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Association of *Strongyloides stercoralis* infection with the development of diabetes mellitus: a meta-analysis

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Research Paper

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Abstract

Previous studies have shown that helminth infection protects against the development of diabetes mellitus (DM), possibly related to the hygiene hypothesis. However, studies involving *Stronglyoides stercoralis* and its possible association with DM are scarce and have shown contradicting results, prompting us to perform this meta-analysis to obtain more precise estimates. Related studies were searched from PubMed, Google Scholar, Science Direct, and Cochrane Library until 1 August 2024. Data on the occurrence of DM in patients positive and negative for *S. stercoralis* were obtained. All analyses were done using Review Manager 5.4. The initial search yielded a total of 1725 studies, and after thorough screening and exclusion, only five articles involving 2106 participants (536 cases and 1570 controls) were included in the meta-analysis. Heterogeneity was assessed, and outlier studies were excluded using a funnel plot. Results showed a significant association of *S. stercoralis* infection with DM, suggesting that those with the infection are less likely to develop DM. Overall, the results suggest that *S. stercoralis* infection may decrease the likelihood of developing DM, potentially supporting the hygiene hypothesis.

Introduction

Intestinal parasitic infections continue to pose a significant public health challenge, particularly in regions lacking adequate sanitation. With an estimated 3.5 billion people globally affected by various parasitic infections, the resulting diseases impact approximately 450 million individuals annually (Fauziah *et al.* 2022). Recent research has uncovered complex interactions between infectious diseases and chronic conditions, notably in the context of helminth infections and their potential link to the development of diabetes mellitus (DM), which is probably related to the hygiene hypothesis formulated by David Strachan in 1989. The association between *Strongyloides stercoralis* (*S. stercoralis*) infection and DM has garnered significant interest (Htun *et al.* 2018; Yingklang *et al.* 2022).

As noted in the study by Amer *et al.* (2023), various host factors, including genetic predisposition, immunological responses, and metabolic changes, can significantly influence host–parasite interactions. These factors may disrupt critical parasite functions such as oviposition, worm development, and the pathophysiology of the resulting infection. However, it is important to note that this study used mice as the experimental model (Amer *et al.* 2023). Recent studies show that helminth infection, such as that caused by *Strongyloides stercoralis*, might have a protective effect against the development of DM, probably concerning the hygiene hypothesis. People are assumed to become more susceptible to autoimmune and metabolic diseases in an advanced environment with less exposure to germs (Santiago and Nutman 2016). While some pathophysiological mechanisms suggest that helminth infections may increase insulin sensitivity, the study by Salvador *et al.* (2023) found no association between *S. stercoralis* infection and type 2 DM or other metabolic diseases (Salvador *et al.* 2023). The association of *S. stercoralis* infection with DM has remained poorly explored and quite conflicting; hence, further clinical studies are needed to better understand the potential interaction between these diseases.

The current paper presents a meta-analysis of previous studies to shed light on the association between *S. stercoralis* infection and the risk of developing DM. Results are expected to contribute to a general understanding of how parasitic infections may affect DM epidemiology and guide future research on areas where both DM and helminth infection prevalence is high.

Materials and Methods

Target population, controls, and outcomes of the study

Patients diagnosed with *S. stercoralis* infections were grouped as the case population, and those without any sign of the parasitic infection or those who were generally healthy were tagged as controls. Intervention or exposure was not applied in this study. The outcome of interest in this meta-analysis is the susceptibility to develop DM.

Literature search strategy

PROSPERO, Cochrane Library, and PubMed were initially searched to determine if an ongoing or published meta-analysis was done on the topic. After verifying the non-existence of a meta-analysis on the topic, a thorough search was done using PubMed, ScienceDirect, Google Scholar (title search only), and Web of Science. The search concluded on August 1, 2024. In doing the full search, a combination of the following key search terms was used: "*Strongyloides*" OR "*Strongyloides stercoralis*" OR "*S. stercoralis*" OR "helminths" AND "diabetes" OR "T2D". All resulting studies from the various database sites were collated, sorted, and cleaned to remove duplicate studies. After removing duplicate studies, the screening was done by initially checking the title and abstract for relevance, namely if they were conducted among humans, involved patients infected with *S. stercoralis*, and patients diagnosed with DM. Full papers of those who passed the initial screening were retrieved and reviewed. Full papers were only included if they contained the number of patients with and without *S. stercoralis* infection who developed or did not develop DM. No restrictions on the year and type of publication were set. Papers such as letters to editors, clinical trials, and brief/short communications were included as long as relevant data could be extracted. Two authors (R.E.T. and M.J.D.) screened the included studies.

