Toxoplasmosis and Schizophrenia: A Systematic Review and Meta-Analysis of Prevalence and Associations and Future Directions

Despina G. Contopoulos-Ioannidis, MD, Maria Gianniki, MD, MS, Angeline Ai-Nhi Truong, MS, Jose G. Montoya, MD

Background: A potential link between toxoplasmosis with schizophrenia (SCZ) has been extensively studied over the past 2 decades. Our study was aimed to determine whether, beyond an association, the field is primed for randomized clinical trials of anti-Toxoplasma prophylaxis in Toxoplasma seropositive patients with SCZ.

Methods: We performed a methodological appraisal of toxoplasmosis-SCZ association studies, a meta-analysis, and a compilation of claims and pathophysiologic hypotheses.

Results: We analyzed 66 studies with 11,540 patients with SCZ and 69,491 controls. For patients with SCZ, 54 studies targeted Toxoplasma-IgG seropositivity, 18 targeted Toxoplasma-IgG serointensity, and 17 targeted Toxoplasma-IgM seropositivity. For SCZ-phenotypes, 26 targeted Toxoplasma-IgG seropositivity, six targeted Toxoplasma-IgG serointensity, and three targeted Toxoplasma-IgM seropositivity. Two-thirds of these studies reported a positive association. Statistically significant associations with SCZ were reported in 31/54 studies, 11/18 studies, and 3/17 studies. Significant associations with SCZ-phenotypes were reported in 20/26 studies, 2/6 studies, and 0/3 studies, respectively. Toxoplasma-IgG seropositivity increased the odds of SCZ (OR = 1.91; 95% CI: 1.61–2.27). Heterogeneity across studies was large (I² = 80.03%). Adjusted analyses for at least age and socioeconomic status/place of residence were done in 17 studies; temporality was addressed only in 4.

Conclusion: A large number of observational studies revealed a modest to large association between toxoplasmosis and SCZ. Although important methodological biases were identified, further association studies are unlikely to change this association and are not justified. It is time to test this association in randomized double-blind placebo-controlled clinical trials of first line anti-Toxoplasma prophylaxis in Toxoplasma seropositive patients with SCZ.
prophylaxis in Toxoplasma seropositive patients with SCZ. Towards that end, we performed a methodological appraisal of toxoplasmosis-schizophrenia association studies. We also performed a quantitative meta-analysis of this association and created a compilation of claims and pathophysiologic hypotheses. The latest meta-analysis for the association between toxoplasmosis and SCZ was published in 2015 (19) and since then, several additional studies have been published. Studies in this field have examined different types of toxoplasmosis exposures and/or types of SCZ outcomes. This diversity may introduce both heterogeneity in the results, as well as bias, and it is important to understand the possible methodological limitations of the available evidence. Insights from this systematic assessment were used to discuss future directions in the research agenda in this field.

**METHODS**

**Search strategy**

We considered studies included in previous meta-analyses (19,21,24–26) and performed updated PubMed searches to bring the database up to date (last search February 2021; Figure 1). Our search strategy is listed in Appendix 1. We also perused the reference lists of key review papers for the identification of additional pertinent studies. Articles were screened for eligibility by two independent reviewers (Maria Gianniki, Despina G. Contopoulous-Ioannidis).

**Inclusion and exclusion criteria**

We included studies of any type of study design (case-control studies, SCZ cohort studies and population cohorts) that reported the association between toxoplasmosis and SCZ and/or specific SCZ phenotypes. We kept the definitions for toxoplasmosis and SCZ used by the study authors. The Toxoplasma infection status could have been ascertained by serologic qualitative methods (Toxoplasma IgG or IgM seropositivity), serologic quantitative methods (Toxoplasma IgG or IgM titers/serointensity), or molecular methods. When more than one study existed from the same team with overlapping patients for the same type of SCZ outcome (SCZ or SCZ phenotype), we kept only the publication with the largest number of patients with SCZ. Studies exploring the association between maternal Toxoplasma seropositivity and SCZ in the offspring (27–34) were not included in our analysis. Positive Toxoplasma IgG antibodies in the newborn infant’s Guthrie card blood sample reflect the maternal T. gondii infection status from transplacentally transferred maternal Toxoplasma IgG antibodies to the fetus, and additional neonatal testing is required to confirm whether the newborn infant is congenitally infected or not. We excluded reviews, commentaries and editorials with no original data.

**Data extraction**

From each eligible study we extracted the following information: author, year of publication, country of patients with SCZ, chronologic period of SCZ patients follow-up, study design, diagnostic method for ascertainment of toxoplasmosis infection status, type of SCZ outcome targeted (e.g., SCZ and/or specific SCZ phenotypes), study sample size, N of patients with SCZ, N of controls analyzed, N of patients with additional mental health conditions targeted, inclusion criteria for patients with SCZ, types of selected controls (e.g., healthy volunteers, relatives of patients, random sample of patients from other hospital wards, etc.), types of adjustments or matching for confounders between cases and controls, adequacy of adjustments (e.g., adjustments for at least age and socioeconomic status/place of residence), and addressing of temporality (e.g., toxoplasmosis diagnosed before the diagnosis of SCZ).

We considered the following types of toxoplasmosis exposures: Toxoplasma IgG (or IgG/IgM) seropositivity, Toxoplasma IgG serointensity (Toxoplasma IgG titers analyzed as a continuous, categorical or binary variable), Toxoplasma IgM seropositivity, Toxoplasma IgM HIGHLIGHTS

- We performed a methodological appraisal of 66 association studies published over the past 2 decades exploring the association between toxoplasmosis and schizophrenia (SCZ) or SCZ phenotypes, a meta-analysis, and a compilation of claims and proposed pathophysiologic hypotheses.
- Two-thirds of the studies reported a positive association and Toxoplasma-IgG seropositivity was associated with an increase in the odds of SCZ; however, important methodological limitations were identified.
- Further association studies are unlikely to change this association and are not justified.
- It is time to test the hypothesis that prevention of intermittent subclinical reactivations of T.gondii in the brain of Toxoplasma seropositive patients with SCZ may have a positive impact in their SCZ-course in randomized double-blind placebo-controlled clinical trial settings using first line anti-Toxoplasma prophylaxis medications.
- Selection of first line primary-prophylaxis anti-Toxoplasma medication (such as trimethoprim/sulfamethoxazole), as has been the strategy in other clinical setting for high-risk immunocompromised patients (e.g., Toxoplasma seropositive transplant patients or patients with acquired immune deficiency syndrome) is critical.
serointensity (Toxoplasma IgM titers analyzed as a continuous or categorical variable) or Toxoplasma polymerase chain reaction [PCR].

