2016; Sugden et al., 2016; Ansari-Lari et al., 2017; Bak et al., 2018; Burgdorf et al., 2019; Sutterland et al., 2019), with an overall OR of 1.39 (95% CI 1.10–1.76, $p = 0006$), see Fig. 3. One of the studies provided data on suicide deaths, violent SA as well as self-directed violence (Pedersen et al., 2012). Subjects with self-directed violence were excluded from the analysis. The Egger's test did not indicate the presence of publication bias ($p = 0.15$) and Duval and Tweedie's trim and fill analysis using the random-effects model rendered a similar and significant OR. There was evidence of heterogeneity ($I^2 = 55\%$, $p = 0.003$, $\tau^2 = 0.103$).

To explore heterogeneity, moderators were assessed for their impact on the between-study variance. Two moderators had a significant impact on the between-study variance: the proportion of patients with schizophrenia (schizophrenia only v. various psychiatric disorders) [$OR_{schizophrenia} = 0.87$ (95% CI 0.51–1.49), $p = 0.62$ v. $OR_{various} = 1.8$ (95% CI 1.44–2.24), $p < 0.001$] and whether the control population consisted of healthy controls or patients with psychiatric disorders [$OR_{healthy\ controls} = 1.9$ (95% CI 1.48–2.44), $p < 0.001$ v. $OR_{psychiatric\ controls} = 1.06$ (95% CI 0.70–1.61), $p = 0.78$] (Table 2b). In order to determine whether the effect of one moderator could drive the other, the effect of diagnosis within studies that used controls with psychiatric disorders was assessed post-hoc in studies with various psychiatric disorders as control subjects ($n = 4$) compared with only schizophrenia as control subjects ($n = 5$). A non-significant larger association was found [$OR_{various} = 1.49$ (95% CI 0.71–3.15), $p = 0.29$ v. $OR_{schizophrenia} = 0.87$ (95% CI 0.51–1.49), $p = 0.62$; Q-between 1.32, $p = 0.25$, $R^2 = 0\%$]. It was not possible to investigate the reverse, since all studies investigating SA in subjects with schizophrenia did not use healthy controls as a comparison.

Importantly, studies that selectively assessed SA within a prospective design as well as fatal SA showed significant associations with *T. gondii* infection (Table 2b).

Even though the type of diagnosis of case population or type of control population explained a (trend-)significant amount of between-study variance, the estimated proportion of between-study variance was 0% for both moderators as expressed by R^2.

Serointensity and SA

Eight studies reported serointensity (Arling et al., 2009; Okusaga et al., 2011; Pedersen et al., 2012; Zhang et al., 2012; Alvarado-Esquivel et al., 2013; Fond et al., 2015; Ansari-Lari et al., 2017; Bak et al., 2018), rendering an overall OR of 1.22 (95% CI 0.96–1.55, $p = 0.11$). There was no indication of publication bias (Egger's test $p = 0.17$). The heterogeneity of the observed effects between studies was high ($I^2 = 62\%$, $p = 0.004$, $\tau = 0.252$). When exploring possible reasons for the heterogeneity, there was a significant effect of studies focussing on subjects with schizophrenia ($n = 5$) v. various other psychiatric disorders ($n = 5$): OR 0.99 (95% CI 0.77–1.29) v. OR 1.66 (95% CI 1.29–2.12, $p < 0.001$), $R^2 = 61\%$, $p = 0.004$.

Table 1b. (b) Study characteristics of studies reporting *T. gondii* infection and suicide attempts