Data extraction and computation

The same authors (R.E.T. and M.J.D.) who screened the included studies also extracted the needed data. A third author (E.J.C.) further verified the accuracy of the collated data. A customized spreadsheet was created as the primary data abstraction tool. For each included study, the following data were collected: (1) first author's last name; (2) year of publication; (3) geographic location where the study was conducted; (4) method of identifying *S. stercoralis* infection; (5) method of identifying DM; (6) number of cases and controls; and (8) number of patients who developed and did not develop DM per case and control group.

Assessment of study quality

The Newcastle-Ottawa Scale assessment tool was used to check for the quality of the eligible studies. Studies were judged based on selection, comparability, and exposure. The rating system has scores ranging from 0 to 9 points. Studies scoring 5–6 and ≥7 points were considered moderate and high-quality, respectively.

Meta-analysis protocol

Review Manager 5.4. was used (Copenhagen: Nordic Cochrane Centre, Cochrane Collaboration, 2014) to compute the odds ratio (OR) and 95% confidence interval (CI). The data encoded in the software followed the following format:

With *S. stercoralis* infection (case group)		Without *S. stercoralis* infection (control group)	
Number of patients that developed DM	Total number of participants (with DM + controls)	Number of patients that developed DM	Total number of participants (with DM + controls)

Heterogeneity was assessed using the chi-square-based Q test and I^2 statistics. Both random-effects (significant heterogeneity) and fixed-effects (non-significant heterogeneity) models were used in the study (DerSimonian and Laird 1986; Mantel and Haenszel 1959). *P* values are significant if they are less than .05 for association testing and less than .10 for heterogeneity testing (DerSimonian and Laird 1986; Higgins 2003; Higgins and Thompson 2002). Publication bias testing was no longer performed due to the limited studies included (Dalton *et al.* 2016; Ioannidis 2008).

Results

The summary of the literature search is highlighted in Figure 1. The full search yielded a total of 1725 studies. After removing duplicates and thorough screening, only five studies consisting of 2106 participants (536 cases and 1570 controls) were included in the meta-analysis. The characteristics of the included studies are summarised in Table 1. Most of the studies (Hays *et al.* 2016; McGuire *et al.* 2019; Salvador *et al.* 2023; Talukder *et al.* 2022) were done in non-Asian countries and identified *S. stercoralis* infection using an enzyme-linked immunoassay serology. The study by Yingklang *et al.* (2022) used conventional methods such as the modified agar plate culture and the formalin-ethyl acetate concentration technique to identify *S. stercoralis* infection (Yingklang *et al.* 2022). As assessed using the Newcastle-Ottawa Scale, the overall quality of the included studies is 6.00 (±1.22) with a median of 6.00.

The overall analysis (Figure 2) showed non-significant ($P = .75$) but highly heterogeneous ($I^2 = 95\%$, $P < .00001$), which warranted us to determine the cause using a Funnel plot (Figure 3). The funnel plot identified two outlier studies, namely the studies of Hays *et al.* (2016) and McGuire *et al.* (2019). Subsequent analysis was done where the outlier studies were removed. Based on the results of the post-outlier analysis (Figure 4), a significant ($P = .02$) and homogenous ($I^2 = 0\%$, $P = .55$) outcome was achieved.

Discussion

Summary and interpretation of findings

The post-outlier analysis summarizes the results of three studies involving 1418 participants, including 349 cases and 1069 controls. Initially, five studies were considered for inclusion. By pooling the ORs and 95% CIs from the individual articles, we demonstrated that individuals with *S. stercoralis* infection are less likely to develop DM. Overall, the likelihood of developing DM was diminished among individuals infected with *S. stercoralis* (OR: 0.71; 95% CI, 0.53–0.94). Furthermore, the results were homogeneous ($I^2 = 0\%$) and significant ($P = .02$) after excluding two outlier studies, reinforcing the association between *S. stercoralis* infection and a reduced likelihood of developing DM.