Moreover, we considered the following types of SCZ outcomes: SCZ (any type) or specific SCZ phenotypes (according to age at onset, duration of illness, total SCZ symptom score, positive and negative symptom scores, patient’s awareness of illness, patient’s compliance with medications, specific SCZ course [e.g., first episode, single episode with remission, single episode with partial remission, episodic without residual symptoms, episodic with residual symptoms, continuous], specific SCZ status [e.g., chronic, partially cured, cured], and types of SCZ [e.g., catatonic, disorganized, paranoid, residual, undifferentiated]).

Data extraction from each study was done by two independent investigators (Maria Gianniki/Angeline Ai-Nhi Truong and Despina G. Contopoulos-Ioannidis); discrepancies were reached by consensus.

**Qualitative data analysis**

We analyzed the prevalence of Toxoplasma IgG (or IgG/IgM combined) seropositivity rate in SCZ and in SCZ phenotypes thereof, the prevalence of Toxoplasma IgM seropositivity in SCZ and SCZ phenotypes thereof, the prevalence of Toxoplasma PCR positivity in SCZ and SCZ phenotypes thereof.
phenotypes thereof, and the prevalence of *Toxoplasma* IgG (or IgG/IgM) seropositivity in controls (if applicable). We analyzed the reported associations (and statistical significance thereof along with 95% confidence intervals [CI]) between toxoplasmosis and SCZ (and/or SCZ phenotypes). Moreover, we created a compilation list of reported claims and pathophysiologic theories to support the biologic plausibility of these associations.

**Quantitative data analyses**

We used descriptive statistics to analyze the study characteristics. We generated a world-map of the countries of patients with SCZ.

Quantitative data were synthesized by proportion and association meta-analyses. Proportion meta-analyses were also used as not all studies had a control group to allow for the calculation of an association effect size. Proportion meta-analyses synthesized across studies the *Toxoplasma* IgG (or IgG/M) and IgM seropositivity rates in patients with SCZ (and in controls respectively) and calculated an average *Toxoplasma* IgG (or IgG/IgM) and IgM seropositivity rate in these two groups (and 95% CI thereof) across studies. Association meta-analyses synthesized across studies the effect sizes for the association of toxoplasmosis in SCZ versus controls, and calculated a summary odds ratio (OR) of *Toxoplasma* IgG (or IgG/IgM) seropositivity in SCZ and 95% CI thereof. When both adjusted and unadjusted effect sizes or raw data were reported, we always preferred the adjusted effect sizes over other metrics. The data across studies were synthesized using the DerSimonian and Laird random effects model (REM) method (35). Studies in these models were weighted by the inverse of their variance (38). The heterogeneity across studies was calculated using the $I^2$ metric (36). $I^2 > 75\%$ was considered a large heterogeneity. When there is large heterogeneity across studies in a meta-analysis, the average estimates may be misleading; in those cases, reporting of the median and interquartile range (IQR) of the respective estimates across studies may be more informative. The Egger’s test of bias (37) was applied to test for small study effect bias; the Begg’s funnel plot was also created.

Predefined subgroup association meta-analyses were performed according to study adjustment status between SCZ and controls (studies with and without adjustment for important confounders [e.g., age, socioeconomic status/place of residence]), according to the assessment of the temporality of *Toxoplasma* IgG seropositivity in relation to the time of SCZ diagnosis, and according to study design (population cohorts or case control studies).

We used meta-regression analyses to analyze across studies the association between the effect size (logarithm of the OR [logOR]) of the association between *Toxoplasma* IgG (or IgG/IgM) seropositivity and SCZ) and the control group *Toxoplasma* IgG (or IgG/IgM) seroprevalence. The *metareg* STATA command was used. Moreover, we used multivariate regression analyses to explore the impact of different factors (adjustment for confounders; assessment of temporality, study design or sample size) in the reported effect size of the association. The results of the meta-analysis were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (38) (Appendix 2).

**Statistical analyses**

Analyses were performed in STATA software (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP). The Comprehensive Meta-analysis software (Comprehensive Meta-Analysis Version 3 Bor-enstein, M., Hedges, L., Higgins, J., & Rothstein, H. Biostat, Englewood, NJ 2013) was also used to compile effect size data reported in diverse formats across studies (raw 2 × 2 data, OR, risk ratio [RR] or hazard ratio [HR]).

**RESULTS**

**Study characteristics**

We identified 66 studies with non-overlapping SCZ patient populations published over the past 2 decades (2001–2020), with 11,540 patients with SCZ and 64,491 controls (Appendix 3). Figure 1 shows the flow chart for the identification of these studies. Patients with SCZ were from 24 countries, with top contributing countries being USA (10/66), Iran (10/66), Turkey (7/66), China (4/66), France (4/66), and Germany (4/66; Appendix 4a,b). There were 51 (77.3%) case control studies, four (6.1%) population cohorts, and 11 (16.7%) cohort studies that included only patients with SCZ (Table 1). The median number of patients with SCZ analyzed in these studies was 95 (IQR: 45–180; range: 5–1719). Additional psychiatric patients, except for patients with SCZ, were targeted in 26 (39.4%) studies (Table 1).

**Proportion meta-analyses.** The average *Toxoplasma* IgG (or IgG/IgM) and IgM seropositivity rates (by REM) among patients with SCZ were 45% (95% CI: 36%–53%; $I^2 = 99.12\%$) and 5% (95% CI: 2%–9%; $I^2 = 91.38\%$), respectively (Appendix 4c,4e). The respective seropositivity rates among controls were 30% (95% CI: 27%–34%; $I^2 = 98.59\%$) and 1% (0%–2%; $I^2 = 67.33\%$) (Appendix 4d, f). The respective median and interquartile (IQR) of seroprevalence rates are shown in Table 2.

**Associations with SCZ.** Diverse types of toxoplasmosis exposure and SCZ outcomes metrics were targeted across studies. Some studies targeted more than one type of toxoplasmosis exposure metrics, and more than one type of SCZ outcome metrics. Figure 2 demonstrates the multifarious types of targeted toxoplasmosis exposure metrics (*Toxoplasma* IgG/or IgG/IgM seropositivity, *Toxoplasma* IgG serointensity-as a continuous/categorical/
or binary variable—Toxoplasma IgM seropositivity, Toxoplasma PCR positivity—and SCZ outcome-metrics (SCZ/or SCZ phenotypes) across studies and the statistical significance thereof of the targeted association-analyses. Moreover, the number of studies with positive association claims across studies is shown in Appendix 5. Two thirds of the studies (44/66) reported a positive association between at least one targeted type of toxoplasmosis exposure and a SCZ/or SCZ phenotype outcome. A compilation list of all positive and negative claims per individual studies is shown in Appendix 6.