Study (year)	Country	Case population	Control population	Outcome measure	Analysis method	Findings (*n*, % in cases and controls respectively)[a]
Alvarado-Esquivel et al. (2013)	Mexico	Outpatients with various psychiatric disorders (*n* = 156) Age(±s.D.): 34.0(±10.3) years Gender: 24% male	Outpatients with various psychiatric disorders (*n* = 127) Age(±s.D.): 38.3(±11.6) years Gender: 40% male	History of suicide attempt(s)	ELISA	Seropositivity: 7/156 (5%) *v.* 10/127 (8%) High antibody titres (>150 IU/ml): 7/7 (100%) *v.* 5/10 (50%)
Ansari-Lari et al. (2017)	Iran	Patients with schizophrenia (*n* = 42) Age(±s.D.): 43.5(±8.1) years Gender: 76.2% male	Patients with schizophrenia (*n* = 57). Age(±s.D.): 38.0(±11.1) years Gender: 70.2% male	History of suicide attempt(s)	ELISA	Seropositivity: 8/42 (19%) *v.* 21/57 (37%) Mean IgG titres(±s.D.): 7.7(±11.7) *v.* 12.5(±13.7)
Arling et al. (2009)	USA	Patients with mood disorders (major depressive disorder or bipolar I or II disorder), (*n* = 99) Age(±s.D.): 40.3(±9.8) years Gender: 39% male	Patients with mood disorders (major depressive disorder or bipolar I or II disorder), (*n* = 119) Age(±s.D.): 43.4(±10.9) years Gender: 36% male	History of suicide attempt(s) measured by Columbia suicide history form identifying suicide attempts with (some) intent to die, interrupted attempt and ambiguous attempt	Solid phase ELISA	OR 1.62 (95% CI 0.72–3.65) Geometric Mean IgG values (±s.D.), adjusted for age, gender and race: 0.51(±0.46) *v.* 0.37(±0.50)
Bak et al. (2018)	Korea	In- and outpatients seeking treatment for suicide attempts with depressive symptoms (*n* = 155) Age: 43.7 years Gender: 48.4% male	Healthy controls with no history of psychiatric disorders (*n* = 135). Age: 41.6 years Gender: 48.9% male	History of suicide attempt(s) (non-suicidal automutilation ruled out)	CLIA	Seropositivity: 21/155 (14%) *v.* 8/135 (6%) High antibody titres (>150 IU/ml): 7/21 (33%) *v.* 2/8 (25%)
Burgdorf et al. (2019)	Denmark	Blood donors with registered suicide attempt or suicide (*n* = 655) Age 37.4 years (overall) Gender: 42.4% male	Blood donors without registered suicide attempt or suicide, matched on age, sex and parental history of psychiatric disorder with cases on time of blood sampling (*n* = 6503). Cases with a psychiatric disorder without suicide (attempt) were included as controls	Registered suicide attempt in Danish national patient register or suicide in Danish register of causes of death	Solid phase ELISA	Seropositivity: 193/655 (29%) *v.* 1633/6503 (25%) Prospective subgroup; outcome after blood sampling: 3/23 (13%) *v.* 1319/5259 (25%) Seerointensity: not available
Coryell et al. (2016)	USA	Adolescents starting treatment with SSRI, in- and outpatients (*n* = 17) Age(±s.D.): 17.5(±1.7) years Gender: 29% male	Adolescents starting treatment with SSRI, in- and outpatients (*n* = 91) Age(±s.D.): 19.0(±1.6) years Gender: 24% male	History of suicide attempt(s), defined as any self-harm intended to cause death	ELISA	2/17 (12%) *v.* 2/91 (2%) seropositive Mean IgG titres (±s.D.): Adjusted for age and gender
Fond et al. (2015)	France	Inpatients with bipolar disorder type I and II (*n* = 54). Age(±s.D.): 48.1(±12.0) years Gender: 46% male	Inpatients with bipolar disorder type I and II (*n* = 97). Age(±s.D.): 42.3(±13.7) years Gender: 52% male	History of suicide attempt(s) and suicide intentionality and lethality according to the Columbia-suicide severity rating scale	Solid phase ELISA	Seropositive: 45/54 (83%) *v.* 69/97 (71%) Seerointensity (mean titre ±s.D.): 3.30(±1.47) *v.* 2.84(±1.69)

