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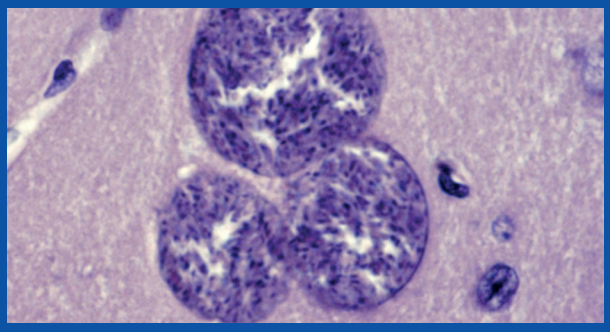


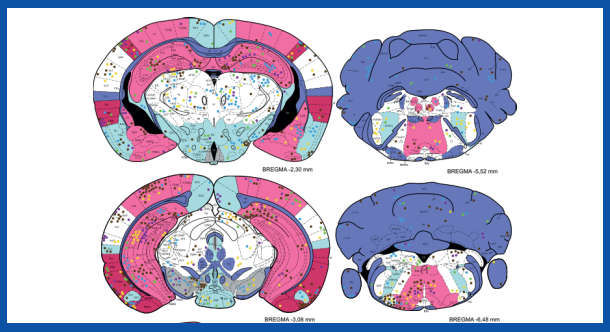

Special Issue

Effects of Latent Toxoplasmosis: Three Decades of Studies

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Special Issue on Toxoplasmosis OPEN ACCESS

Association between type-2 diabetes and *Toxoplasma gondii* seropositivity: a systematic review and meta-analysis

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Abstract: A metabolic disease resulting in elevated blood glucose levels, type-2 diabetes affects approximately 462 million people globally. Although its prevalence appears to be increasing, type-2 diabetes has been associated with various potentially preventable risk factors, including infectious diseases. The protozoal infection with *Toxoplasma gondii* (Nicolle et Manceaux, 1908) has been associated with type-2 diabetes in two previous meta-analyses. Since the publication of the last meta-analysis supporting an association between type-2 diabetes and *T. gondii*, several new primary studies have investigated this association. In this meta-analysis, we sought to further characterise the association between type-2 diabetes and *T. gondii*. We identified primary studies using PubMed, Embase, Scopus and Web of Science. Twenty-five studies met our inclusion criteria for a total of 4,639 patients with type-2 diabetes and 3,492 controls. Eighteen primary studies found a positive association between type-2 diabetes and *T. gondii*, whereas seven did not. Using a frequentist random-effects meta-analysis model, we found an overall summary odds ratio of 2.77 (95-percent confidence interval: 2.03–3.76), suggesting that the odds people will have type-2 diabetes is 2.7 times higher for people seropositive for *T. gondii*. Future studies should investigate this association in additional geographical regions and explore whether this association is due to the immunosuppressive effects of type-2 diabetes or whether *T. gondii* directly or indirectly affects glucose metabolism, or both.

Keywords: diabetes mellitus, insulin-resistant diabetes, toxoplasmosis, protozoal infection, metabolic disorder

This article contains supporting files (Table S1, Fig. S1) online at http://folia.paru.cas.cz/suppl/2025-72-024.pdf

Type-2 diabetes is a metabolic disorder characterised by elevated blood glucose levels. In type-2 diabetes, defective insulin secretion from pancreatic beta cells secondary to stress from obesity and insulin-resistant tissues throughout the body create a harmful negative feedback loop (Galicia-Garcia et al. 2020), eventually disrupting glucose homeostasis and resulting in hyperglycemia. Increased adipose tissue also promotes insulin resistance through free fatty acid release and adipokine deregulation, contributing to the large percentage of obese individuals diagnosed with type-2 diabetes (Galicia-Garcia et al. 2020).

Type-2 diabetes affects approximately 462 million people worldwide, accounting for up to 95 percent of all diabetes cases (Khan et al. 2020). It is associated with numerous adverse outcomes due to a weakened immune system and elevated blood sugar (Berbudi et al. 2020). Type-2 diabetes weakens immunity through decreased cytokine production, phagocytosis mutations, cell dysfunction and impaired ability to eliminate pathogens (Berbudi et al. 2020).

In addition, in response to high blood sugar, harmful dicarbonyls – products of glucose that hinder immune responses – may be released, further weakening the immune system (Kiselar et al. 2015). Bacterial infections, neuropathy and atherosclerosis are common in individuals with type-2 diabetes, as are heart disease, kidney disease and vision loss (Berbudi et al. 2020). Despite genetic contributions (Galaviz et al. 2018), some risk factors of type-2 diabetes are potentially preventable (Pradeepa and Mohan 2017) through physical activity, diet, and maintaining a healthy body weight.