The Toxoplasma-IgG (or IgG/IgM) seropositivity in SCZ versus controls was targeted in 54 studies (81.8%); but only 51/54 provided quantitative data in such a format that could be included in the association meta-analysis (e.g., 2 × 2 table or odds ratio/RR/HR with 95% CI thereof).

### TABLE 1. Study characteristic and types of analyses targeted per study

| Study characteristics | N (%) of studies (or median N [IQR, range] of patients) |
|-----------------------|----------------------------------------------------------|
| Number of studies     | 66 (100%) studies                                        |
| Study design          |                                                          |
| Case control studies  | 51 (77.3%) studies                                       |
| Population cohorts    | 4 (6.1%) studies                                         |
| Cohorts of only SCZ patients | 11 (16.7%) studies                                   |
| Top countries (for location of SCZ patients) |                                                          |
| USA                   | 10 (15.2%) studies                                       |
| Iran                  | 10 (15.2%) studies                                       |
| Turkey                | 7 (10.6%) studies                                        |
| China                 | 4 (6.1%) studies                                         |
| France                | 4 (6.1%) studies                                         |
| Germany               | 4 (6.1%) studies                                         |
| Type of psychiatric patients targeted |                                                          |
| Only SCZ patients     | 40 (60.6%) studies                                       |
| SCZ along with other psychiatric patients | 26 (39.4%) studies                                  |
| Study sample size     |                                                          |
| All study patients (median [IQR, range]) | 198 (113–423; 51–45,609)                     |
| SCZ patients (median [IQR, range]; total N) | 95 (45–180; 5–1719); 11,540 SCZ patients |
| Controls (median [IQR, range]; total N) | 95 (50–214; 20–45,529); 69,491 subjects |
| Types of analyses targeted |                                                          |
| N (%) of studies included in the qualitative data analyses | 66 (100%) studies                                      |
| N (%) of studies included in the quantitative data meta-analyses: |                                                          |
| Proportion meta-analysis of Toxoplasma IgG (or IgG/IgM) seropositivity in SCZ | 58 (87.9%) studies                                        |
| Association meta-analysis of Toxoplasma IgG (or IgG/IgM) seropositivity in SCZ versus controls | 51 (77.3%) studies                                        |
| N (%) of studies included in the association analyses |                                                          |
| Associations with SCZ |                                                          |
| Toxoplasma IgG (or IgG/IgM) seropositivity in SCZ (vs. controls) | 54 (81.8%) studies                                        |
| Toxoplasma IgG serointensity in SCZ (vs. controls) | 18 (27.3%) studies                                       |
| Toxoplasma IgM seropositivity in SCZ (vs. controls) | 17 (25.7%) studies                                       |
| Toxoplasma PCR in SCZ (vs. controls) | 1 (1.5%) study                                           |
| Associations with SCZ phenotypes |                                                          |
| Toxoplasma IgG (or IgG/IgM) seropositivity in SCZ phenotypes | 26 (39.4%) studies                                       |
| Toxoplasma IgG serointensity in SCZ phenotypes | 6 (9.0%) studies                                         |
| Toxoplasma IgM seropositivity in SCZ phenotypes (vs. controls) | 3 (4.5%) studies                                         |
| Adjustments in the association effect sizes |                                                          |
| No adjustments/matching (between cases and controls) | 49 (74.2%) studies                                       |
| Adjustment/matching for at least age and socioeconomic status/or place of residence (between cases and controls) | 17 (25.8%) studies                                       |
| Temporality |                                                          |
| Study addressed temporality (toxoplasmosis diagnosed before SCZ diagnosis) | 4 (6%)                                                 |

* Not all studies included in the proportion meta-analyses provided comparative data in SCZ patients versus controls to be included also in the association meta-analysis of toxoplasmosis and SCZ.

* The association between Toxoplasma IgG seropositivity and SCZ was explored in 54 studies; but only 51/54 provided quantitative data in such a format that could be included in the association meta-analysis (e.g., 2 × 2 table or odds ratio/RR/HR with 95% CI thereof).

* The study sample size might have been larger than the number of SCZ patients (and controls) analyzed, as patients with additional psychiatric conditions might have been included.
TABLE 2. Meta-analyses: proportion and association meta-analyses

| Description                                                                 | Effect size (summary proportion [%] or summary odds ratio [OR]) and 95% confidence intervals thereof ($I^2$) |
|-----------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
| **Proportion meta-analyses (by random effect models [REM])**^a              |                                                                                                      |
| *Toxoplasma* IgG (or IgG/IgM) seropositivity rates across studies^b,c       | 45% (36%–53%; $I^2 = 99.1$)                                                                         |
| Proportion meta-analysis of IgG (or IgG/IgM) seropositivity rate in SCZ    |                                                                                                      |
| Proportion meta-analysis of IgM (or IgG/IgM) seropositivity rate in controls |                                                                                                      |
| *Toxoplasma* IgM seropositivity rates across studies^d,e                     | 5% (2%–9%; $I^2 = 91.4$)                                                                             |
| Proportion meta-analysis of IgM seropositivity rate in SCZ                  |                                                                                                      |
| Proportion meta-analysis of IgM seropositivity rate in controls             |                                                                                                      |
| **Association meta-analyses (REM)**^f                                        |                                                                                                      |
| Meta-analysis of *Toxoplasma* IgG (or IgG/IgM) seropositivity rate in SCZ  | 1.91 (1.61–2.27; $I^2 = 80.0$)                                                                       |
| (vs controls; summary OR by REM)                                             |                                                                                                      |
| **Subgroup association meta-analyses**                                      |                                                                                                      |
| Association meta-analyses according to adjustment status                    |                                                                                                      |
| Studies with adjustment/matching for age and socioeconomic status/or place of residence (summary OR by REM) | 2.21 (1.63–3.02; $I^2 = 67.3$)                                                                        |
| Studies with no such adjustments (summary OR by REM)                        | 1.79 (1.47–2.19; $I^2 = 80.8$)                                                                        |
| Association meta-analyses according to temporality assessment status        |                                                                                                      |
| Studies addressing temporality (summary OR by REM)                          | 1.68 (1.23–2.31; $I^2 = 0$)                                                                          |
| Studies not addressing temporality (summary OR by REM)                      | 1.94 (1.62–2.32; $I^2 = 81.2$)                                                                        |

Abbreviation: REM, random effect model meta-analysis.

* All studies included in the proportion meta-analyses provided comparative data versus controls to be included also in the association meta-analyses of toxoplasmosis and SCZ.

The median (IQR) of *Toxoplasma* seroprevalence rates in SCZ and controls was: 41.27% (IQR: 27.27%–57.14%).