Fond *et al.* (2015)	France	Inpatients with schizophrenia or schizoaffective disorder (*n* = 43) Age(±s.d.): 36.2(±11.4) years Gender: 70% male	Inpatients with schizophrenia or schizoaffective disorder (*n* = 61) Age(±s.d.): 35.4(±11.5) years Gender: 75% male	History of suicide attempt(s) and suicide intentionality and lethality according to the Columbia-suicide severity rating scale	Solid phase ELISA	Seropositive: 30/43 (70%) *v.* 44/61 (72%) Serointensity (mean titre ±s.d.): 2.68(±1.69) *v.* 2.53(±1.81)
Sutterland *et al.* (2019)	The Netherlands	Outpatients with schizophrenia (*n* = 34) Age(±s.d.): 30.2(±6.8) years Gender: 68% male	Outpatients with schizophrenia (*n* = 285) Age(±s.d.): 29.7(±6.4) years Gender: 78% male	History of suicide attempt(s)	ELISA	Seropositive: 2/33 (6%) *v.* 49/285 (17%)
Okusaga *et al.* (2011)	Germany	In- and outpatients with schizophrenia (*n* = 372) Age(±s.d.): 40.8 (±11.8) years Gender: 51% male	In- and outpatients with schizophrenia (*n* = 578) Age(±s.d.): 36.1 (±11.1) years Gender: 57% male	History of non-fatal suicidal self-directed violence	Solid phase ELISA	Seropositivity, adjusted for gender, education, PANSS, duration of illness and plate: Adjusted OR (<38 years): 1.57 (1.03–2.38) Adjusted OR (>38 years): 0.79 (0.53–1.19) Serointensity: Adjusted OR (<38 years): 1.23 (1.04–1.47) Adjusted OR (>38 years): 0.90 (0.76–1.01)
Pedersen *et al.* (2012)	Denmark	Mothers giving birth to first child between 5/15/1992 and 1/15/1995 and followed up to 2006 (*n* = 488) Age: not available, but all analyses adjusted for age Gender: 0% male	Mothers giving birth to first child between 5/15/1992 and 1/15/1995 and followed up to 2006 (*n* = 44 783) Age: not applicable, but all analyses adjusted for age Gender: 0% male	Three groups were included: self-directed violence (SDV), defined as a hospital treatment due to suicide attempt or poisoning in combination with mental illness or automutilation or poisoning with certain drugs or diagnosis of suicide or deliberate self-harm (*n* = 488) Violent suicide attempt (VSA), defined as hospital contact only due to suicide attempt using potentially lethal methods excluding poisoning (*n* = 84) Completed suicide (CS), (*n* = 18)	ELISA	Seropositivity: SDV: 168/488 (34%) *v.* 11 949/44 783 (26%) TS: 32/84 (38%) *v.* 120/433 (27%) (matched healthy control mothers) CS: adjusted relative risk (RR): 2.05 (95% CI 0.78–2.39) Serointensity: SDV: IgG levels split into 6 categories with rising adjusted RR (adjusted for age, follow-up time, psychiatric contact and history): 0–24 (seronegative) taken as reference, with 25–45 showing RR of 1.08 (95% CI 0.70–1.58) and eventually >84 showing RR of 1.91 (95% CI 1.25–2.79)
Samojlowicz *et al.* (2013)	Poland	People who died suddenly due to suicide (*n* = 41) Age: 18–81, median = 40 years Gender: 88% male	People who died suddenly due to disease, hypothermia, alcohol intoxication, injuries as passenger or being murdered (*n* = 83) Age: 20–89, median = 51 years Gender: 92% male	Deceased due to suicide.	IF	Seropositivity: 26/41 (63%) *v.* 41/83 (49%) Average titres not available

(*Continued*)

Table 1b. (*Continued.*)

Study (year)	Country	Case population	Control population	Outcome measure	Analysis method	Findings (*n*, % in cases and controls respectively)[a]
Sugden *et al.* (2016)	New Zealand	Dunedin birth cohort who were *T. gondii* positive and tested at age 38 (*n* = 236) Age: 38 Gender: 58% male	Dunedin birth cohort who were *T. gondii* negative and tested at age 38 (*n* = 601) Age: 38 Gender: 47% male	History of suicide attempt(s) with non-suicidal self-injury ruled out, occurring since last assessment at age 32	ELISA	Suicide attempt since age 32: 8/236 (3.4%) *v.* 8/601 (1.3%)
Yagmur *et al.* (2010)	Turkey	Patients with various psychiatric disorders presenting at the emergency department with a suicide attempt (*n* = 200) Age(±s.d.): 24.3(±7.6) years Gender: 21% male	Healthy controls, including health caseworkers and relatives/visitors of patients (*n* = 200) Age(±s.d.): 24.3(±8.0) years Gender: 23% male	Presentation with suicide attempt at emergency department	ELISA	Seropositivity: 82/200 (41%) *v.* 56/200 (28%) Matched on age, gender, SES, urbanicity and dietary habits
Zhang *et al.* (2012)	Sweden	Inpatients with various psychiatric disorders admitted (*n* = 54) Age(±s.d.): 38.4(±14.4) years Gender: 43% male	Healthy controls recruited in same municipality (*n* = 30) Age(±s.d.): 39.8(±14.2) years Gender: 37% male	Admitted due to a suicide attempt, defined as actual or seemingly life-threatening behaviour with intent to jeopardize his/her life or to give such appearance, not resulting in death	ELISA	Seropositivity: 22/54 (41%) *v.* 6/30 (20%) Age-adjusted log-transformed mean IgG titres(±s.d.): 3.0(±0.1) *v.* 2.6(±0.2)

ELISA, enzyme linked immunoassays; CFT, complement fixation test; IF, indirect fluorescence test; CLIA, chemiluminescent immunoassay.
[a]Data of cases are presented first, control population second.
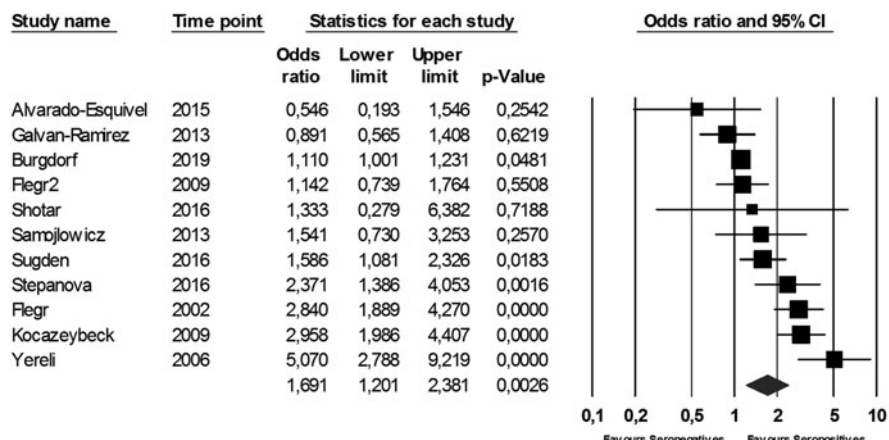
Toxoplasmosis and Traffic Accidents

