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, Pudmed and PsycInfo, 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 (OR=1.69; %95 CI: 1.20 – 2.38, p=0.003) and SA (OR=1.39; %95 CI: 1.10-1.76, p=0,006). 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 versus $OR_{psychiatric\ controls}$=1.06, p=0.87) and whether subjects with schizophrenia only were analysed ($OR_{schizophrenia}$=0.87, p=0.62 versus $OR_{various}$=1.8, p<0.001). The association was significantly stronger with higher antibody titers 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 latent *T.gondii* infection may play a role in the prevention of traffic accidents or suicide attempts, although uncertainty remains whether this infection is 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 ten 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 to 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(Lutz *et al.*, 2017, Turecki and Brent, 2016). Resources are directed at addressing modifiable factors in policymaking(Goniewicz *et al.*, 2016, Herbert *et al.*, 2017, Perron *et al.*, 2013) (i.e. making more difficult to jump of bridges, increasing road safety, preventing drug abuse) and healthcare(Gilissen *et al.*, 2017, Goniewicz *et al.*, 2016, Turecki and Brent, 2016) (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 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, 2007b), 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, Peng *et al.*, 2018, Sugden *et al.*, 2016b). 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 Appendix 1) throughout Medline, PsychInfo and EMBASE until 11th 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 hemagglutination, 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 of 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 that had committed suicide attempts as cases (for example cases presented at the emergency department due to a suicide attempt) and collected healthy controls as a control population in order to compare antibody levels against *T.gondii*. In contrast, other studies looked at subjects with certain psychiatric disorder(s) cross-sectionally and defined caseness as having a history of suicide attempt(s) and control population as subjects not having this history. In order to study whether this difference in sampling method mattered, we stratified these 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 eye-balling and calculating I-squared (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 fulfilment of one of the following two criteria: a. The study was designed as a longitudinal cohort study whereby the 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 measurement of IgG antibodies against *T.gondii* (since these antibodies are indicative of a latent infection and emerge months after primary infection).

Considering diagnosis of cases, specifically for SA, studies were grouped in studies that had included only cases with schizophrenia (schizophrenia only) compared to 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 variance of the true effect, regression analyses were performed investigating the moderator as covariate. The amount of variance was expressed by R-squared. Due to the number of included studies, moderator effects were analyzed individually(Borenstein *et al.*, 2009).

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

Higher average antibody titers (compared to controls) has been called serointensity, whereby preferably numbers on high versus low, but still positive, antibody titers were used to see if this influenced magnitude of the OR. If these were not available, average titers 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 traffic accidents and suicide attempts 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 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 total 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 12234 controls in TA and 2259 cases and 9400 controls in SA (see Figure 1 for flowchart and Table 1 for study characteristics).

Traffic Accidents:

In total eleven studies comparing seropositivity to *T.gondii* with the risk of being involved in a traffic accident were identified (Alvarado-Esquivel *et al.*, 2015, Burgdorf *et al.*, 2019, Flegr *et al.*, 2002b, Flegr *et al.*, 2009, Galvan-Ramirez Mde *et al.*, 2013, Kocazeybek *et al.*, 2009b, Samojlowicz *et al.*, 2013, Shotar *et al.*, 2016, Stepanova *et al.*, 2017, Sugden *et al.*, 2016a, Yereli *et al.*, 2006), showing an overall OR of 1.69 (%95 CI: 1.20 – 2.38, P = 0.003), see Figure 2. The Egger's test did indicate 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 (Appendix 2). Heterogeneity was considerable and significant (I^2= 86%, p<0.0001, Tau^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 traffic accidents (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 significant impact on the variance of the overall effect.

Serointensity and TA

In total five studies reported serointensity(Flegr *et al.*, 2002a, Flegr *et al.*, 2009, Galvan-Ramirez *et al.*, 2013, Kocazeybek *et al.*, 2009a, Shotar *et al.*, 2016). Overall, the odds for TA were increased in cases with high titers compared to low titers; OR 1.75 (95% CI 1.28 – 2.38; p<0.001). Significant heterogeneity was present (I^2=65%, Tau 0.299), for which no explanation was found with available moderators (seroprevalence, age, quality, study design).