The median (IQR) of *Toxoplasma* IgG (or IgG/IgM) seropositivity in controls was 26.80% (IQR: 16.53%–37.10%).

The median (IQR) of *Toxoplasma* IgM seropositivity in controls was 3.96% (IQR: 0–11.25%).

The median (IQR) of *Toxoplasma* IgM seropositivity in controls was 0.33% (0–2.31%).

The median (IQR) of *Toxoplasma* ORs for SCZ was: 1.97 (IQR: 1.24–3.22).

for *Toxoplasma* IgM seropositivity and SCZ, and 0/1 studies (0%) for *Toxoplasma* PCR positivity and SCZ, respectively (Figure 2, Appendix 5).

The median number of association-categories (types of *Toxoplasma* exposures and SCZ outcomes) targeted per study were 2 (IQR: 1–3; range 1–5; Figure 2); however, the number of actual analyses performed per study was much larger, as several different types of SCZ phenotypes were often targeted for the same type of *Toxoplasma* exposure (e.g., age of SCZ onset, duration of SCZ symptoms, individual types of SCZ, specific SCZ symptoms scores, etc.). Moreover, the types of toxoplasmosis exposures were often analyzed in more than one way (e.g., *Toxoplasma* IgG serointensity analyzed as a continuous variable, binary variable and/or categorical variable).

Among studies targeting *Toxoplasma* IgG serointensity and SCZ, the analyzed associations always pertained to higher mean *Toxoplasma* IgG titers (or higher number of patients with SCZ in the higher *Toxoplasma* IgG-titer percentile thereof), except for 1 study (Kezai et al (39)) where SCZ was associated with lower IgG titers. The types of reported *Toxoplasma*-IgG serointensity data across studies (e.g., mean *Toxoplasma* IgG titer, % patients on the top 10th % of *Toxoplasma* IgG titers, % of patients on the top 25th % of *Toxoplasma* IgG titers etc.) were too diverse to allow for a meaningful meta-analysis.

Association meta-analysis for SCZ. The average OR (by REM) of *Toxoplasma*-IgG (or IgG/IgM) seropositivity in patients with SCZ versus controls was 1.91 (95% CI: 1.61–2.27; Figure 3, Table 2). There was large heterogeneity across studies ($I^2 = 80.03$%). The median OR across studies was 1.97 (IQR: 1.24–3.22; Figure 3, Table 2).

Biases. There was evidence for small-study effect bias (Egger’s test for bias $p < 0.001$; Appendix 7). Adjusted analyses for at least age and socioeconomic status/place of residence were done only in 17 studies (26%). Moreover, the issue of temporality (diagnosis of toxoplasmosis preceding the diagnosis of SCZ) was addressed only in four studies (6%).

Subgroup meta-analyses according to adjustment for age/socioeconomic status/place of residence, according to temporality assessment or according to study design, gave similar results (Table 2, Appendix 4g-i).

Meta-regression analysis showed a non-statistically significant downward trend in the association between the effect size (logOR) and the *Toxoplasma* seropositivity rate in the control group ($p = 0.141$; Appendix 4j).
Moreover, multivariate regression analysis showed no statistically significant association between the OR and the adjustment for age/socioeconomic status/place of residence ($p = 0.327$), temporality assessment ($p = 0.397$), study design ($p = 0.693$), or number of SCZ-patients analyzed ($p = 0.953$).
Associations with SCZ phenotypes. The Toxoplasma-IgG (or IgG/IgM) seropositivity in SCZ phenotypes was targeted in 26 (39.4%) studies; 6 (9.0%) targeted Toxoplasma-IgG serointensity and 3 (4.5%) targeted Toxoplasma-IgM seropositivity. Statistically significant associations were reported in 20/26 studies (30.3%), 2/6 (3.0%) studies, and 0/3 (0%) studies, respectively (Figure 2, Appendix 5).
Biological plausibility
Several pathophysiological hypotheses have been proposed for the association between toxoplasmosis and SCZ. Appendix 8 shows a compilation list of these proposed hypotheses as reported in the analyzed studies.

DISCUSSION
We analyzed 66 studies published over the past 2 decades with 11,540 patients with SCZ and 69,491 controls, exploring the association between toxoplasmosis and SCZ or SCZ phenotypes. This large accumulated research agenda reflects the great interest of the scientific community for the identification of potentially preventable and/or treatable risk factors for SCZ (40). Although there was large heterogeneity across studies in the types of toxoplasmosis exposures and SCZ outcomes targeted, on average, 45% of patients with SCZ were Toxoplasma IgG (or IgG/IgM) seropositive versus 30% of controls. Toxoplasma IgG (or IgG/IgM) seropositivity increased the odds of SCZ by 1.91-fold. This is similar to the estimate from an earlier meta-analysis by Sutterland et al. in 2015 (OR = 1.81; 95% CI 1.52–2.17) (19).

Most studies targeted only Toxoplasma IgG (or IgG/IgM) seropositivity in SCZ. In contrast, the association with specific SCZ phenotypes was targeted in less than half of the studies. A positive association between Toxoplasma IgG (or IgG/IgM) seropositivity and at least one SCZ phenotype was reported in only a third of the analyzed studies. We did not perform a meta-analysis for the association between toxoplasmosis and SCZ phenotypes as a meta-analysis for this association was recently published by Sutterland et al. (25) in 2020. In this meta-analysis no overall association was seen between Toxoplasma IgG seropositivity and severity of total, positive or negative SCZ symptoms (25). A significant association was only detected in the subgroup of patients with SCZ with a shorter duration of illness (less than 10 years), with Toxoplasma IgG seropositivity being associated with more severe positive symptoms (25).

We identified important methodological biases in the analyzed studies. Approximately 75% of the studies did not perform adjustments for important confounders such as age and socioeconomic status, or place of residence. Moreover, only four studies (41–44) had addressed whether the Toxoplasma infection preceded the diagnosis of SCZ. In the absence of temporality assessment, causality is uncertain. Toxoplasma infections may be the cause or the result of SCZ (e.g., due to common environmental exposures during hospitalization of patients with SCZ). Three out of 4 studies properly addressing temporality documented a positive association between Toxoplasma infection and SCZ. Burgdorf et al. 2019, a large prospective cohort study in Denmark, showed increased rates of Toxoplasma infection preceding the diagnosis of SCZ (41).

Another prospective population cohort study from Denmark by Pedersen et al. of 45,609 women also showed that high Toxoplasma IgG levels before delivery were associated with a significantly increased risk of developing SCZ spectrum disorders subsequently (44). Furthermore, a study among US military personnel in whom Toxoplasma IgG levels were obtained before the diagnosis of SCZ also showed an association between higher Toxoplasma IgG levels and SCZ (43).

