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Association between *Toxoplasma gondii* and systemic lupus erythematosus: A systematic review and meta-analysis

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ABSTRACT

Infecting approximately one-third of the world's population, the intraneuronal parasite *Toxoplasma gondii* has been associated with several autoimmune diseases. While *Toxoplasma gondii* may be protective against multiple sclerosis, other findings have negatively associated *Toxoplasma gondii* with different autoimmune diseases, including systemic lupus erythematosus. To further characterize the association between *Toxoplasma gondii* and systemic lupus erythematosus, we completed a systematic review and meta-analysis of published studies looking at the association between *Toxoplasma gondii* and systemic lupus erythematosus. The primary results of a random-effects model showed an odds ratio of 2.34 (95% confidence interval 1.17–4.69, $P = 0.017$), indicating the odds of *Toxoplasma gondii* seropositivity were 2.34 times higher in the group with systemic lupus erythematosus than in the healthy control group. Few available source studies, an overall lack of information about immunosuppressive status, and little information about sex composition and assays limit this finding and indicate the need for additional research to further characterize the association between systemic lupus erythematosus and *Toxoplasma gondii*.

1. Introduction

Autoimmune diseases are characterized by the immune system failing to distinguish between itself and foreign tissues. At present, more than 80 diseases have been classified as autoimmune. In addition to genetic factors, infectious diseases including viruses and bacteria have been associated with autoimmune diseases [1]. In some cases, the association between the infectious diseases is positive, such as the association between Epstein-Barr virus and the autoimmune disease multiple sclerosis, wherein infection with Epstein-Barr virus appears to act as a risk factor for multiple sclerosis [2]. In other associations between infectious and autoimmune diseases, the infectious disease could be protective against the autoimmune disease, such as the negative association between *Toxoplasma gondii* and multiple sclerosis, where *Toxoplasma gondii* seropositivity appears to be protective against multiple sclerosis [3]. Infectious diseases could cause autoimmune diseases through several mechanisms, including molecular mimicry and expansion of active autoreactive immune cells [1].

Systemic lupus erythematosus (SLE) is an autoimmune disease with an incidence in the United States of 5.1 per 100,000 person-years [4] and a prevalence in the United States of 72.8 per 100,000 person-years [5]. In the United States, the incidence of SLE is seven times higher in women than in men [4], and the prevalence is nine times higher in women than in men [5]. Clinically, SLE is an inflammatory disease characterized by fatigue, kidney disease, hair loss, rash, and dramatic weight change. Central nervous system manifestations of SLE include seizures, psychosis [6–9], cognitive dysfunction, and abnormal brain resting-state functional connectivity [10]. The etiology of SLE remains poorly understood [11], but both genetic and environmental factors such as infectious diseases are likely involved [12].

SLE is associated with a divergent innate immune response, generating tissue inflammation with the release of cytokines. This innate response then leads to the activation of T and B cells, which produce autoantibodies against nucleic acids and their binding proteins, increasing the autoimmune response. Genetic, immunological, endocrine, and environmental factors all influence this loss of immunological tolerance against self-antigens, leading to the formation of the autoantibodies that cause tissue damage in SLE [13].

Among the infectious diseases associated with SLE is *Toxoplasma gondii* [14–16], an obligate apicomplexan parasite that infects an

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estimated one-third of the world's human population [17]. While members of the cat family are the definitive hosts of *Toxoplasma gondii,* many animals, including mammals and birds, serve as intermediate hosts. Infectious transmission can occur via contaminated water and undercooked meat or after contact with oocysts shed from cats [18]. Oocysts develop into tachyzoites, which can invade muscle and brain tissue, where they form metabolically active cysts. Immunocompromise can result in cysts reactivating to tachyzoites. Despite host immune responses, *Toxoplasma gondii* can persist for the lifetime of the host [19].