Exposure to infectious diseases including viral infections such as coronavirus, influenza and hepatitis B is also associated with type-2 diabetes (Casqueiro et al. 2012). The adverse effect of hyperglycemia on the immune system could produce this association between type-2 diabetes and infectious diseases through altering the environment of immune-system cells, affecting the inflammatory response, or causing oxidative stress (Chávez-Reyes et

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al. 2021). Consistent with this evidence, some bacterial infections are associated with hypercaloric diets and stressful lifestyles, producing hyperglycemia and increasing the chances of contracting a bacterial infection (Chávez-Reyes et al. 2021). Infectious diseases could also result in type-2 diabetes, possibly via autoimmunity (Prandota 2013).

Among the infectious diseases associated with type-2 diabetes is *Toxoplasma gondii* (Nicolle et Manceaux, 1908) (Özçelik et al. 2020), a neurotropic intracellular protozoan infecting approximately one-third of the global population (Montoya and Liesenfeld 2004). Members of the cat family, including domestic cats, are the definitive hosts of *T. gondii* (Smith et al. 2021), but many animals can be infected. Humans can become infected by ingesting eggs shed from cats, by ingesting contaminated food and water (Montoya and Liesenfeld 2004), or via maternal-foetal transmission (Smith et al. 2021).

In immunocompromised individuals, *T. gondii* infection can cause severe eye, lung and neurological problems (Mariuz et al. 1997, Inceboz and Inceboz 2021, Kalogeropoulos et al. 2022). Once considered benign in immunocompetent humans, accumulating findings demonstrate that *T. gondii* infection can be associated with changes in behaviour and cognitive function (Xiao et al. 2022). Infection with *T. gondii* has also been associated with schizophrenia and cancer (Smith et al. 2021).

Evidence suggests associations between *T. gondii* infection and metabolic disorders (Salem et al. 2021) including type-2 diabetes. In this regard, a previous meta-analysis of four studies found a positive association between *T. gondii* and type-2 diabetes (odds ratio: 2.39, 95-percent CI: 1.2 to 4.75) (Majidiani et al. 2016). More recently, an additional meta-analysis based on ten primary studies again found an association between *T. gondii* and type-2 diabetes diagnosis (odds ratio: 2.32; 95-percent CI: 1.66 to 3.24) (Molan et al. 2020).

Given the increasing prevalence of type-2 diabetes worldwide, its potential for prevention and the high seroprevalence of *T. gondii*, we sought to further characterise the association between *T. gondii* and type-2 diabetes. Since the 2020 meta-analysis of ten studies investigating the association between *T. gondii* infection and type-2 diabetes, several new primary studies evaluating the association between type-2 diabetes and *T. gondii* have been published. Including these additional studies in a meta-analysis would enhance generalisability, increase statistical power and provide more reliable results on which to base future investigation.

MATERIALS AND METHODS

Information source and search strategy

Using the PubMed, Web of Science, Scopus and Embase databases, we searched for published articles regarding the association between type-2 diabetes and *Toxoplasma gondii* infection. We searched for "*Toxoplasma gondii*", "*Toxoplasma*", "*T. gondii*", "toxoplasmosis", "type-2 diabetes", "T2D", "type-2 diabetes mellitus", "type II diabetes", and "insulin resistant diabetes". We also searched the reference lists of included studies to identify other sources. We followed the preferred reporting items for systematic review and meta-analyses (PRISMA) guidelines (Page et al. 2021).

Article selection criteria

In our selection of studies, we included peer-reviewed published studies containing data on the seroprevalence of *T. gondii* infection in type-2 diabetes and control groups. We did not limit our search criteria by year but did restrict language to English. The following databases were used in our search: PubMed, Embase, Web of Science and Scopus. We identified 255 articles from our initial literature searches. During our search, we examined the reference sections of qualifying studies and also received a publication alert; these efforts, identified as 'other' in Fig. 1, resulted in four additional publications for a total of 259 records. After removal of duplicates and initial screening, there were 175 records, and from these, we sought 35 for retrieval and assessed them for eligibility. Twenty-five studies met our inclusion criteria (Fig. 1). In screening reports, we excluded studies that did not differentiate between type-1 and type-2 diabetes or that did not provide relevant data by which to do a meta-analysis. In cases in which we had questions about the reported data, we attempted to contact the corresponding authors of the relevant articles.