Schizophrenia has traditionally been assumed to be largely a genetic condition, with high heritability (45). However, there is concern that the genetic etiology of SCZ might have been overestimated given the inability to detect large genetic effects (45). Schizophrenia may result from a complex interplay between genetic and environmental factors (46). For example, HLA genes of the major histo-compatibility complex (MHC) have the strongest genetic predisposition for SCZ in genome-wide association studies (47). Similarly, MHC genes may affect susceptibility to Toxoplasma infections (48,49). Certain HLA alleles (e.g., HLA C*04:01 allele) have been shown to decrease susceptibility to T. gondii infection in patients with SCZ but not in controls (49). Interactions between genetic and environmental risk factors merit further investigation (46). Environmental factors may be extremely complex and heterogeneous regarding infections by different strains and timing of infection.

Although most studies studied the role of chronic latent toxoplasmosis (IgG seropositivity) with SCZ, approximately a quarter of the studies also studied the potential association of acute toxoplasmosis (IgM seropositivity) with SCZ. On average, 5% of patients with SCZ were Toxoplasma IgM seropositive, versus 0% of controls. A significant association between Toxoplasma IgM seropositivity and SCZ was shown in less than 5% of the studies. An earlier meta-analysis by Monroe et al. (21) showed that Toxoplasma IgM seropositivity was associated with an increase in the odds of acute psychosis. However, positive Toxoplasma IgM results with commercially available tests are often false positive and thus, they cannot be used to diagnose acute Toxoplasma infection (50,51). Positive Toxoplasma IgM results in commercial labs should always be confirmed with additional tests before the diagnosis of acute toxoplasmosis is made. Studies claiming an association between acute Toxoplasma infection and SCZ based only on positive Toxoplasma IgM results, without additional confirmatory testing, should be viewed with caution.

There is speculated biological plausibility for the role of toxoplasmosis in SCZ. Several experimental lines of research addressing parasite-induced anatomical, histological, and physiological changes have been published; however, there is heterogeneity in reported results (14). During the chronic latent stage of the infection, formation of bradyzoites in the brain could directly alter the dopaminergic disturbances involved in psychotic disorders (52,53). The elicited anti-T. gondii immune responses may cross-react with host
N-methyl-D-aspartate receptors (NMDAR), causing disruption of neural circuits and cognitive deficits (13). Autoantibodies that bind to the NMDARs may underlie glutamate receptor dysfunction and cognitive impairment found in SCZ (54). Latent Toxoplasma infection has been associated with upregulation of the complement C1q classic immune pathway, which aids in the clearance of the parasite from the central nervous system with subsequent consequences for the connectivity of neighboring cells and synapses, suggested to be involved in SCZ onset (10). Moreover, complement C4 genes have been proposed in gene-environment interaction studies as potential susceptibility loci for SCZ and infections (including T. gondii infections) (55). Patients with SCZ have increased plasma levels of complement C4 protein activation products, causing increases in blood brain barrier permeability (56). However, there is heterogeneity in the animal studies about the proposed underlying pathophysiologic mechanisms (e.g., alterations in neurotransmitter release, cyst location, and neuroinflammation) for the association of toxoplasmosis with SCZ (14,17,57,58). This heterogeneity may arise from differences in the behavioral assays used, the timing of the behavioral assays, the T. gondii and mice strains utilized, and the route of infection (14). If T. gondii influences human behavior or disease, the effect may depend on the genetic background of the individual and the context of the T. gondii infection (14).

Several neuroleptic antipsychotic and mood stabilizers have been tested for their ability to inhibit replication of T. gondii (59). Among those, the antipsychotic haloperidol and the mood stabilizer valproic acid have been shown to most effectively inhibit T. gondii growth in vitro (60). McFarland et al. (61) and Neville et al. (62) recently reviewed experimental compounds (61) and clinical approved drugs (62) with anti-Toxoplasma activity. Chorlton et al. (63) identified four published RCTs (64–67) testing different medications in patients with SCZ. Several important limitations were identified that likely biased the results towards the null; including failure to target specifically Toxoplasma seropositive patients with SCZ (in 2/4 of these trials) and selecting not clinically appropriate medications. The medications tested in those trials included azithromycin (64), trimethoprim (TMP) monotherapy (65), artemisinin therapy (66) and artemether therapy (67). These medications are not considered first line anti-Toxoplasma treatments (64) and most of those are not even considered acceptable anti-Toxoplasma treatments (65–67) and have not been used in other clinical settings (e.g., for treatment or prophylaxis of high-risk Toxoplasma seropositive patients) (68,69). Four additional small RCTs are currently listed in ClinicalTrials.gov, testing pyrimethamine monotherapy (70), artemisin plus risperidone (71), valproate (72) and L-tetrahydrodipalmatine (73) in patients with SCZ. These trials similarly do not use first line medications and are not targeting only Toxoplasma seropositive patients with SCZ.

Further association studies are unlikely to offer more solid evidence at this point. We believe that randomized double-blind placebo-controlled clinical trials are urgently needed to test the role of anti-Toxoplasma primary prophylaxis (with first line anti-Toxoplasma prophylaxis medications) in Toxoplasma seropositive patients with SCZ. These trials should be ideally simple in design, pragmatic, multicenter, and with few clinically important endpoints. The COVID-19 era has taught us that only well designed, large, RCTs are able to provide solid clinical evidence in a timely fashion and to change our clinical practices (74,75).

The hypothesis underlying a study testing a first line anti-Toxoplasma prophylaxis medication in Toxoplasma seropositive patients with SCZ is that prevention of local intermittent subclinical reactivations of Toxoplasma cysts in the brain of these patients may positively impact their SCZ course. Currently, there are no clinically available medications for the eradication of bradyzoite tissue cysts (the T. gondii tissue form in chronic latent Toxoplasma infection) (76). The goal of such a study in patients with SCZ should be the prevention of intermittent subclinical reactivation rather than eradication of latent T. gondii infection. This has been the strategy for prophylaxis of immunocompromised patients who are Toxoplasma seropositive (69,77,78). The proposed mechanism on how anti-Toxoplasma prophylaxis may help SCZ is that prevention of subclinical reactivations of Toxoplasma cysts may prevent secondary alterations in neurotransmitters’ release and/or neuroinflammation and subsequent worsening of SCZ clinical course. A proof-of-concept for such prophylaxis study will require at least 1 year of prophylactic drug since reactivations may be periodic and spaced over time.