Study name	Time point	Odds ratio	Lower limit	Upper limit	p-Value	Odds ratio and 95% CI
Alvarado-Esquivel	2015	0,546	0,193	1,546	0,2542	
Galvan-Ramirez	2013	0,891	0,565	1,408	0,6219	
Burgdorf	2019	1,110	1,001	1,231	0,0481	
Flegr2	2009	1,142	0,739	1,764	0,5508	
Shotar	2016	1,333	0,279	6,382	0,7188	
Samojlowicz	2013	1,541	0,730	3,253	0,2570	
Sugden	2016	1,586	1,081	2,326	0,0183	
Stepanova	2016	2,371	1,386	4,053	0,0016	
Flegr	2002	2,840	1,889	4,270	0,0000	
Kocazeybeck	2009	2,958	1,986	4,407	0,0000	
Yereli	2006	5,070	2,788	9,219	0,0000	
		1,691	1,201	2,381	0,0026	

0,1 0,2 0,5 1 2 5 10

Favours Seronegatives Favours Seropositives

Fig. 2. Forest plot toxoplasmosis and traffic, accidents using the random-effects model.

Population attributable fraction

Assuming an average infection rate of *T. gondii* of 30% in humans globally, the calculated PAF, $[0.3 \times (OR - 1)]/[0.3 \times (OR - 1) + 1]$, showed that if *T. gondii* infection would theoretically be completely prevented, the casualties due to TA would decrease with approximately 17% (95% CI 6–29%) and due to SA with 10% (95% CI 3–19%).

Discussion

Overall we found significant associations between a *T. gondii* infection and both SA and TA. Importantly, the associations did not seem to be influenced by publication bias. If the associations would be explained by the causal hypothesis, i.e. that the *T. gondii* infection influences the risk of committing a SA or suffering a TA, this would imply that a latent *T. gondii* infection would lead to much more morbidity and mortality than hitherto assumed. Taking into account the calculated PAFs, *T. gondii* infection would emerge as a major public health concern, comparable with global meningitis mortality, with estimated 318 000 annual deaths potentially due to the behavioural effects of this infection (Naghavi *et al.*, 2017). Therefore, it is paramount to evaluate whether the results of the current meta-analysis and the available literature to date indeed provide enough support for the plausibility of a causal relationship and whether alternative explanations for these associations could be given.

When assessing whether a factor (here a *T. gondii* infection) could be causal to a certain condition, Koch's postulates of causality can be used as a theoretical framework (Antonelli and Cutler, 2016). The postulates that need to be addressed in order for a factor to be considered causal to a certain condition are: consistency of the relationship, a temporal relationship (the factor preceding the emergence of the condition), a gradient in the relationship (more exposure to the factor leads to a higher risk of getting the condition), experimental proof of the relationship and a plausible biological mechanism.

The consistency of the relationship is addressed with the current meta-analysis. Overall the associations were significant, although the amount of studies was modest and heterogeneity high. In TA the Egger's test indicated the presence of publication bias. Nevertheless, statistical adjustment for possible bias by the Duval and Tweedie's trim and fill analysis did not change the overall finding. This is probably due to the different underlying mathematical method these tests use. The Egger's test relies on the fixed-effects model to see whether the sample size influences overall effect, whereas the Duval and Tweedie's trim and fill analysis can be applied to both the fixed- and random-effects model (Borenstein *et al.*, 2009). This implies that the Egger's test relies more heavily on sample size, whereby the large Danish cohort study that found a small but significant association of *T. gondii* with TA has a very large weight (>70%) relative to the other studies (all 5% or less) (Burgdorf *et al.*, 2019). When funnel plots were examined using both the fixed- and random-effects model, it became clear that with the random-effects model (which gives relatively less weight to large studies than the fixed-effects model) there does not seem to be a publication bias (see online Supplementary Appendix 2). Additionally, even when the fixed-effects model was used for statistical correction, the OR remained significantly increased albeit smaller (data available upon request). In our view, despite the significant Egger's test, the data still indicate a relationship between *T. gondii* and TA, although the magnitude is less certain. When exploring heterogeneity in TA, assessable moderators explained a negligible and non-significant amount of the observed variance. In favour of the consistency of the relationship with TA was that the OR seemed to be stronger when studies were grouped which had carefully selected subjects with a higher chance to have influenced their own risk of becoming involved in TA (not intoxicated, having caused the accident as a driver).