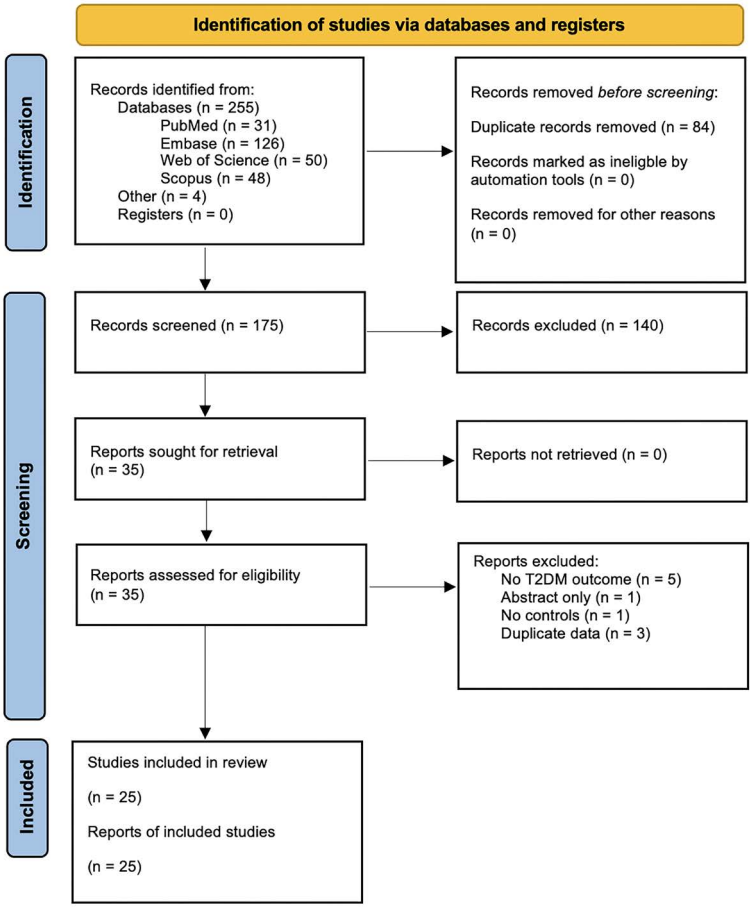

Fig. 1. Study selection process for meta-analysis of *Toxoplasma gondii* and type-2 diabetes.

Data extraction

Two research group members independently extracted data from the primary studies and then met and compared their findings and resolved any discrepancies. We extracted the last name of the first author, publication date, country where the study occurred, mean age of the type-2 diabetes and control groups, percent female of the type-2 diabetes and control groups, number of individuals in the type-2 diabetes and control groups, number of individuals seropositive for *T. gondii* in the type-2 diabetes and control groups, the p-value, and the type of assay used in each study. We also reached out to the corresponding authors of each study after data extraction to fill in any gaps, such as mean age or percent female.

Risk of bias assessment for included studies

To evaluate the quality of the primary studies that met inclusion criteria, we used the Newcastle-Ottawa Scale (NOS), a tool developed to assess the quality of non-randomised studies, including case-control and cohort designs (Wells 2001). In our evaluation, we used only the items applicable to case-control studies. NOS quality scores can range from 0 to 9, with higher scores indicating better study quality. The NOS evaluates the risk of bias across three categories: selection, comparability and exposure. The selection domain assesses how cases and controls were defined and recruited, including their representativeness. Comparability examines whether studies controlled for confounding variables. The exposure domain evaluates non-response rate and ascertainment of exposure. Two research group members independently rated each primary study's quality and then met to resolve any discrepancies and to reach a consensus on the final NOS score for each study.

Data analysis

All analyses were conducted in R (R Core Team 2024) using the metafor package (Viechtbauer 2010). We conducted a meta-analysis and meta-regression of studies that met our predefined eligibility criteria summarising individual study results using odds ratios and their corresponding 95-percent confidence intervals. To pool effect estimates, we used a frequentist random-effects model, with study weights calculated using the inverse-variance method. We explored multiple estimators for the between-study heterogeneity variance, including the DerSimonian-Laird, Paule-Mandel, restricted maximum likelihood, and Sidik-Jonkman estimators. We report results based on the Sidik-Jonkman estimator, which is often more conservative and robust in the presence of heterogeneity.

Pooled confidence intervals were constructed using the Hartung-Knapp-Sidik-Jonkman method, which employs a refined variance estimator and uses the t-distribution as opposed to the standard normal distribution (Hartung and Knapp 2001a,b, Sidik and Jonkman 2002). Based on previous results from Molan et al. (2020), we planned to use a random-effects model from the outset, though, given the newly included studies, we also formally assessed heterogeneity using Cochran's Q test and the I^2 statistic.

Publication bias was assessed visually with a contour-enhanced funnel plot (Peters et al. 2008), which displays areas of statistical significance on a funnel plot. This plot more directly assesses publication bias, as publication bias is not the only possible cause of asymmetry in a traditional funnel plot. In a contour-enhanced funnel plot, if studies appear missing in non-significant areas, this suggests asymmetry due to publication bias based on statistical significance. Conversely, if studies appear missing in significant areas, this implies asymmetry due to other factors. We also used Begg's rank correlation test (Begg and Mazumdar 1994) and Peter's test (Peters et al. 2006) of funnel plot asymmetry.

To examine potential sources of heterogeneity, we evaluated three potential moderators for inclusion in univariate meta-regression analyses: assay type, study region and risk of bias score. The first two were pre-specified. The type of assay used to detect *Toxoplasma gondii* seropositivity distinguished between studies using ELISA (n = 23) and those using other methods (n = 2, including enzyme immunoassay kits, Roche Elecsys Toxo IgG assay kits, or chemiluminescence immunoassay). Due to the limited number of non-ELISA studies, however, there was insufficient variation to support a stable meta-regression analysis for this moderator.