In pregnant women and those with compromised immune systems, infection with *Toxoplasma gondii* can be severe and create an increased risk of miscarriage, stillbirth, or severe infection [20]. In contrast, in immunocompetent people, initial infection with *Toxoplasma gondii* can be asymptomatic or characterized by lymphadenopathy [21]. Although infection with *Toxoplasma gondii* in immunocompetent people was once considered benign [22], accumulating evidence suggests that *Toxoplasma gondii* is associated with behavioral changes [23], deficits in cognitive function [24], and schizophrenia [25]. In addition, *Toxoplasma gondii* has been associated with autoimmune disease [26]. In this regard, *Toxoplasma gondii* may be a risk factor for rheumatoid arthritis [27], but a meta-analysis found that the parasite might be protective against multiple sclerosis [3]. In addition, *Toxoplasma gondii* has been associated with SLE [14]. Given the high prevalence of *Toxoplasma gondii* infection and its possible associations with SLE [14–16], we sought to quantitatively characterize the association between *Toxoplasma gondii* and SLE with a meta-analysis of available published studies that have examined associations between *Toxoplasma gondii* and SLE.

2. Material and methods

2.1. Information source and search strategy

We searched for published articles that quantified the association between *Toxoplasma gondii* and SLE using the PubMed electronic database. The search terms were "Systemic lupus erythematosus", "SLE", "*Toxoplasma gondii*", and "*Toxoplasmosis*". We also reviewed reference lists of identified articles for other potentially relevant articles.

2.2. Selection criteria

We identified studies that sought to evaluate associations between *Toxoplasma gondii* and systemic lupus erythematosus in humans and searched for articles through April 2022. Inclusion criteria were articles published in peer-reviewed journals that contained data about the prevalence of *Toxoplasma gondii* in an SLE sample and the prevalence of *Toxoplasma gondii* in a sample of healthy controls. There were no restrictions on publication date or language. We excluded case studies and articles without a healthy control group.

2.3. Data extraction

From the identified articles meeting inclusion and exclusion criteria, we extracted author names, date of publication, the region or country where the study was completed, number of participants, number seropositive, percent female, mean age of the SLE and control groups, and type of assay used to determine *Toxoplasma gondii* seropositivity. In that immunosuppressive treatment could confound associations between *Toxoplasma gondii* and SLE [28], we also extracted any reported information regarding whether the SLE participants were on any immunosuppressive treatment during the study.

2.4. Data analysis

To better understand the relationship between *Toxoplasma gondii* and SLE, we conducted a meta-analysis using the *meta* package from the R software [29,30]. We computed individual study odds ratios and 95% confidence intervals and created a forest plot to visualize these results and the heterogeneity among the studies. We further assessed heterogeneity using the Cochran Q test and I^2 statistics. For the meta-analysis, we used the random-effects Mantel-Haenszel method. Various heterogeneity estimators were applied, including the DerSimonian-Laird, Paule-Mandel, restricted maximum likelihood, and Sidik-Jonkman estimators. Results varied minimally across the estimators, so we report results using the DerSimonian-Laird estimator.

Due to the small number of studies included in the analysis, we did not formally test publication bias. Additionally, we performed sensitivity analyses to determine the impact of certain individual studies. Meta-regression was not conducted due to the small number of studies (and the studies' lack of information about the other variables considered, such as percent female and mean age).

3. Results

The searches returned 159 unique articles, from which we reviewed 23 abstracts and retrieved 11 full articles. Of these, five articles [14–16, 26,31] containing six unique datasets (the Shapira et al., 2012 study [26] contains two independent datasets) met inclusion and exclusion criteria (Fig. 1). In the Wilcox et al., 1990 study [31], two different assays were used to determine *Toxoplasma gondii* seropositivity, resulting in two sets of data for the same set of patients. Here, we present results from the data where the latex agglutination test was used since the data is more conservative. Supplementary Fig. 1 and 2 contain results for the other Wilcox et al., 1990 [31] dataset where the dye test was used.