In SA there was no indication of publication bias, but (trend-)significant effects on heterogeneity were found among studies that included subjects with schizophrenia only and those that used healthy subjects as control population. A secondary analysis seemed to indicate that selection of schizophrenia cases is particularly important, whereby the association of *T. gondii* infection with SA was absent in cases with schizophrenia. This might be due to the fact that *T. gondii* infection is a risk factor for schizophrenia in itself (Sutterland *et al.*, 2015) or that the infection has little effect on suicidality in schizophrenia specifically, where other factors may overshadow such a relationship. For example, Toxoplasma infection has been associated with dopamine

Table 2a. (a) Moderator assessment in association traffic accidents with toxoplasmosis

Moderator assessed	Number of studies available	Analysis method	Findings
Seroprevalence of control population	11	Regression analysis with methods of moments	Coefficient −0.016 (95% CI −0.047 to −0.015) p = 0.32. R^2 = 10%
Seroprevalence of control population (dichotomized in low v. high seroprevalence)	11 (5 and 6)	Mixed-effects analysis	OR low(<24%) = 1.99 (95% CI 1.08–3.68) **p = 0.03** OR high(>24%) = 1.49 (95% CI 1.02–2.18) **p = 0.04** Q between = 0.61, p = 0.43 R^2 = 15%
Average age of controls	7	Regression analysis with methods of moments	Coefficient 0.001 (95% CI −0.040 to −0.043) p = 0.96 R^2 = 0%
Gender (male or female)	10 (5 and 5)	Mixed-effects analysis	OR male = 2.85 (95% CI 1.77–4.58) **p = 0.007** OR female = 2.14 (95% CI 1.24–3.71) **p < 0.001** Q between = 0.59, p = 0.42 R^2 = 0%
Quality of studies (continuous)	11	Regression analysis with methods of moments	Coefficient −0.020 (95% CI −0.115 to −0.076) p = 0.69 R^2 = 10%
Quality of studies (dichotomized)	11 (5 + 6)	Mixed-effects analysis	OR (<4) = 1.87 (95% CI 0.92–3.76) p = 0.08 OR (>4) = 1.56 (95% CI 1.07–2.68) **p = 0.02** Q between = 0.19, p = 0.66 R^2 = 9%
Quality of traffic accident definition[a]	11 (4 and 7)	Mixed-effects analysis	OR (poor) 1.36 (95% CI 0.91–2.02) p = 0.13 OR (good) 1.92 (95% CI 1.22–3.02) **p = 0.005** Q between = 1.29, p = 0.26 R^2 = 0%
Fatality of traffic accidents (fatal or non-fatal)[b]	12 (one dataset split on fatality) (2 and 10)	Mixed-effects analysis	OR fatal 2.08 (95% CI 1.38–3.15) **p = 0.001** OR non-fatal 1.70 (95% CI 1.19–2.44) **p = 0.004** Q between = 0.52, p = 0.47 R^2 = 0%
Timing of measurement traffic accidents (prospective or retrospective)	11 (6 and 5)	Mixed-effects analysis	OR prospective 1.60 (95% CI 1.04–2.48) **p = 0.03** OR retrospective 1.89 (95% CI 1.18–2.80) **p = 0.01** Q between = 0.25, p = 0.62 R^2 = 12%

p-values < 0.05 are highlighted in bold.
[a]Good definition of being a case suffering a traffic accident in a study is assuring the case is the driver, which has (most probably) caused the traffic accident, excluding people who had drunk alcohol and/or used drugs.
[b]Studies reporting both fatal and non-fatal were excluded when separate data were not available.
[b]For this moderator prospective data only were analysed for the study of Burgdorf et al.

Table 2b. (b) Moderator assessment in association suicide attempts with toxoplasmosis