To avoid generating unstable or potentially misleading estimates, assay type was excluded from further analysis. The region variable categorised studies by geographical location: Middle East (15 studies conducted in Iraq, Iran, Saudi Arabia and Turkey), North Africa (6 studies from Egypt and Libya), and 'Other' (4 studies from Bangladesh, Mexico, Australia and China). The third moderator, risk of bias score, was evaluated in a *post hoc* analysis to explore whether study quality was associated with variation in effect size.

Because only one of the meta-regression analyses was pre-specified, no correction for multiple comparisons was applied. The risk of bias analysis was exploratory and is interpreted accordingly. For all meta-regression models, we used the Hartung-Knapp-Sidik-Jonkman method and conducted approximate permutation tests with 20,000 random permutations to obtain p-values less dependent on asymptotic assumptions. Residual plots, influence diagnostics and other model diagnostics were examined to assess model assumptions. Mild deviations from normality were observed, which, along with the small number of included studies, reinforced the decision to use the Hartung-Knapp-Sidik-Jonkman method and permutation-based inference to support more robust and cautiously interpreted results.

For the *post hoc* risk of bias analysis, we created a bubble plot displaying study-level log odds ratios against risk of bias scores. Circle sizes were proportional to inverse-variance weights, and a fitted regression line with 95-percent confidence interval bounds was overlaid to summarise the relationship between risk of bias and effect size.

Lastly, we conducted sensitivity analyses by excluding studies rated as high risk of bias, which we predefined as those with Newcastle-Ottawa Scale scores below 5. We re-estimated both the main random-effects meta-analysis and the pre-specified meta-regression using this reduced dataset to assess the robustness of our findings.

RESULTS

Source studies

Twenty-five studies met inclusion criteria (Fig. 1) and we evaluated publication bias (Fig. 2). Included studies are listed in Fig. 3 and appear in the Reference section. Across the 25 included studies, there were 4,639 participants with