The significant findings provide strong evidence for the possible association between *S. stercoralis* infection and DM. This association

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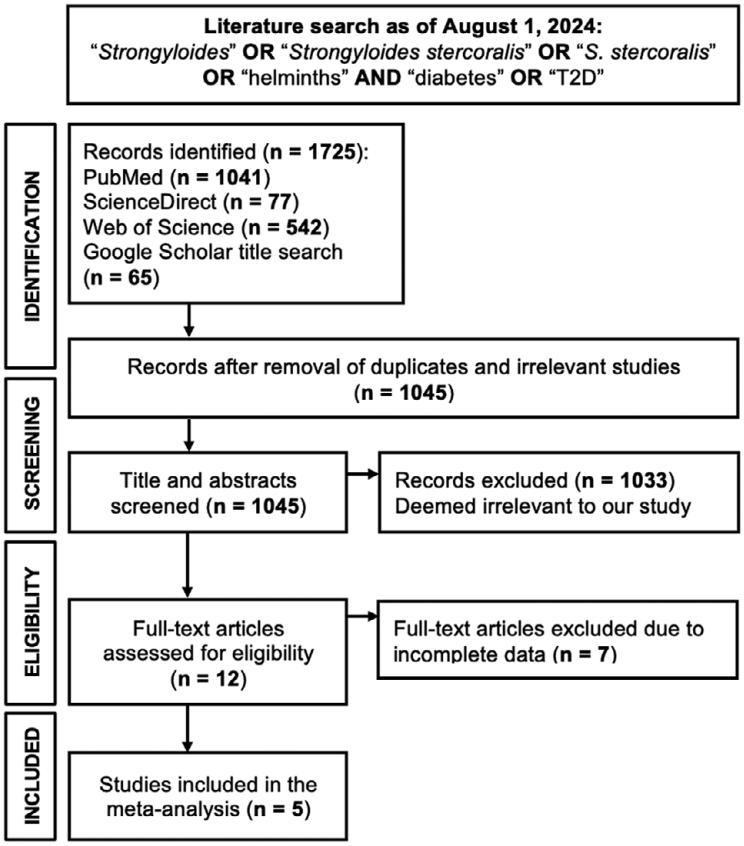

Figure 1. Summary of the literature search.

Table 1. Characteristics of the included studies

Author	Year	Geography	Identification of *S. stercoralis* infection	Identification of DM	No. of participants with *S. Stercoralis* infection	No. of participants without *S. Stercoralis* infection	Total number of participants	NOS score
Hays	2016	Australia	Serology using ELISA	Medical records review	87	152	239	**7**
McGuire	2019	London	Serology using ELISA	Having had a glycated haemoglobin A1c (HbA1c) reading ≥6.5%, or a random blood glucose >11.1 mmol/litre, or a fasting blood glucose of >7.0 mmol/litre in the past, or by being on treatment for diabetes	100	349	449	**6**
Salvador	2023	Spain	Serology using ELISA	Medical records review	95	83	178	**6**
Talukder	2022	Australia	Serology using ELISA	Medical records review or prescribed with diabetes medication	147	389	536	**4**
Yingklang	2022	Thailand	Modified agar plate culture: mAPC, and the formalin-ethyl acetate concentration technique: FECT	Fasting plasma glucose (FPG) and/or glycated hemoglobin (HbA1c) levels	107	597	704	**7**

DM: diabetes mellitus; ELISA: enzyme-linked immunoassay; NOS: Newcastle-Ottawa scale.

is supported by the homogeneity of the post-outlier results, indicating the combinability of the individual studies. Moreover, the high degree of statistical significance, the consistent precision of effects, and the robustness of the post-outlier outcomes enhance the evidence presented in this meta-analysis.