Moderator assessed	Datasets available	Method	Findings
Seroprevalence of control population	17	Regression analysis with methods of moments	Coefficient 0.0001 (95% CI −0.014 to 0.014) $p = 0.99$ $R^2 = 0\%$
Average age of controls	11	Regression analysis with methods of moments	Coefficient −0.008 (95% CI −0.07 to 0.05) $p = 0.80$ $R^2 = 0\%$
Gender (male or female)	6 (3 and 3)	Mixed-effects analysis	OR male = 0.97 (95% CI 0.53–1.76) $p = 0.91$ OR female = 1.73 (95% CI 0.37–7.97) $p = 0.48$ Q between = 0.49, $p = 0.49$
Quality of studies (continuous)	17	Regression analysis with methods of moments	Coefficient 0.048 (95% CI −0.14 to 0.23) $p = 0.61$ $R^2 = 0\%$
Quality of studies (dichotomized)	17 (8 and 9)	Mixed-effects analysis	OR (<5) 1.36 (95% CI 0.89–2.07) $p = 0.16$ OR (> = 5) 1.40 (95% CI 1.04–1.88) **$p = 0.03$** Q between = 0.01, $p = 0.91$ $R^2 = 0\%$
Fatality of suicide attempts (fatal or non-fatal)[a]	17 (2 and 15)	Mixed-effects analysis	OR fatal 1.91 (95% CI 1.05–3.45) **$p = 0.03$** OR non-fatal 1.34 (95% CI 1.04–1.73) **$p = 0.04$** Q between = 1.12, $p = 0.29$ $R^2 = 0\%$
Diagnosis (schizophrenia or any psychiatric disorder)	17 (5 and 12)	Mixed-effects analysis	OR schizophrenia 0.87 (95% CI 0.51–1.49) $p = 0.62$ OR any 1.64 (95% CI 1.27–2.11) **$p < 0.001$** Q between = 4.30, **$p = 0.04$** $R^2 = 0\%$
Type of control population (psychiatric disorders or healthy controls)	17 (9 and 8)	Mixed-effects analysis	OR psychiatric disorders 1.06 (95% CI 0.70–1.61) $p = 0.78$ OR healthy controls 1.67 (95% CI 1.27–2.20) **$p < 0.001$** Q between = 3.16, $p = 0.08$ $R^2 = 0\%$
Timing of measurement suicide attempts in regard to seropositivity to *T. gondii* (prospective or retrospective)	17 (11 and 6)[b]		OR retrospective 1.24 (0.83–1.83) $p = 0.29$ OR prospective 1.68 (1.25–2.26) **$p = 0.001$** Q between = 1.50, $p = 0.22$ $R^2 = 3\%$

p-values < 0.05 are highlighted in bold.
[a]Studies reporting both fatal and non-fatal suicide attempts were excluded when separate data were not available. To measure the OR for fatal suicide attempts in the study of Pedersen *et al.*, the adjusted relative risk had to be used.
[b]For this moderator prospective data only were analysed for the study of Burgdorf *et al*.

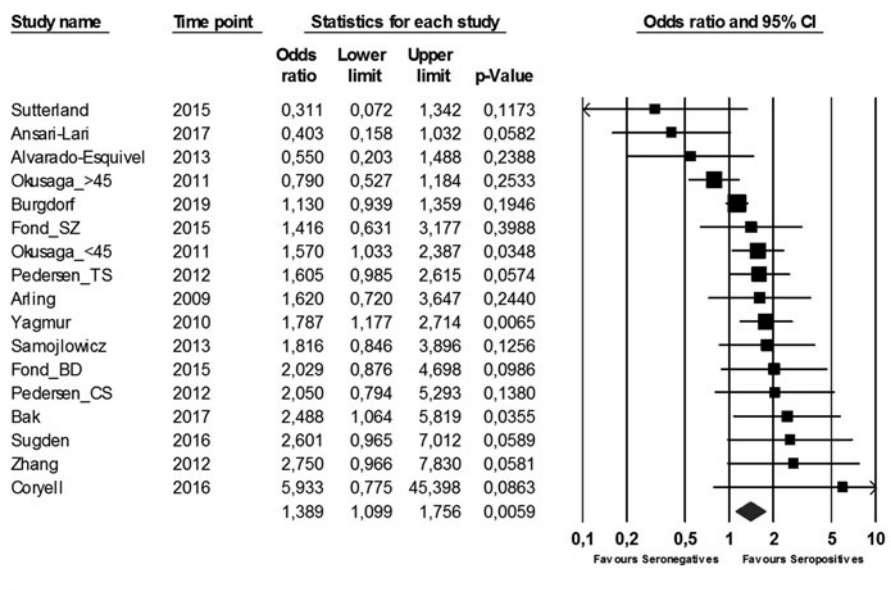## Toxoplasmosis and Suicide Attempts

Study name	Time point	Odds ratio	Lower limit	Upper limit	p-Value
Sutterland	2015	0,311	0,072	1,342	0,1173
Ansari-Lari	2017	0,403	0,158	1,032	0,0582
Alvarado-Esquivel	2013	0,550	0,203	1,488	0,2388
Okusaga_>45	2011	0,790	0,527	1,184	0,2533
Burgdorf	2019	1,130	0,939	1,359	0,1946
Fond_SZ	2015	1,416	0,631	3,177	0,3988
Okusaga_<45	2011	1,570	1,033	2,387	0,0348
Pedersen_TS	2012	1,605	0,985	2,615	0,0574
Arling	2009	1,620	0,720	3,647	0,2440
Yagmur	2010	1,787	1,177	2,714	0,0065
Samojlowicz	2013	1,816	0,846	3,896	0,1256
Fond_BD	2015	2,029	0,876	4,698	0,0986
Pedersen_CS	2012	2,050	0,794	5,293	0,1380
Bak	2017	2,488	1,064	5,819	0,0355
Sugden	2016	2,601	0,965	7,012	0,0589
Zhang	2012	2,750	0,966	7,830	0,0581
Coryell	2016	5,933	0,775	45,398	0,0863
		1,389	1,099	1,756	0,0059