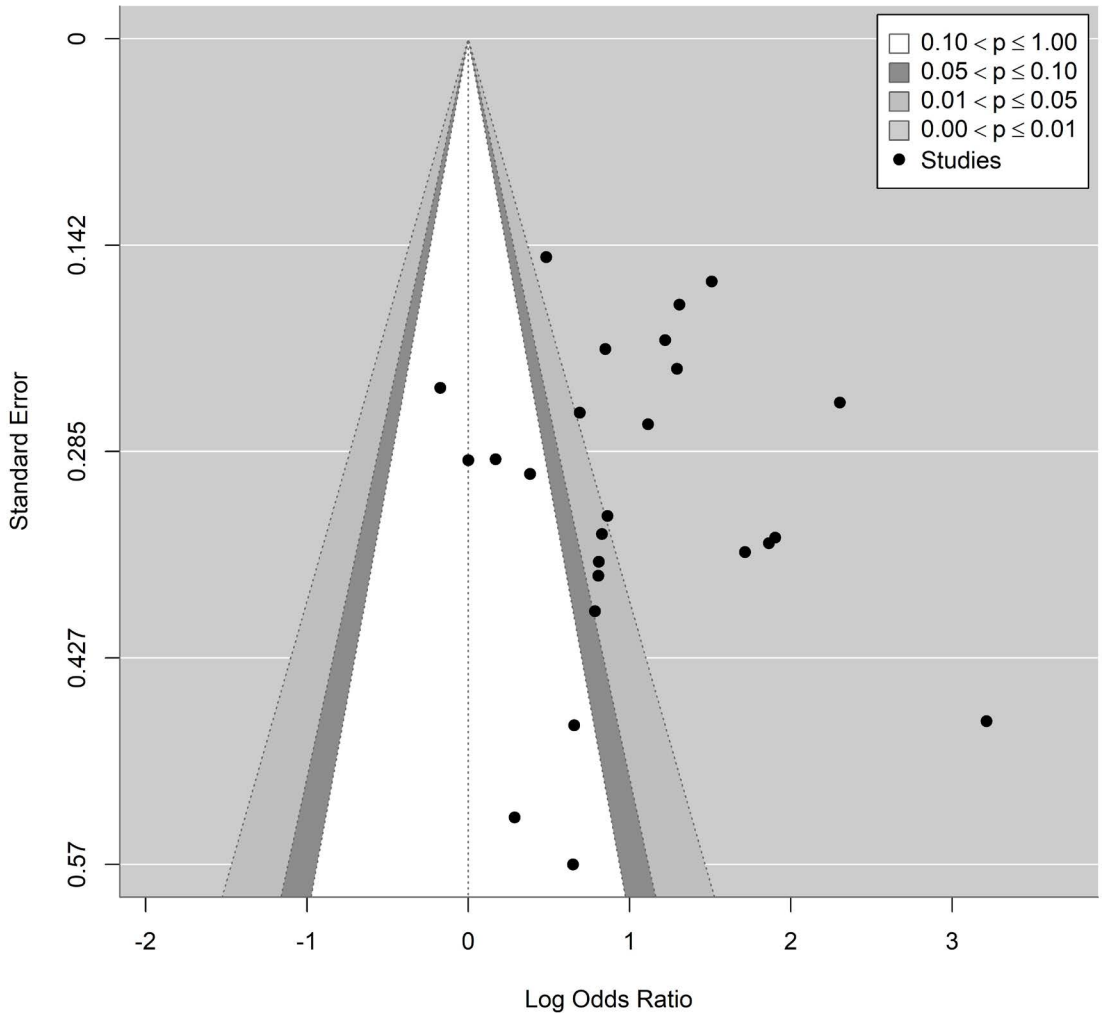

Fig. 2. Contour-enhanced funnel plot assessing potential publication bias across studies examining the association between *Toxoplasma gondii* seropositivity and type 2 diabetes. Each point represents an individual study plotted by its log odds ratio (x-axis) and standard error (y-axis). The shaded regions correspond to different levels of statistical significance.

type-2 diabetes and 3,492 participants in the control group. The median percentage of *Toxoplasma gondii* seropositivity was 56 percent (range 6–91%) in the type-2 diabetes group compared to 32 percent (range 3–66%) in the control group. Eighteen of the 25 studies suggest a positive association between type-2 diabetes and *T. gondii* infection, while the other seven found no significant difference between the groups (Fig. 3). The average age and percentage of females were not uniformly reported across the 25 studies. Six studies were done in North Africa, 15 in the Middle East and 4 in other regions (Australia, Bangladesh, China, Mexico) (Fig. 4).

Risk of bias

The median Newcastle-Ottawa score assessing the risk of bias is 5/9 (range 3/9 to 8/9), with several studies having low-quality scores. Figure 2 depicts a contour-enhanced funnel plot to help assess publication bias. This plot shows clear asymmetry, with a relative absence of studies on the left side of the funnel, including in areas corresponding to very small p-values, suggesting possible publication bias or selective non-reporting of studies with negative or null associations between *T. gondii* seropositivity and type-2 diabetes. However, formal statistical tests did not detect evidence of funnel plot asymmetry: Begg's rank correlation test ($p = 0.76$) and Peter's regression test ($p = 0.65$) were both non-significant. As with other methods for detecting publication bias, these results may be influenced by sampling variability or by the substantial heterogeneity observed across studies, discussed further in the next sections. High between-study heterogeneity can distort funnel plot symmetry and complicate the interpretation of both visual and statistical assessments of bias (Ioannidis and Trikalinos 2007). As such, the evidence for publication bias should be interpreted cautiously.

Meta-analysis and sensitivity analysis

Across the heterogeneity variance estimators considered, estimates ranged from 0.37 to 0.47, and the I^2 statistic ranged from 83.7 percent to 86.5 percent, indicating substantial heterogeneity. Cochran's Q test also suggests substantial heterogeneity across all estimators (p-values < 0.001).