Suicide Attempts or Suicide

Thirteen studies studying the association between SA and latent *T.gondii* infection and one unpublished study were identified(Alvarado-Esquivel *et al.*, 2013, Ansari-Lari *et al.*, 2017, Arling *et al.*, 2009, Bak *et al.*, 2018, Burgdorf *et al.*, 2019, Coryell *et al.*, 2016, Fond *et al.*, 2015, Kuiper *et al.*, Okusaga *et al.*, 2011, Pedersen *et al.*, 2012, Samojlowicz *et al.*, 2013, Sugden *et al.*, 2016b, Yagmur *et al.*, 2010, Zhang *et al.*, 2012), with an overall OR of 1.39 (%95 CI: 1.10-1.76, p=0,006), see Figure 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 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 significant impact on the between study variance: the proportion of patients with schizophrenia (schizophrenia only versus various psychiatric disorders) ($OR_{schizophrenia}$=0.87 (95%CI: 0.51 – 1.49), p= 0.62 versus $OR_{various}$=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 versus $OR_{psychiatric\ controls}$=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 versus $OR_{schizophrenia}$=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 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 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(Alvarado-Esquivel *et al.*, 2013, Ansari-Lari *et al.*, 2017, Arling *et al.*, 2009, Bak *et al.*, 2018, Fond *et al.*, 2015, Okusaga *et al.*, 2011, Pedersen *et al.*, 2012,

Zhang *et al.*, 2012), 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) versus various other psychiatric disorders (n=5): OR 0.99 (95%CI: 0.77 – 1.29) versus OR 1.66 (95%CI: 1.29 – 2.12, p<0.001), R^2=61%, p=0.004.

PAF

Assuming an average infection rate of *T.gondii* of 30% in humans globally the calculated PAF, (0.3*(OR-1))/(0.3*(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 suicide attempts 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 commiting 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 an estimated 318 thousand 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 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 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 publication bias (see 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 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 confouding seems less likely as the large cohort study of Pedersen and colleagues 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 and colleagues 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, whereby strains of *T.gondii* differ in virulence and possibly in ability to influence human behaviour(Xiao *et al.*, 2009). This strain hypothesis was first explored by a study of Xiao et al., whereby the association of *T.gondii* infection with affective psychosis was only found in a subgroup who were infected with strain type I and not with type II or other types (Xiao *et al.,* 2009). Since then, one 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 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 side, suicide numbers have varied considerably the last decades, while it has been suggested that *T.gondii* prevalence steadily decreased in the same time period(Dyvesether *et al.*, 2018, Gargate *et al.*, 2016, Huikari *et al.*, 2019, Jones *et al.*, 2014). This last fact could be explained by other factors that have a bigger impact on suicide numbers than Toxoplasmosis (which has an estimated PAF of 10%), such as 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 for 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(Daniels *et al.*, 2015, Tan *et al.*, 2015, Webster, 2007a). These factors can increase the risk of both TA and SA. However, the methodology underlying these findings have 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.*, 2016b).

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(Erhardt *et al.*, 2013, Steiner *et al.*, 2012, Sublette *et al.*, 2011). Okusaga and colleagues 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 a N-methyl-D-aspartate (NMDA) receptor agonist and considered to be neurotoxic, whereby recent evidence indicates that ketamine, a 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(Prandovszky *et al.*, 2011, Skallova *et al.*, 2006). 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 and are to date still unclear(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(Ghaffar *et al.*, 2004, Hawton and van Heeringen, 2009, Qin *et al.*, 2003). There is 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 to 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 looking into 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 were 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 provides substantial evidence that a latent *T.gondii* infection may play an important role in the risk of TA and SA. 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 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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