Odds ratio and 95% CI: 0,1 0,2 0,5 1 2 5 10
Favours Seronegatives   Favours Seropositives

Fig. 3. Forest plot toxoplasmosis and suicide attempts using the random effects model.

modulation in brain neurons (Prandovszky *et al.*, 2011), while dopamine disturbances are generally recognized abnormalities described in the brain of most subjects with schizophrenia whether or not they are infected with *T. gondii* (Howes *et al.*, 2017). Nonetheless, the association of *T. gondii* infection with SA being partly explained by using healthy subjects as controls remains a concern, suggesting the higher prevalence of antibodies against *T. gondii* in several psychiatric disorders might drive the association. On one hand this possible confounding seems less likely as the large cohort study of Pedersen *et al.* was able to control for psychiatric disorders in the population and still showed a significant association between *T. gondii* infection and suicidal behaviour (Pedersen *et al.*, 2012), but on the other hand the study of Burgdorf *et al.* found a small but non-significant effect, whereby they used a different method to control for psychiatric disorders in the population (Burgdorf *et al.*, 2019). Future studies should keep trying to disentangle these confounding factors and assess other potential factors influencing heterogeneity.

One of those candidates is Rhesus factor positivity, which has been suggested as relevant (Flegr *et al.*, 2009; Flegr *et al.*, 2013). For example, cognitive dysfunction was only found in subjects with a latent *T. gondii* infection which were Rhesus negative. Why the Rhesus factor could protect humans against deletorial effects of *T. gondii* is unclear. Another candidate to explore is the strain hypothesis, which states that strains of *T. gondii* differ in virulence and in ability to influence human behaviour (Xiao *et al.*, 2009). This strain hypothesis is supported by the finding of Xiao *et al.*, that the association of *T. gondii* infection with affective psychosis was only found in a subgroup who were infected with strain type I and not in those infected with type II or other types (Xiao *et al.*, 2009). Since then, one other study has found a similar effect with strain type I in humans (Groer *et al.*, 2011).

The postulate of a temporal relationship seemed plausible as studies with a prospective design rendered similar findings indicating the infection preceded the outcome. Additionally, the serointensity analyses showed that significant increases in the ORs were found with higher antibody titres for TA and for SA, the latter within studies that did not include schizophrenia cases only. This could imply that the severity of the infection plays a role, indicating a gradient in the relationship. Nevertheless, it is much less clear if *Toxoplasma* prevalence influences the numbers of SA and TA. One study has suggested that a relationship between national *T. gondii* prevalence and suicide incidence in European countries exists (Lester, 2010). On the other hand, suicide numbers have varied considerably the last decades, while it has been suggested that *T. gondii* prevalence steadily decreased in the same time period (Jones *et al.*, 2014; Gargate *et al.*, 2016; Dyvesether *et al.*, 2018; Huikari *et al.*, 2019). This could be explained by other factors that have a larger impact on the occurrence of suicide than Toxoplasmosis (which has an estimated PAF of 10%), such as, for instance, the unemployment rates (Huikari *et al.*, 2019). Concerning TA, no study to date has examined if regional *T. gondii* prevalence is related to TA numbers.

The experimental proof for a relationship is challenging with the studied outcomes. Animal models have been examined, which could be applicable to these outcomes. Several behavioural changes after infection with *T. gondii* in mice and rats have been documented, including increased reaction time, slower neural processing speed, decreased attention span and increased risk-taking behaviour (Webster, 2007; Daniels *et al.*, 2015; Tan *et al.*, 2015). These factors can increase the risk of both TA and SA. However, the methodology underlying these findings has been questioned (Worth *et al.*, 2014). Human studies have indicated cognitive abnormalities concurring with *T. gondii* infection, increasing the risk of suffering from TA (Guenter *et al.*, 2012; Pearce *et al.*, 2013; Pearce *et al.*, 2014). However, these findings were not always replicated (Gale *et al.*, 2015; Sugden *et al.*, 2016).

Finally, a plausible biological mechanism should be available to explain how a latent *T. gondii* infection could lead to an increased risk of causing TA and SA. Several biological mechanisms have been postulated. First of all, as tryptophan is essential for *T. gondii* replication, increased tryptophan breakdown by activating the kynurenine pathway is a major line of defence for the host against *T. gondii* infection, leading to increased kynurenine (KYN) and quinolinic acid (QUIN) levels (Miller *et al.*, 2009).