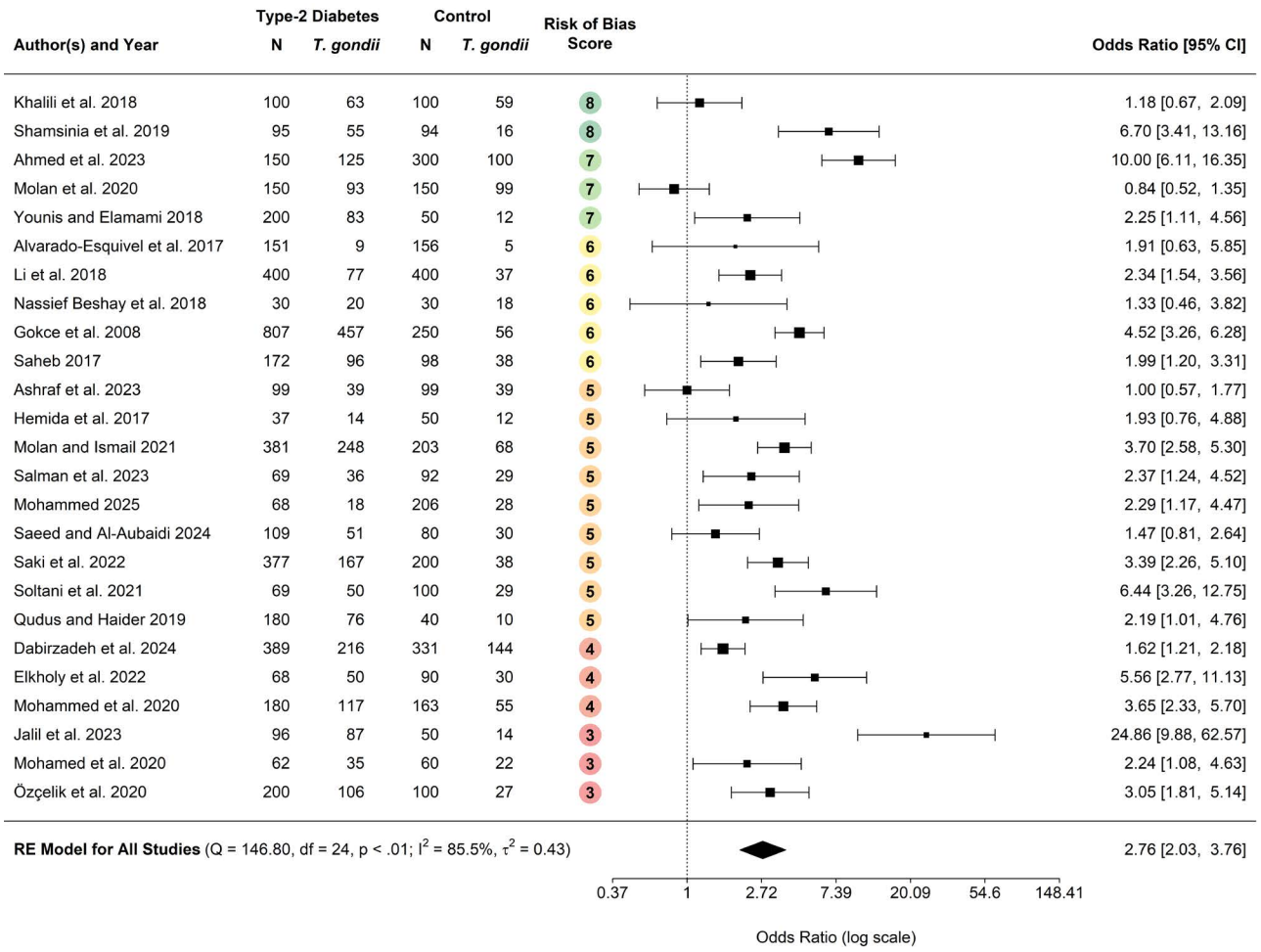

Fig. 3. Forest plot of all included studies assessing the association between *Toxoplasma gondii* seropositivity and type-2 diabetes, with corresponding Newcastle-Ottawa Scale risk of bias scores. Scores are colour-coded by level of bias, with darker red indicating higher risk and darker green indicating lower risk. The pooled estimate from the random-effects meta-analysis is shown at the bottom. Odds ratios greater than 1 suggest higher odds of *Toxoplasma gondii* seropositivity among individuals with type-2 diabetes compared to controls. *Abbreviation*: CI – confidence interval; RE – random-effects

Figure 3 shows results from the random-effects meta-analysis model using all 25 included studies. The pooled odds ratio was 2.77 (95 percent CI: 2.03–3.76, permutation p-value < 0.001), suggesting that individuals with type-2 diabetes had between 2.03- and 3.76-times greater odds of *T. gondii* seropositivity compared to controls, with 95 percent confidence.

A sensitivity analysis excluding six studies with high risk of bias (Newcastle-Ottawa Scale scores < 5) did not materially change the conclusions. The pooled odds ratio was slightly reduced to 2.49 (95 percent CI: 1.80–3.44, permutation p-value < 0.001), and heterogeneity decreased modestly (variance estimates: 0.35 to 0.38, I^2: 82.0 83.1%, Cochran's Q test p-value < 0.001).

Meta-regression: region

To explore whether study region explained some of the observed heterogeneity, a meta-regression was conducted using geographic region as a categorical moderator (Fig. 4). Region accounted for approximately 10% of the heterogeneity, and the overall model F-test suggests no significant difference in effect sizes based on region (permutation p-value = 0.10). However, one contrast suggested a potential association: studies from the 'Other' region category (Bangladesh, Mexico, Australia and China) showed a lower pooled effect compared to those from the Middle East (odds ratio: 0.43, 95 percent CI: 0.19–0.99, permutation p-value: 0.04). This finding should be interpreted cautiously given the non-significant omnibus test and the small number of studies in the 'Other' category (n = 4).

In a sensitivity analysis excluding high-risk-of-bias studies, the pattern remained similar but less pronounced. Region explained roughly 13% of heterogeneity, with a model F-test permutation p-value of 0.14. The comparison between 'Other' and 'Middle East' regions yielded an odds ratio of 0.47 (95 percent CI: 0.22–1.03, permutation p-value: 0.06).

Further sensitivity analysis, excluding an influential study (Ahmed et al. 2023) from North Africa, increased the heterogeneity explained to 21% and reduced the model F-test permutation p-value to 0.08. Under this model, the odds ratio comparing 'Other' to 'Middle East' was 0.38 (95 percent CI: 0.16–0.92, permutation p-value: 0.03).