The preferred first line anti-Toxoplasma primary prophylaxis regimen is TMP/sulfamethoxazole (TMP/SMX; one double-strength or one single strength tablet once daily) (69,77,78). Long-term experience exists for the safety and efficacy of TMP/SMX prophylaxis in several high-risk immunocompromised patients, for example, Toxoplasma seropositive transplant patients (69,77) or patients with acquired immune deficiency syndrome (78). The majority of these patients tolerate TMP/SMX without toxicities altering the benefit/risk ratio. Primary prophylaxis in Toxoplasma seropositive hematopoietic stem cell transplant patients is routinely recommended for at least 6 months or even longer for certain patients considered significantly immunosuppressed-requiring prophylaxis-for more prolonged periods (69,77). Prolonged secondary prophylaxis with TMP/SMX is also recommended in patients with recurrent toxoplasmic eye disease in vision threatening areas (e.g., for 12–20 months for certain patients) (79,80) and for Pneumocystis jiroveci prophylaxis in severely immunocompromised patients (e.g., up to 6–12 months for certain transplant patients) (81).

We propose that Toxoplasma IgG seropositive patients with SCZ should be randomized to primary prophylaxis with a first line anti-Toxoplasma medication such as TMP/
SMX versus placebo. The selection of an appropriate first line anti-Toxoplasma medication, similar to what is routinely used for primary prophylaxis in other clinical settings, is critical. Moreover, the duration of the prophylactic therapy (e.g., at least 1 year) would be an additional key factor to allow for proper assessment of clinically important impact on SCZ course. Multidisciplinary collaboration between psychiatrists, infectious diseases experts, and research methodologists in the design of such a pragmatic clinical trial should be a priority.

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CONFLICT OF INTEREST

All authors report no conflict of interest to declare.

AUTHOR AND ARTICLE INFORMATION

Send correspondence to Despina G. Contopoulou-loannidis, Department of Pediatrics, Division of Infectious Diseases, Stanford University School of Medicine, Center for Academic Medicine, Room 454C2, 453 Quarry Road Stanford, CA 94304, USA. (dcontop@stanford.edu).

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REFERENCES

1. Stepanova EV, Kondrashin AV, Sergiev VP, Morozova LF, Turbabina NA, Maksimova MS, et al. Toxoplasmosis and mental disorders in the Russian Federation (with special reference to schizophrenia). PLoS One. 2019;14:e0219454.

2. Rostami A, Riahi SM, Gamble HR, Fakhri Y, Nourallahpour Shiadeh M, Danesh M, et al. Global prevalence of latent toxoplasmosis in pregnant women: a systematic review and meta-analysis. Clin Microbiol Infect. 2020;26:673–83.

3. Pappas G, Roussos N, Falagas ME. Toxoplasmosis snapshots: global status of Toxoplasma gondii seroprevalence and implications for pregnancy and congenital toxoplasmosis. Int J Parasitol. 2009;39:1385–94.

4. Del Grande C, Galli L, Schiavi E, Dell’Osso L, Bruschi F. Is Toxoplasma gondii a trigger of bipolar disorder? Pathogens. 2017;6.

5. Fuglewicz AJ, Pietrowski P, Stodolak A. Relationship between toxoplasmosis and schizophrenia: a review. Adv Clin Exp Med. 2017;26:1031–6.

6. Webster JP, Kaushik M, Bristow GC, McConkey GA. Toxoplasma gondii infection, from predation to schizophrenia: can animal behaviour help us understand human behaviour? J Exp Biol. 2013;216:99–112.

7. Berdoy M, Webster JP, Macdonald DW. Fatal attraction in rats infected with Toxoplasma gondii. Proc Biol Sci. 2000;267:1591–4.

8. Vyas A, Kim SK, Giacomini N, Boothroyd JC, Sapolsky RM. Behavioral changes induced by toxoplasma infection of rodents are highly specific to aversion of cat odors. Proc Natl Acad Sci U S A. 2007;104:6442–7.

9. Poirotte C, Kappeler PM, Ngoubangoye B, Bourgeois S, Moussodji M, Charpentier MJ. Morbid attraction to leopard urine in toxoplasma-infected chimpanzees. Curr Biol. 2016;26:R98–9.

10. Xiao J, Li Y, Gesssi KL, He H, Kannan G, Schultz TL, et al. Cerebral complement C1q activation in chronic toxoplasma infection. Brain Behav Immun. 2016;58:52–6.

11. Prandovszky E, Gaskell E, Martin H, Dubey JP, Webster JP, McConkey GA. The neutrotropic parasite Toxoplasma gondii increases dopamine metabolism. PLoS One. 2011;6:e23866.

12. Fond G, Boyer L, Schurhoff F, Berna F, Godin O, Bulzacca E, et al. Latent toxoplasma infection in real-world schizophrenia: results from the National FACE-SZ Cohort. Schizophr Res. 2018;201:373–80.

13. Lucchese G. From toxoplasmosis to schizophrenia via NMDA dysfunction: peptide overlap between Toxoplasma gondii and N-Methyl-d-Aspartate receptors as a potential mechanistic link. Front Psychiatr. 2017;8:57.

14. Johnson HJ, Koshy AA. Latent toxoplasmosis effects on rodents and humans: how much is real and how much is media hype? mBio. 2020:3.

15. Lori A, Avramopoulos D, Wang AW, Mulle J, Massa N, Duncan EJ, et al. Polygenic risk scores differentiate schizophrenia patients with Toxoplasma gondii compared to toxoplasma seronegative patients. Compr Psychiatry. 2021;107:15236.

16. Charlson F, Ferrari AJ, Santomauro DF, Diminic S, Stockings E, Scott JG, et al. Global epidemiology and burden of schizophrenia: findings from the Global Burden of Disease Study 2016. Schizophr Bull. 2018;44:1195–203.

17. Afonc0 C, Paixao VB, Klaus A, Lunghi M, Piro F, Emilianii C, et al. Toxoplasma-induced changes in host risk behaviour are independent of parasite-derived AaaH2 tyrosine hydroxylase. Sci Rep. 2017;7:13822.

18. Fond G, Capdevielle D, Macgregor A, Attal J, Larue A, Britten M, et al. Toxoplasma gondii: a potential role in the genetics of psychiatric disorders. Encephale. 2018;39:38–43.

19. Sutterland AL, Fond G, Kuin A, Koeter MW, Lutter R, van Gool T, et al. Beyond the association. Toxoplasma gondii in schizophrenia, bipolar disorder, and addiction: systematic review and meta-analysis. Acta Psychiatr Scand. 2015;132:161–79.

20. Arias I, Sorlozano A, Villegas E, de Dios Luna J, McKenney K, Cervilla J, et al. Infectious agents associated with schizophrenia: a meta-analysis. Schizophr Res. 2012;136:128–36.