Comparison with other studies

This meta-analysis' findings align with previous studies' results (Salvador *et al.* 2023; Talukder *et al.* 2022; Yingklang *et al.* 2022). According to Yingklang *et al.* (2022), there is an inverse

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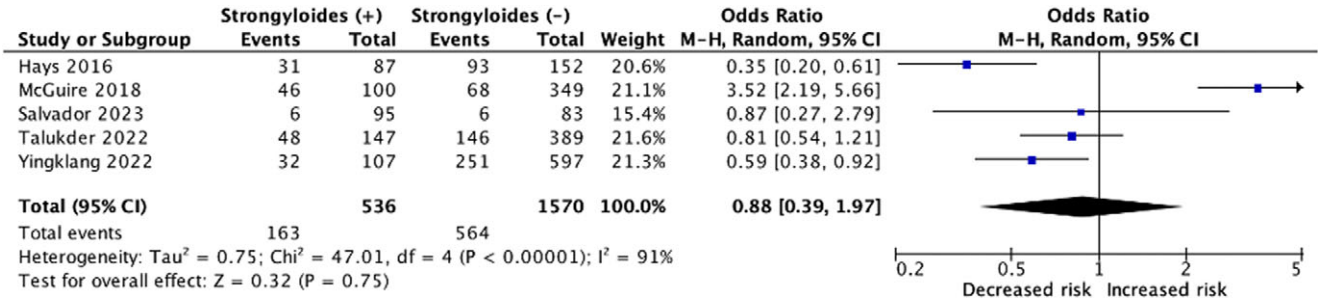

Figure 2. Forest plot analysis on the association of *S. stercoralis* infection with diabetes mellitus development.

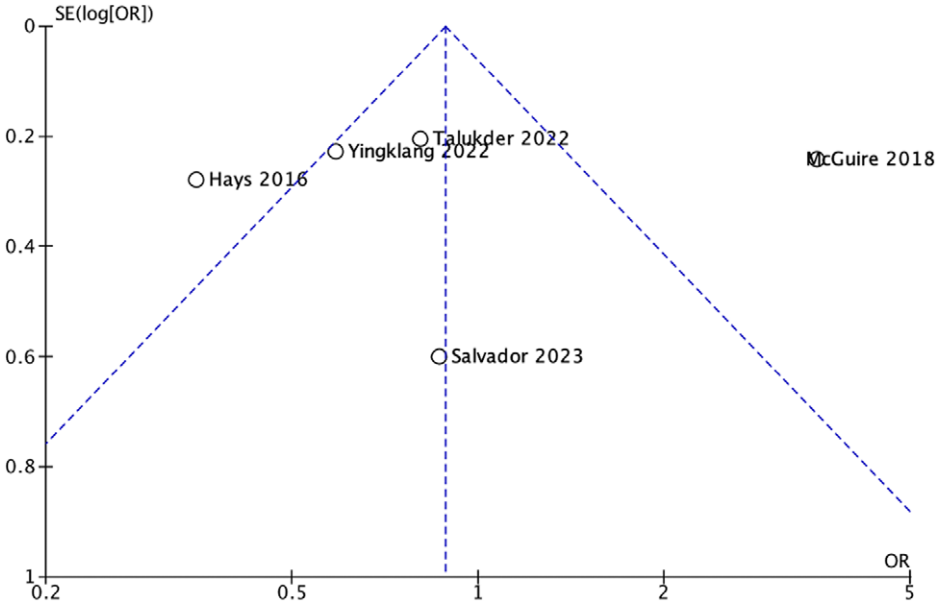

Figure 3. Funnel plot analysis for the identification of outlier studies.