In the Cao et al., 2020 study [15], only the abstract was in English. However, we had a native speaker of Mandarin Chinese read the body of the paper to extract any additional information relevant to our analysis that was not in the abstract. There was a total of 568 participants in the group with systemic lupus erythematosus and 894 participants in the healthy control group. Across these six source studies, the percentage of *Toxoplasma gondii* seropositivity ranged from 3.6% to 36% in the control group compared to 10% to 60% in the SLE group (Table 1). Only three of the six datasets contained information about the use of

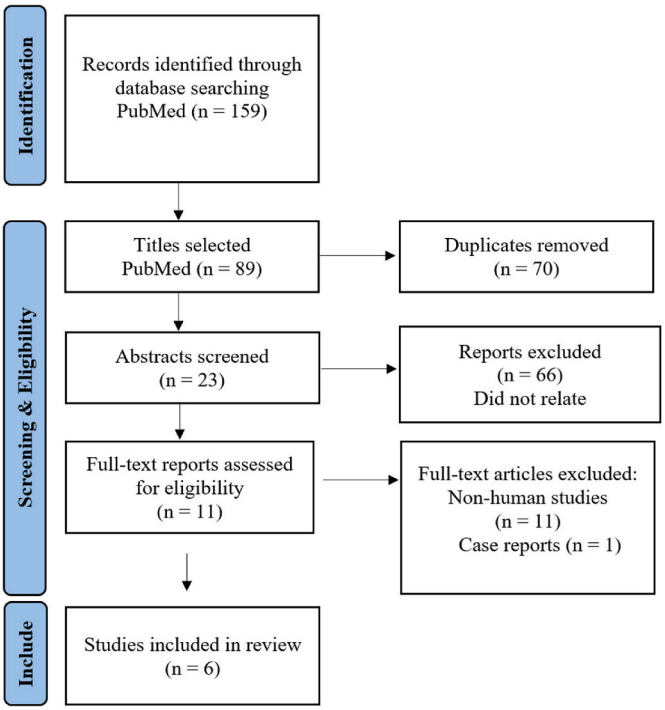

Fig. 1. Flow chart of study selection.

Table 1
Identified source studies comparing percent of antibodies against *Toxoplasma gondii* in groups with and without systemic lupus erythematosus.

Author, year	SLE Group				Control Group				Immunosuppressants
	Cases, n	Female, %	Mean age, years	*T. gondii* seropositive, n	Cases, n	Female, %	Mean age, years	*T. gondii* seropositive, n	
Cao et al., 2020	79	–	–	25	237	–	–	10	Not mentioned
Hamza et al., 2017[a]	30	96.7%	34	18	30	56.7%	35	9	Yes
Berkun et al., 2009	120	99.2%	38	12	140	92.9%	39	5	Not mentioned
Shapira et al., 2012	169	–	–	54	297	–	–	77	Not mentioned
Shapira et al., 2012	120	–	–	42	140	–	–	50	Not mentioned
Wilcox et al., 1990	50	–	56	25	50	–	–	10	Not used
Wilcox et al., 1990	50	–	56	19	50	–	–	15	Not used

Note: Dashes identify data not reported.
[a] The SLE group had lupus nephritis and both IgG and IgM antibodies were used.

immunosuppressant treatment (Table 1), and only two of the six datasets reported the sex composition of the participants. In addition, some studies failed to report the type of assay used to determine *Toxoplasma gondii* seropositivity. Three of the six identified datasets reported a positive association between *Toxoplasma gondii* and systemic lupus erythematosus (*P* values ranging from <0.0001 to 0.045).

Fig. 2 depicts a forest plot summarizing the six individual study results and the pooled meta-analysis results. Visually, we see a wide range of effect estimates from the individual studies, with evidence of substantial heterogeneity further supported by Cochran's Q test ($P < 0.0001$) and the I^2 statistic (83%, where values above 75% are typically considered to indicate considerable heterogeneity). These results indicate that the included studies are estimating different true effects and that a random-effects model should be used. The Mantel-Haenszel random-effects meta-analysis, using the DerSimonian and Laird heterogeneity estimator, produced a pooled odds ratio of 2.34 (95% confidence interval 1.17–4.69, $P = 0.017$, Fig. 2), suggesting the odds of *Toxoplasma gondii* seropositivity are 2.34 times higher for those with SLE compared to healthy controls.