21. Monroe JM, Buckley PF, Miller BJ. Meta-analysis of anti-toxoplasma gondii IgM antibodies in acute psychosis. Schizophr Bull. 2015;41:989–98.

22. Gutierrez-Fernandez J, Del Castillo JD, Mananes-Gonzalez S, Carrillo-Avila JA, Gutierrez B, Cervilla JA, et al. Different prevalence of Chlamydia pneumoniae, herpes simplex virus type 1, human herpes virus 6, and Toxoplasma gondii in schizophrenia: meta-analysis and analytical study. Neuropsychiatric Dis Treat. 2015;11:843–52.

23. Torrey EF, Bartko JJ, Lun ZR, Yolkien RH. Antibodies to Toxoplasma gondii in patients with schizophrenia: a meta-analysis. Schizophr Bull. 2007;33:729–36.

24. Dare LO, Bruand PE, Gerard D, Marin B, Lameyre V, Boumediene F, et al. Associations of mental disorders and neurotropic parasitic diseases: a meta-analysis in developing and emerging countries. BMC Publ Health. 2019;19:1645.
25. Sutherland AL, Mourir DA, Ribbens JJ, Kuiper B, van Gool T, de Haan L. Toxoplasma gondii infection and clinical characteristics of patients with schizophrenia: a systematic review and meta-analysis. Schizophrenia Bulletin. 2020. https://academic.oup.com/schizbullopen/article/1/1/gaa042/5897194

26. Torrey EF, Bartko JJ, Yolken RH. Toxoplasma gondii and other risk factors for schizophrenia: an update. Schizophr Bull. 2012;38:642–7.

27. Blomstrom A, Gardner RM, Dalman C, Yolken RH, Karlsson H. Influence of maternal infections on neonatal acute phase proteins and their interaction in the development of non-affective psychosis. Transl Psychiatry. 2015;5:e502.

28. Blomstrom A, Karlsson H, Wicks S, Yang S, Yolken RH, Dalman C. Maternal antibodies to infectious agents and risk for non-affective psychoses in the offspring—a matched case-control study. Schizophr Res. 2012;140:25–30.

29. Brown AS, Patterson PH. Maternal infection and schizophrenia: implications for prevention. Schizophr Bull. 2011;37:284–90.

30. Brown AS, Schaefer CA, Quesenberry CP Jr., Liu L, Babulas VP, Susser ES. Maternal exposure to toxoplasmosis and risk of schizophrenia in adult offspring. Am J Psychiatr. 2005;162:767–73.

31. Brown AS, Vinogradov S, Kremen WS, Poole JH, Deicken RF, Penner JD, et al. Prenatal exposure to maternal infection and executive dysfunction in adult schizophrenia. Am J Psychiatr. 2009;166:683–90.

32. Buja SL, Tsuang MT, Torrey EF, Klebanoff MA, Bernstein D, Yolken RH. Maternal infections and subsequent psychosis among offspring. Arch Gen Psychiatr. 2001;58:1032–7.

33. Freedman D, Bao Y, Shen L, Schaefer CA, Brown AS. Maternal T. gondii, offspring bipolar disorder and neurocognition. Psychiatr Res. 2016;243:82–9.

34. Khandaker GM, Zimbron J, Lewis G, Jones PB. Prenatal maternal infection, neurodevelopment and adult schizophrenia: a systematic review of population-based studies. Psychol Med. 2013;43:239–57.

35. DerSimonian R, Laird N. Meta-analysis in clinical trials. Contr Clin Trials. 1986;7:177–88.

36. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557–60.

37. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis: detection, assessment, and adjustment for reportable studies. J Clin Epidemiol. 1997;50:119–27.

38. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, et al. The PRISMA 2020 Statement: an updated guideline for reporting systematic reviews. PLoS Med. 2021;18:1:e1003583.

39. Kezai AM, Lecoeur C, Hot D, Bounoucha M, Alouani ML, Marion S. Association between schizophrenia and Toxoplasma gondii infection in Algeria. Psychiatr Res. 2020;291:113293.

40. Radua J, Ramella-Cravaro V, Ioannidis JPA, Reichenberg A, Phiphopthatsanee N, Amir T, et al. What causes psychosis? An umbrella review of risk and protective factors. World Psychiatr. 2018;17:49–66.

41. Burgdorf KS, Trabjerg BB, Pedersen MG, Nissen J, Banakis P, Pedersen OB, et al. Large-scale study of toxoplasmosis and cytomegalovirus shows an association between infection and serious psychiatric disorders. Brain Behav Immun. 2019;79:152–8.

42. Lin HA, Chien WC, Huang KY, Chung CH, Chen LC, Lin HC, et al. Infection with Toxoplasma gondii increases the risk of psychiatric disorders in Taiwan: a nationwide population-based cohort study. Parasitology. 2020;147:1577–86.

43. Niebuhr DW, Millikan AM, Cowan DN, Yolken R, Li Y, Weber NS. Selected infectious agents and risk of schizophrenia among U.S. Military Personnel. Am J Psychiatr. 2008;165:99–106.

44. Pedersen MG, Stevens H, Pedersen CB, Norgaard-Pedersen B, Mortensen PB. Toxoplasma infection and later development of schizophrenia in mothers. Am J Psychiatr. 2011;168:814–21.

45. Torrey EF, Yolken RH. Schizophrenia as a pseudogenetic disease: a call for more gene-environmental studies. Psychiatr Res. 2019;278:146–50.

46. Robinson N, Bergen SE. Environmental risk factors for schizophrenia and bipolar disorder and their relationship to genetic risk: current knowledge and future directions. Front Genet. 2021;12:68666.

47. Corvin A, Morris DW. Genome-wide association studies: findings at the major histocompatibility complex locus in psychosis. Biol Psychiatr. 2014;75:276–83.

48. Blackwell JM, Roberts CW, Alexander J. Influence of genes within the MHC on mortality and brain cyto development in mice infected with Toxoplasma gondii: kinetics of immune regulation in BALB H-2 congenic mice. Parasite Immunol. 1993;15:317–24.

49. Parks S, Avramopoulos D, Muller J, McGrath J, Wang R, Goes FS, et al. HLA typing using genome wide data reveals susceptibility types for infections in a psychiatric disease enriched sample. Brain Behav Immun. 2018;70:203–13.

50. Liesenfeld O, Press C, Montoya JG, Gill R, Isaac-Jenton RL, Hedman K, et al. False-positive results in immunoglobulin M (IgM) toxoplasma antibody tests and importance of confirmatory testing: the Platelia Toxo IgM test. J Clin Microbiol. 1997;35:174–8.

51. Dhakal R, Gajurel K, Pomares C, Talucod J, Press CJ, Montoya JG. Significance of a positive toxoplasma immunoglobulin M test result in the United States. J Clin Microbiol. 2015;53:361–5.