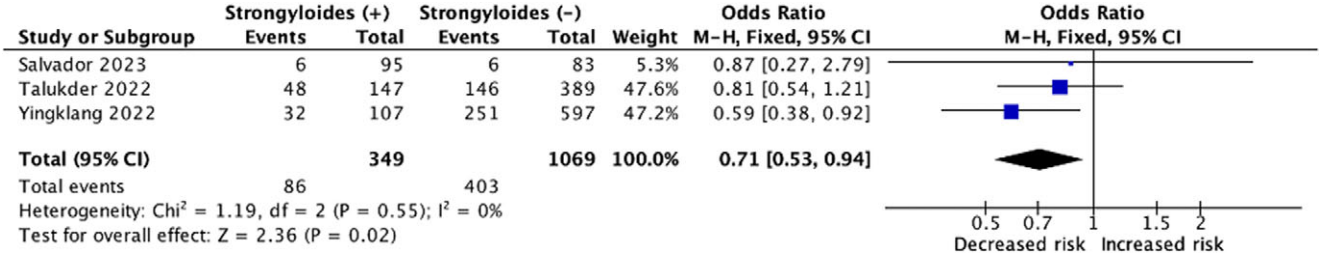

Figure 4. Forest plot analysis on the association of *S. stercoralis* infection with diabetes mellitus development after removal of the outlier studies.

relationship between *S. stercoralis* infection and type 2 DM. However, individuals with this infection exhibit a low estimated glomerular filtration rate, higher alanine aminotransferase levels, and an increased urine albumin-creatinine ratio. This relationship is attributed to nutrition, gut homeostasis, and the immunoregulatory response during parasitic infection. Moreover, Yingklang *et al.* (2022) suggested that helminth infection can alter intestinal microbial diversity and physiological processes at the cellular level, leading to increased insulin sensitivity.

Similarly, Talukder *et al.* (2022) reported that changes in the gut microbiome due to *S. stercoralis* and other helminths reduce the risk of developing DM by regulating glucose uptake, inflammation, and insulin sensitivity. They also noted that the reductions in insulin and glucagon levels associated with *S. stercoralis* infection were reversed during anti-helminthic therapy, which increases the likelihood of developing DM. Additionally, Salvador *et al.* (2023) confirmed that pathophysiological mechanisms reinforce the concept that helminth infections may enhance insulin sensitivity and promote the production of anti-inflammatory cytokines.

Protective role of Strongyloidiasis against DM

An inverse relationship between allergic diseases and bacterial infections was proposed during early childhood, aligning with the

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hygiene hypothesis (Rajamanickam *et al.* 2019). Over time, this hypothesis was expanded to encompass helminthic infections, as immunomodulation observed during chronic helminthic infections protects against allergic and autoimmune diseases (Pineda and Ramos 2012a, 2012b). As studied by other researchers, this association has expanded to include metabolic diseases such as DM. The incidence of type 2 DM and the mechanisms involved in its development show an inverse relationship with the prevalence of helminthic infections, particularly those caused by *S. stercoralis*. This suggests that helminths may be protective against type 2 DM, as supported by the hygiene hypothesis (Talukder *et al.* 2022; Yingklang *et al.* 2022). Several factors and pathophysiological changes influence the protective mechanism of *S. stercoralis* infection against DM (Rajamanickam *et al.* 2019). Other factors that may explain the protective mechanism of strongyloidiasis against DM are explained below.

Alteration of gut microbiota

The gut microbiota comprises various microbial communities that inhabit the gastrointestinal tract (Nguyen *et al.* 2022). These microorganisms exert beneficial and harmful effects on the human host. However, they predominantly confer benefits, including protection against infections, the development of immunity, the absorption of nutrients, and the synthesis of vitamins (D'Argenio and Salvatore 2015).

In line with this, *Strongyloides* spp., which inhabit the gastrointestinal tract, interact with the host's gut microbiota, leading to substantial changes in its composition. Notably, *Strongyloides* spp. increase the abundance of certain microorganisms, including *Lactobacillus* spp., *Blautia*, and the *Ruminococcus torques* group (Pace *et al.* 2018; Tran *et al.* 2023). These microbes are known for their ability to produce short-chain fatty acids (SCFAs), with acetic acid, propionic acid, and butyric acid being the principal SCFAs. Remarkably, the presence of SCFAs in the bloodstream influences glucose storage in the muscle, liver, and fat by stimulating the secretion of glucagon-like peptide-1, which indirectly increases insulin secretion and decreases pancreatic glucagon secretion (He *et al.* 2020; Kim 2018). This process helps regulate blood glucose levels and may contribute to a reduction in the risk of type 2 DM. Additionally, high levels of these metabolites enhance energy harvest capacity, promote an anti-inflammatory status, and increase satiety, leading to better overall health (Nguyen *et al.* 2022).