Since two of the studies, Cao et al., 2020 [15] and Hamza et al., 2017 [16], have unique characteristics, we performed sensitivity analyses to determine their impact on the meta-analysis results. First, because the odds ratio of the Cao et al., 2020 study [15] was three times larger than the next largest odds ratio in the included study, we completed a meta-analysis that did not include the results of the Cao et al., 2020 study [15]. Fig. 3 depicts the meta-analysis results after excluding the Cao et al., 2020 study [15]. In this analysis, the range of the individual study effect estimates was reduced, and only moderate heterogeneity was present (Cochran's Q test *P* value of 0.143, I^2 statistic of 42%). The same random-effects meta-analysis model resulted in a smaller, but still statistically significant at the 0.04 level, odds ratio estimate of 1.53 (95% confidence interval 1.02–2.30, $P = 0.040$, Fig. 3).

Second, the Hamza et al., 2017 study [16] used immunosuppressants, which could have confounded the association between *Toxoplasma gondii* seropositivity and SLE; Fig. 4 depicts the meta-analysis results after removing the Hamza et al., 2017 study [16]. While there is still considerable heterogeneity present (Cochran's Q test *P* value < 0.0001, I^2 statistic of 85%), removing this study drops the odds ratio estimate from 2.34 to 2.20 (95% confidence interval 1.01–4.76, $P = 0.046$, Fig. 4). Removing both the Cao et al., 2020 study [15] and the Hamza et al., 2017 study [16] results in a non-significant odds ratio estimate of 1.33 (95% confidence interval 0.94–1.89, $P = 0.104$), as seen in Fig. 5. Additionally, there is now little statistical heterogeneity present in the data (Cochran's Q test *P* value = 0.280, I^2 statistic of 22%).

Supplemental Fig. 1-4 repeat the above analyses but use the Wilcox et al., 1990 study [31] data with the other assay (dye test) to detect *Toxoplasma gondii* seropositivity. In summary, while the statistical significance of the analyses remains the same as when the latex agglutination test was used, using the dye test results in an increase in the estimated odds ratio of between 0.39 and 0.43. Supplemental Fig. 1 models the results using all six studies (odds ratio estimate of 2.73 with a 95% confidence interval of 1.31–5.69, $P = 0.007$). Supplemental Fig. 2 contains the results after excluding the Cao et al., 2020 study [15] (estimated odds ratio of 1.93 with a 95% confidence interval of 1.12–3.34, $P = 0.018$). Supplemental Fig. 3 displays results after removing the Hamza et al., 2017 study [16] (odds ratio estimate of 2.63 with a 95% confidence interval of 1.16–6.01, $P = 0.021$). Lastly, Supplemental Fig. 4 contains results after removing both the Cao et al., 2020 study [15] and the Hamza et al., 2017 study [16] (estimated odds ratio of 1.74 with a 95% confidence interval of 0.98–3.10, $P = 0.060$).

4. Discussion

In the main analysis of this meta-analysis, the odds of *Toxoplasma*

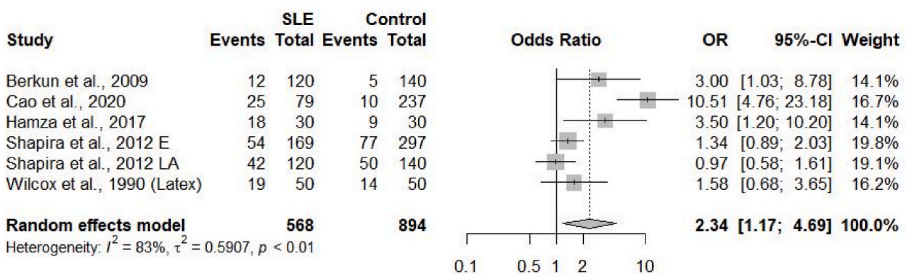

Fig. 2. Meta-analysis results of the association between *Toxoplasma gondii* and systemic lupus erythematosus. Note: This meta-analysis uses all six included studies. The Wilcox et al., 1990 dataset is based on the latex agglutination test. OR, odds ratio; CI, confidence interval.