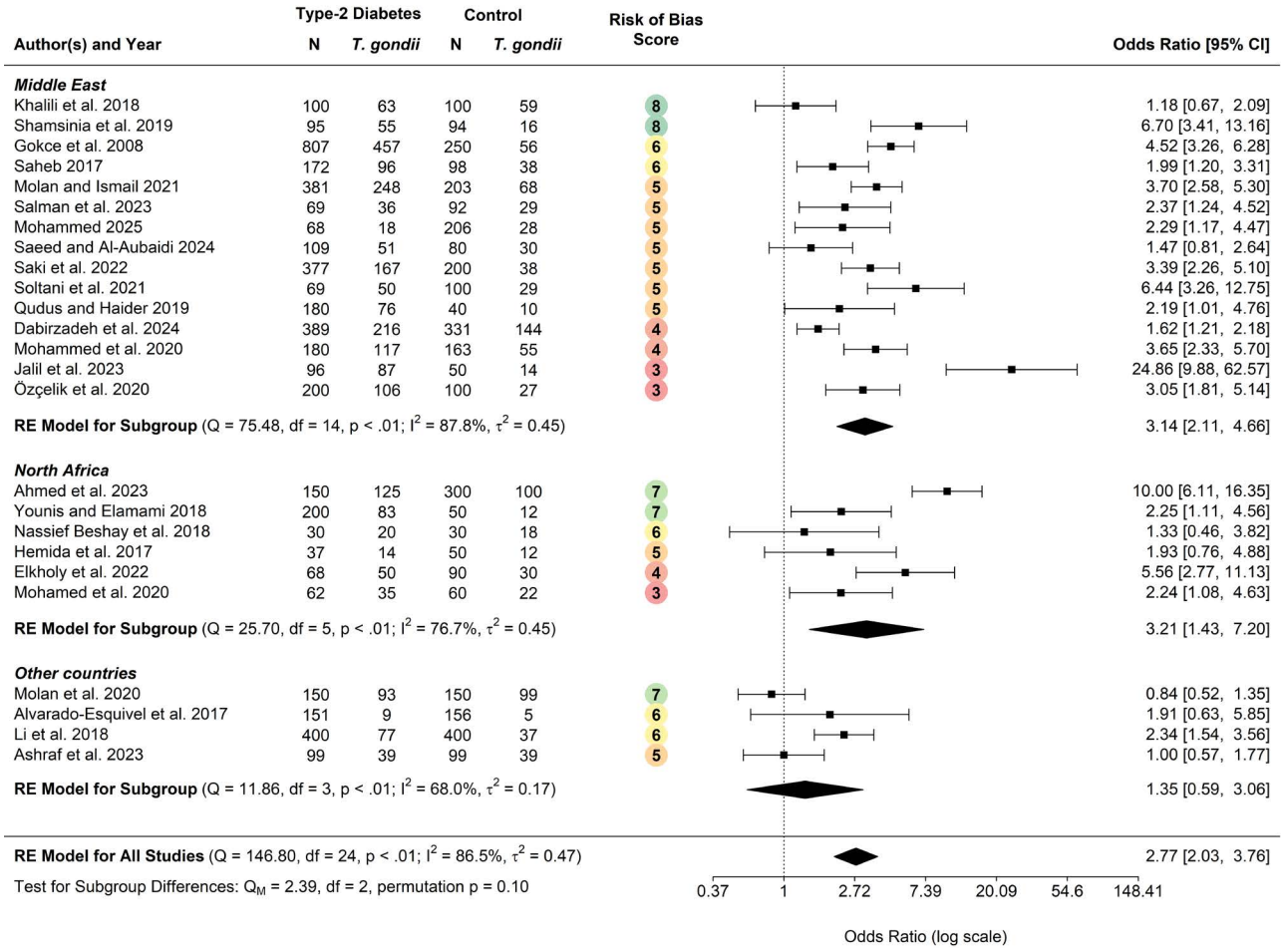

Fig. 4. Forest plot displaying a subgroup analysis by geographic region where each study was conducted. Studies are grouped and presented in the following order: 'Middle East,' 'North Africa,' and 'Other.' Newcastle-Ottawa Scale risk of bias scores are shown alongside each study and are colour-coded by bias level, with darker red indicating higher risk and darker green indicating lower risk. The lower section of the plot shows the overall pooled estimate across all studies (irrespective of region), followed by results from a meta-regression testing for subgroup differences across regions. *Abbreviation*: CI – confidence interval; RE – random-effects.

Meta-regression: risk of bias score

A separate meta-regression using Newcastle-Ottawa Scale risk of bias scores as a continuous moderator found no evidence that study quality was associated with effect size (odds ratio: 0.90, 95 percent CI: 0.72–1.13, permutation p-value of 0.35). This model accounted for none of the observed heterogeneity (0 percent). Results are visualised in Suppl. Fig. S1 and summarised alongside the other meta-regression models in Suppl. Table S1.