Increased KYN as well as QUIN levels, including in CSF and post-mortem, have been associated with suicidal behaviour (Sublette *et al.*, 2011; Steiner *et al.*, 2012; Erhardt *et al.*, 2013). Okusaga *et al.* found that the risk of SA was increased in cases with both seropositivity to *T. gondii* and high KYN levels (Okusaga *et al.*, 2016). QUIN is an *N*-methyl-D-aspartate (NMDA) receptor agonist and considered to be neurotoxic, whereby recent evidence indicates that ketamine, an NMDA receptor antagonist can acutely reduce suicidality (DiazGranados *et al.*, 2010). Secondly, it has been demonstrated that a *T. gondii* infection can increase dopamine levels both *in vitro* and in mice (Skallova *et al.*, 2006; Prandovszky *et al.*, 2011). The genome of *T. gondii* is able to express the enzyme tyrosine hydroxylase in infected cells, which is the rate-limiting enzyme in dopamine synthesis (Prandovszky *et al.*, 2011). Hyperdopaminergic states, together with NMDA agonism, can lead to increased arousal, neurotoxicity and impulsivity (Barake *et al.*, 2014).

Although the suggested biological mechanisms may be plausible, studies confirming the role of one of these mechanisms in humans are challenging and remain scarce (Okusaga *et al.*, 2016).

Alternative explanations for an association between *T. gondii* infection and both SA and TA should be explored as well. As it is known that felines are the definite host of the parasite, households with cats are more prone to get infected by *T. gondii*. While we are unaware of studies showing that families who prefer cats as pets are also more prone to psychiatric illness, SA or TA, this reverse causality cannot be ruled out. Conversely, evidence that households with cats have an increased risk of developing schizophrenia has been published (Torrey *et al.*, 2015), although these findings have been challenged (Solmi *et al.*, 2017).

When elaborating further on factors that could give rise to a so-called spurious association (i.e. toxoplasmosis and TA or SA are not directly related to each other but both rise or fall due to another factor), it should be noted that households with low incomes are known to be at a higher risk of being involved in a TA or committing a SA (Qin *et al.*, 2003; Ghaffar *et al.*, 2004; Hawton and van Heeringen, 2009). There is an indication that this could also be applicable to the risk of contracting a latent *T. gondii* infection (Mareze *et al.*, 2019). Studies included in our meta-analysis did not adjust for socio-economic status, which would be important to examine in future studies.

Furthermore, it is possible that the biological susceptibility of humans to contract a latent *T. gondii* infection, for example, through differences in the immune defence system or reactivity of the kynurenine pathway, also influences the risk of TA and SA. In SA, many studies have shown changes in cytokine profiles in cases compared with controls (Gananca *et al.*, 2016), but in TA this has not been examined as far as we are aware. More studies with a prospective design focussing on biological susceptibility are needed to shed further light on this matter.

Strengths and limitations

One of the strengths of the meta-analysis is the extensive sensitivity analysis addressing heterogeneity, after retrieval of additional data from several authors. This showed variation in the association of SA with *T. gondii* infection, due to several factors, which can guide the field in further research into this topic. It was also able to demonstrate that the severity of *T. gondii* infection further increased the association with SA and TA and that the infection precedes these adverse outcomes. One of the limitations, however, is that the amount of studies was still relatively modest, leaving some uncertainty about the robustness of the finding and limiting options for sensitivity analyses with multiple moderators at once. Another limitation was that it was not possible to use individual patient data.

Conclusion

Overall, the findings of this meta-analysis in conjunction with the available literature provide substantial support for the hypothesis that a latent *T. gondii* infection may play an important role in the risk of TA and SA. However, although there is some support for the interpretation that the association is causal, causality is not proven. Nevertheless, the additional impact that toxoplasmosis potentially has on health [besides the well-known consequences in immunocompromised patients and *de novo* infection during pregnancies and the possible mental health consequences (Montoya and Liesenfeld, 2004)] validates the question what the gain could be for devoting more public health resources into this issue. Further research concerning the prevention of primary infections on a larger scale should be considered. It is presumed that transmission occurs most often through ingestion of intact oocysts containing the parasite, which can be contracted by eating raw or undercooked meat, changing cat litter, by not washing hands after gardening, eating unwashed vegetables or fruit or by drinking contaminated water (Montoya and Liesenfeld, 2004). It would be good to increase the knowledge about the most common route of transmission in humans and try to prevent this. Alternatively, resources could be directed into developing a vaccine for humans or cats. Secondly, little is known how to diminish or prevent deleterious consequences by an acquired latent infection. Targeting specific high-risk populations, such as traffic offenders or people who have committed a SA could be an option to investigate these questions. Finally, possible candidates that could be responsible for the heterogeneous findings (rhesus factor positivity, differences in strain virulence, type of case and control population) should be explored further.

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