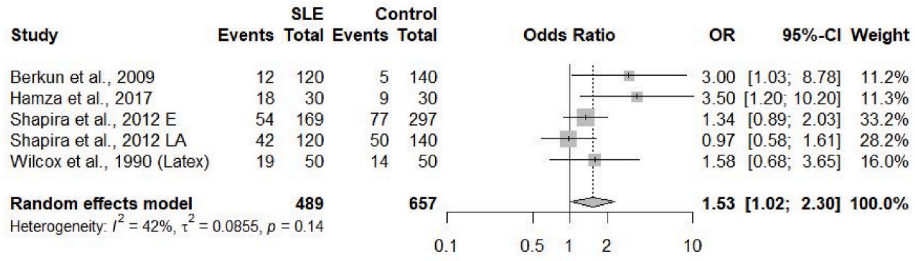

Fig. 3. Meta-analysis results of the association between *Toxoplasma gondii* and systemic lupus erythematosus without Cao et al., 2020. Note: The Cao et al., 2020 study is excluded from this analysis. The Wilcox et al., 1990 dataset is based on the latex agglutination test. OR, odds ratio; CI, confidence interval.

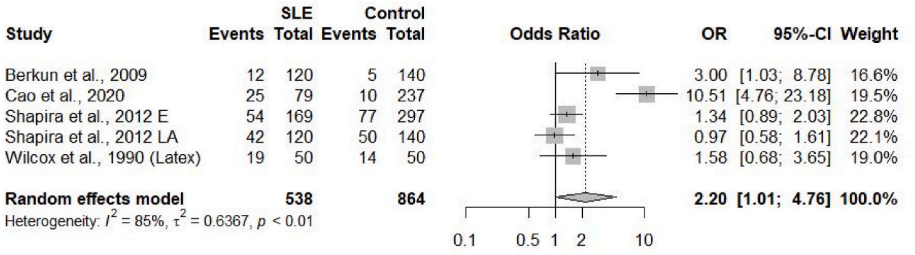

Fig. 4. Meta-analysis results of the association between *Toxoplasma gondii* and systemic lupus erythematosus without Hamza et al., 2017. Note: Hamza et al., 2017 is excluded from the analysis. The Wilcox et al., 1990 dataset is based on the latex agglutination test. OR, odds ratio; CI, confidence interval.

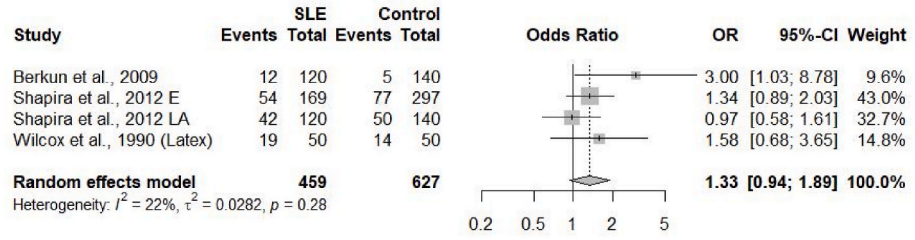

Fig. 5. Meta-analysis results of the association between *Toxoplasma gondii* and systemic lupus erythematosus without Hamza et al., 2017 or Cao et al., 2020 studies. Note: Both Hamza et al., 2017 and Cao et al., 2020 studies are excluded from the analysis. The Wilcox et al., 1990 dataset is based on the latex agglutination test. OR, odds ratio; CI, confidence interval.

gondii seropositivity were 2.34 times higher in the SLE group than in the healthy controls, which suggests that *Toxoplasma gondii* seropositivity could be associated with SLE. Because the effect size of the Cao et al., 2020 study [15] included in our meta-analysis was three times larger than the next largest effect size among the source studies, we ran four additional analyses that excluded the results of Cao et al., 2020 [15] (results illustrated in Figs. 3 and 5 and Supplemental Fig. 2 and 4). With this study removed, the estimated odds ratio dropped from 2.34 to 1.53, when the latex agglutination test data from Wilcox et al., 1990 [31] is used (Fig. 3), and from 2.34 to 1.93, when the dye test from Wilcox et al., 1990 [31] is used (Supplemental Fig. 4). Other than its large effect size compared to the other source studies, we had no other reason to exclude the Cao et al., 2020 study [15] from the analysis; moreover, the Cao et al., 2020 study [15] was the most recent of the included source studies and the second largest.