The alteration of the gut microbiome favors the production of beneficial metabolites such as SCFAs, suggesting that *Strongyloides* spp. may contribute to improved glucose regulation and a reduced risk of type 2 DM. This highlights the potential of *Strongyloides* infection to induce protective mechanisms, aiding in managing type 2 DM.

Immunomodulation

Strongyloidiasis significantly impacts the immunomodulation of glycemic, hormonal, and cytokine parameters, potentially leading to reduced blood glucose levels in the body (Talukder *et al.* 2022). Type 2 DM is a chronic low-grade inflammatory disease characterized by elevated levels of pro-inflammatory cytokines and chemokines, contributing to increased insulin resistance (He *et al.* 2022; Salvador *et al.* 2023). Reduced levels of pro-inflammatory cytokines have been shown to improve the management of type 2 DM (Velikova *et al.* 2021).

Individuals with *Strongyloides* infection have been shown to have significantly reduced circulating levels of pro-inflammatory cytokines and increased levels of Th2-associated and regulatory cytokines (Anuradha *et al.* 2016). Pro-inflammatory cytokines, such as Th1 cytokines (interferon-γ, tumour necrosis factor-α, and interleukin [IL]-2), Th17 cytokines (IL-17A, IL-17F, IL-22, and IL-23), and other pro-inflammatory cytokines (IL-1β and IL-1), are known to induce harmful host inflammation and contribute to the development of inflammatory disorders. During *Strongyloides* infection, the levels of these pro-inflammatory cytokines decrease, providing evidence that strongyloidiasis may help control harmful inflammation. Further studies revealed that Th1 and Th17 cytokines were significantly lower in type 2 DM patients infected with *Strongyloides*, which tends to improve insulin sensitivity and barrier function (Rajamanickam *et al.* 2019). On the other hand, helminthic infections stimulate the production of Th2 cytokines (IL-4, IL-5, IL-9, and IL-13) and regulatory cytokines (IL-10 and transforming growth factor-β), which are believed to modulate pro-inflammatory cytokines (Anuradha *et al.* 2016; Rajamanickam *et al.* 2020). Additionally, Th2 and regulatory cytokines enhance insulin sensitivity by promoting the development of alternatively activated macrophages, encouraging eosinophilic infiltration of adipose tissue, and activating innate lymphoid cells (Rajamanickam *et al.* 2019). Interestingly, following anti-helminthic therapy, the levels of pro-inflammatory cytokines have been observed to increase, while the Th2-associated and regulatory cytokines diminish, suggesting that post-treatment of *Strongyloides* infection may increase the risk of type 2 DM (Anuradha *et al.* 2016; Rajamanickam *et al.* 2020). Strongyloidiasis significantly affects the host's immune system, demonstrating a potentially beneficial role in managing type 2 DM. The reduction of pro-inflammatory cytokines and the increase in Th2-associated and regulatory cytokines are key effects of *Strongyloides*.

The meta-analysis provided more precise estimates on the association of *S. stercoralis* infection with DM development. Overall, results suggest that the infection may decrease the likelihood of developing DM. However, even with the significant findings of this review, care should be taken in applying these results clinically given the study's limitations such as (1) only one of the three post-outlier studies showed significant associations – which may obscure the overall effect of the results, (2) inconsistencies in the method of *S. stercoralis* infection and DM determination as well as the diversity of the ethnicity of the participants leads to significant clinical heterogeneity, and (3) limited studies done in tropics and subtropic areas where strongyloidiasis is endemic. Further longitudinal studies may be done in various ethnic groups and geographic locations may be done to verify these claims.

Author contribution. R.E.T. and M.R.P.C. conceptualized the study; R.E.T., J.A.F., and S.A.D. designed the study protocol; R.E.T., E.J.C., and M.J.D. performed data extraction; R.E.T. and E.M. analyzed the data and interpreted the results. All authors were involved in the drafting and critically revising of the manuscript. All authors read and approved the version of the manuscript to be sent for publication.

Ethical approval. Not required

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Competing interest. None

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