52. Ab-Dargham A. Schizophrenia: overview and dopamine dysfunction. J Clin Psychiatr. 2014;75:e81.

53. Strobl JS, Goodwin DG, Rzigalinski BA, Lindsay DS. Dopamine stimulates propagation of Toxoplasma gondii tachyzoites in human fibroblast and primary neonatal rat astrocyte cell cultures. J Parasitol. 2012;98:1296–9.

54. Kannan G, Gressitt KL, Yang S, Stallings CR, Katsafanas E, Schweinfurth LA, et al. Pathogen-mediated NMDA receptor autoimmunity and cellular barrier dysfunction in schizophrenia. Transl Psychiatry. 2017;7:e1186.

55. Kalinowski A, Lilienthal J, Anker LA, Linkovski O, Culbertson C, Hall JN, et al. Increased activation product of complement 4 protein in plasma of individuals with schizophrenia. Transl Psychiatry. 2021;11:486.

56. Severance EG, Leister F, Lea A, Yang S, Dickerson F, Yolken RH. Complement C4 associations with altered microbial biomarkers exemplify gene-by-environment interactions in schizophrenia. Schizophr Res. 2021;234:87–93.

57. Webster JP. The effect of Toxoplasma gondii and other parasites on activity levels in wild and hybrid Rattus norvegicus. Parasitology. 1994;109 (Pt 5):583–9.

58. Hodkova H, Kodym P, Fleg J. Poorer results of mice with latent toxoplasmic activity of Toxoplasma gondii in Algeria. Psychiatr Res. 2002;113:249–57.

59. Jones-Brando L, Torrey EF, Yolken R. Drugs used in the treatment of schizophrenia and bipolar disorder inhibit the replication of Toxoplasma gondii. Schizophr Res. 2003;62:237–44.

60. McFarland MM, Zach SJ, Wang X, Potluri LP, Neville AJ, Venernstrom JL, et al. Review of experimental compounds demonstrating anti-toxoplasma activity. Antimicrob Agents Chemother. 2016;60:7017–34.
62. Neville AJ, Zach SJ, Wang X, Larson JJ, Judge AK, Davis LA, et al. Clinically available medicines demonstrating anti-toxoplasma activity. Antimicrob Agents Chemother. 2015;59:7161–9.

63. Chorlton SD. Toxoplasma gondii and schizophrenia: a review of published RCTs. Parasitol Res. 2017;116:1793–9.

64. Dickerson FB, Stallings CR, Boronow JJ, Origoni AE, Yolken RH. A double-blind trial of adjunctive azithromycin in individuals with schizophrenia who are seropositive for Toxoplasma gondii. Schizophr Res. 2009;112:198–9.

65. Shibre T, Alem A, Abdulahi A, Araya M, Beyero T, Medhin G, et al. Trimethoprim as adjuvant treatment in schizophrenia: a double-blind, randomized, placebo-controlled clinical trial. Schizophr Bull. 2010;36:846–51.

66. Dickerson F, Stallings C, Vaughan C, Origoni A, Khushalani S, et al. Artemisinin reduces the level of antibodies to gliadin in schizophrenia. Schizophr Res. 2011;129:196–200.

67. Wang HL, Xiang YT, Li QY, Wang XP, Liu ZC, Hao SS, et al. The effect of artemether on psychotic symptoms and cognitive impairment in first-episode, antipsychotic-naive persons with schizophrenia seropositive to Toxoplasma gondii. J Psychiatr Res. 2014;53:119–24.

68. Contopoulos-Ioannidis DG, Cho SM, Bertaina A, Leung AN, Fischbein N, Lanzman B, et al. Toxoplasmosis among 38,751 hematopoietic stem cell transplant recipients: a systematic review of disease prevalence and a compilation of imaging and autopsy findings. Transplantation. 2021.

69. Gajurel K, Dhakal R, Montoya JG. Toxoplasma prophylaxis in hematopoietic cell transplant recipients: a systematic review of the literature and recommendations. Curr Opin Infect Dis. 2015;28:283–92.

70. Hinze-Selch D. Effect of specific anti-toxoplasma add-on medication in toxoplasma gondii seropositive individuals with schizophrenia or major depression. ClinicalTrialsgov NCT00300404.

71. Zhang X. Artemisinin with risperidone for first-episode and drug-naive schizophrenia. ClinicalTrialsgov NCT01391403.

72. Mansour H. Pilot trial of valproate as adjunctive treatment for toxoplasma gondii infection in early course schizophrenia. ClinicalTrialsgovNCT0201750.

73. Kelly D. Treatment of schizophrenia with L-tetrahydropalmatine (L-THP): a novel dopamine antagonist with anti-inflammatory and antiprotozoal activity. ClinicalTrialsgovNCT02118610.

74. Group RC, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 2021;384:693–704.

75. Axfors C, Schmitt AM, Janiaud P, Van’t Hooft J, Abd-Elsalam S, Abdo EF, et al. Mortality outcomes with hydroxychloroquine and chloroquine in COVID-19 from an international collaborative meta-analysis of randomized trials. Nat Commun. 2021;12:2349.

76. Dunay IR, Gajurel K, Dhakal R, Liesenfeld O, Montoya JG. Treatment of toxoplasmosis: historical perspective, animal models, and current clinical practice. Clin Microbiol Rev. 2018 Sep 12;31 (4):e00057–17.

77. Schwenk HT, Khan A, Kohlman K, Bertaina A, Cho S, Montoya JG, et al. Toxoplasmosis in pediatric hematopoietic stem cell transplantation patients. Transplant Cell Ther. 2021;27:292–300.

78. Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of health, and the HIV Medicine Association of the Infectious Diseases Society of America. https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection. Accessed 02 07 2022.

79. Silveira C, Belfort R Jr., Muccioli C, Holland GN, Victora CG, Horta BL, et al. The effect of long-term intermittent trimethoprim/sulfamethoxazole treatment on recurrences of toxoplasmic retinochoroiditis. Am J Ophthalmol. 2002;134:41–6.

80. Felix JP, Lira RP, Zacchia RS, Toribio JM, Nascimento MA, Arieta CE. Trimethoprim-sulfamethoxazole versus placebo to reduce the risk of recurrences of Toxoplasma gondii retinochoroiditis: randomized controlled clinical trial. Am J Ophthalmol. 2014;157:762–6 e761.

81. Fishman JA, Gans H, AST Infectious Diseases Community of Practice. Pneumocystis jiroveci in solid organ transplantation: guidelines from the American Society of Transplantation infectious diseases community of practice. Clin Transplant. 2019 Sep;33 (9):e13587.