Similarly, we performed four additional analyses with the Hamza et al., 2017 study [16] removed since it reported the use of immunosuppressants (results illustrated in Figs. 4 and 5 and Supplemental Fig. 3 and 4). Removing this study resulted in the estimated odds ratio dropping from 2.34 to 2.20, when the latex agglutination test data from Wilcox et al., 1990 [31] is used (Fig. 4), and increasing from 2.34 to 2.63 when the dye test from Wilcox et al., 1990 [31] is used (Supplemental Fig. 3). The decrease when the latex agglutination test is used and the increase when the dye test is used indicates that there may be some interaction between type of assay used to determine *Toxoplasma gondii* seropositivity and the use of immunosuppressants. It is important to note that since four of the six studies failed to comment on the use of immunosuppressants, we do not have a complete understanding of the impact of immunosuppressants or their combined impact with assay type on the association between *Toxoplasma gondii* and systemic lupus erythematosus.

Lastly, removing both the Cao et al., 2020 study [15] and the Hamza et al., 2017 study [16] results in meta-analysis results that are not statistically significant at the 0.05 level. When the latex agglutination test data from Wilcox et al., 1990 [31] is used, the estimated odds ratio drops from 2.34 to 1.33 (Fig. 5). When the dye test data from Wilcox et al., 1990 [31] is used, the estimated odds ratio drops from 2.34 to 1.74 (Supplemental Fig. 4).

While together our results support an association between *Toxoplasma gondii* and SLE, several factors require consideration when interpreting them. Although this is the first meta-analysis to examine the association between *Toxoplasma gondii* and SLE, it included only six unique datasets, two of which were from the same authors. This small number of source studies makes the results sensitive to additional studies. As demonstrated by the Wilcox et al., 1990 study [31], the type of assay used can influence *Toxoplasma gondii* seropositivity, making it

important for future studies investigating the association between *Toxoplasma gondii* seropositivity and SLE to record the type of assay used to determine seropositivity. A factor that further limits our findings is that reporting in the source studies of whether an immunosuppressant was used was sporadic, with several studies not communicating this information. Treatment with immunosuppressant medication could confound any association between *Toxoplasma gondii*, a variable that should be taken into account when investigating associations between *Toxoplasma gondii* and systemic lupus erythematosus.

Overall, there was little information available about the sex and age composition in the samples used in the source studies. It is possible that sex and age might moderate associations between *Toxoplasma gondii* and systemic lupus erythematosus; both sex and age require additional research to determine how they might affect any associations between *Toxoplasma gondii* and SLE. High heterogeneity among the source studies indicates that other variables for which we were unable to control might affect associations between *Toxoplasma gondii* and SLE as well. As a group, these factors suggest that the association we found between *Toxoplasma gondii* and SLE is best regarded as a hypothesis requiring additional research addressing the limiting factors we describe. Given the severity of SLE and as *Toxoplasma gondii* infects approximately one-third of the world's population [17], it is important to continue to investigate whether *Toxoplasma gondii* is a risk factor for SLE, particularly as infection with *Toxoplasma gondii* is potentially preventable.

5. Conclusions

In conclusion, the results of this meta-analysis of six datasets demonstrated that the odds of *Toxoplasma gondii* seropositivity are 2.34 times higher for those with SLE compared to healthy controls. Numerous limitations in this meta-analysis, however, indicate that its results should be considered hypothesis-generating and that additional research is required to better understand the associations between *Toxoplasma gondii* and SLE.

Authors' contributions statement

Pierce Bassett: Conceptualization, Investigation, Methodology, Writing – Original draft preparation, Writing – Reviewing and Editing Brinley Zabriskie: Formal Analysis, Methodology, Software, Validation, Visualization, Writing – Original draft preparation, Writing – Reviewing and Editing Ashley Catchpole: Validation, Writing – Original draft preparation, Writing – Reviewing and Editing, Visualization Dawson Hedges: Conceptualization, Investigation, Methodology, Project administration, Supervision, Writing – Original draft preparation, Writing – Reviewing and Editing.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtauto.2022.100163.

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