DISCUSSION

In this meta-analysis of 25 primary studies with 4,639 patients with type-2 diabetes and 3,492 controls, type-2 diabetes was associated with *Toxoplasma gondii* seropositivity with an odds ratio of 2.77 (95-percent confidence interval: 2.03–3.76), indicating that the odds of *T. gondii* seropositivity are 2.77 times higher for those with type-2 diabetes than in controls. This finding is consistent with the two previous meta-analyses investigating the association between type-2 diabetes and *T. gondii* seropositivity. The first meta-analysis examining this association (Majidiani et al. 2016), based on four primary studies, found an odds ratio of 2.39, and the second (Molan et al. 2020), based on 10 primary studies, found an odds ratio of 2.32.

We found substantial heterogeneity in the overall meta-analysis. To explore potential sources of this heterogeneity, we conducted univariate meta-regressions examining study region and risk of bias score as potential moderators. Although assay type was initially pre-specified as a moderator, it was excluded from analysis due to insufficient variation (only two studies used non-ELISA methods). Across models, we found limited evidence that either region or risk of bias score explained a meaningful proportion of the between-study heterogeneity or materially influenced the pooled log odds ratio. While one comparison in the region model suggested a possible difference between studies conducted in the 'Other' region group and those in the Middle East, the global test for moderator effect was not statistically significant. Overall, the heterogeneity remained largely unexplained by the examined study-level characteristics.

Other variables such as participant sex, age, socioeconomic level, geographic regions, exposure to other infectious diseases, and measures of health including body-mass index could explain this heterogeneity, but we were

unable to include these in our meta-regressions. However, variations in study designs, geographical regions, socioeconomic level, prevalences and strains of *T. gondii*, and prevalence of type-2 diabetes among the primary studies of this meta-analysis could affect the reliability of our point estimate and limit the generalisation of these findings in other populations.

While we found an association between type-2 diabetes and *T. gondii* seropositivity, our meta-analysis was not designed to determine whether type-2 diabetes is a risk factor for subsequent *T. gondii* seropositivity or whether *T. gondii* seropositivity is a risk factor for type-2 diabetes. As such, we were unable to determine causality for the association between *T. gondii* and type-2 diabetes. While more research is needed to elucidate the physiological relationship between type-2 diabetes and *T. gondii* seropositivity, various possible mechanisms either alone or in combination could explain this association. *Toxoplasma gondii* infection could increase susceptibility to type-2 diabetes diagnosis through reduction of beta-cell mass (Molan et al. 2020), pancreatic tissue necrosis (Oz 2014), or pancreatitis (Ahuja et al. 1993). Insulin synthesis and release would be disrupted by the death or inflammation of beta cells in the pancreas, increasing the risk of type-2 diabetes.

Toxoplasma gondii infection could also increase cells' resistance to insulin through increasing levels of inflammatory cytokines (Park et al. 2019), as inflammation has been associated with insulin resistance (Chen et al. 2015). Alternatively, decreased immune system function commonly seen in diabetes could increase susceptibility to *T. gondii* infection (Casqueiro et al. 2012). Insulin has also demonstrated a stimulatory effect on the replicative abilities of *T. gondii* (Oz 2014), providing a potential explanation for the association between the two. Additional research is necessary to better understand the aetiology of the possible association between type-2 diabetes and *T. gondii* seropositivity.

Although our meta-analysis included 25 studies – more than previous reviews – this number remains modest given the global prevalence of both *T. gondii* seropositivity and type-2 diabetes. Moreover, the evidence base is regionally concentrated, with nearly all studies conducted in the Middle East or North Africa, and none from South America, North America or Europe. This limits the generalisability of our findings and highlights the need for additional research across more diverse geographic settings to better understand the potential association. Additionally, the limited and inconsistent reporting of demographic and clinical variables across studies prevented us from examining other potential effect modifiers. As a result, we were unable to assess whether the observed association varies across important subgroups, and as such the potential for residual confounding remains. Results from future studies including any from additional regions could alter our findings.

In conclusion, in this meta-analysis of 25 primary studies with 4,639 patients with type-2 diabetes and 3,492 healthy controls, type-2 diabetes was associated with *T. gondii* seropositivity with an odds ratio of 2.77 (95-percent confidence interval: 2.03–3.76). While these findings suggest a possible association between type-2 diabetes and *T. gondii* seropositivity, additional research including using samples from other world regions and including additional demographic and medical variables that could modify the association between type-2 diabetes and *T. gondii* is required to better understand this association. Additional work investigating potential mechanisms underlying associations between *T. gondii* and type-2 diabetes is also needed.

Author contributions statement. Conceptualisation: D.W.H.; methodology: A.C., B.N.Z., and D.H.; statistical analysis: B.N.Z.; data curation: A.C., B.E., H.K., R.C., G.T., and C.H; writing – original draft preparation: A.C., B.N.Z., B.E., H.K., R.C., G.T., C.H., D.W.H.; writing – review and editing: A.C., C.H., S.D.G., B.N.Z., D.W.H. All authors have read and agreed to the published version of the manuscript.

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