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REVIEW ARTICLE

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Immunological and Metabolic Associations of Latent Tuberculosis Infection in Type 2 Diabetes Mellitus: A Meta-Analysis of HbA1c Levels and IFN-γ Responses

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The intersection of tuberculosis (TB) and type 2 diabetes mellitus (T2DM) represents a major global health challenge. Although T2DM is a recognized risk factor for active TB, its epidemiological impact on latent tuberculosis infection (LTBI) and the underlying immune mechanisms remain unclear. This meta-analysis estimated the global prevalence of LTBI in T2DM, compared LTBI risk with non-diabetic controls, and evaluated the roles of glycated hemoglobin (HbA1c) and interferon-gamma (IFN-γ) in immune dysregulation. HbA1c and IFN-γ were selected because they represent the gold-standard indicators of long-term glycemic control and IGRA-based immune responses, respectively. A systematic search identified observational studies using interferon-gamma release assays (IGRA) to diagnose LTBI in T2DM patients. Random-effects meta-analysis with restricted maximum-likelihood estimation was performed to calculate pooled prevalence, odds ratios (ORs), mean differences (MDs) for HbA1c, and standardized mean differences (SMDs) for IFN-γ levels. Ten studies involving 1,740 T2DM patients and non-diabetic controls were included. The pooled LTBI prevalence in T2DM was 27% (95% CI: 23%–32%; I^2 = 76%). Compared with non-diabetic individuals, T2DM patients had an 86% higher risk of LTBI (OR 1.86; 95% CI: 1.41–2.45; p<0.0001; I^2 = 0%). T2DM patients with LTBI also showed poorer glycemic control, with HbA1c levels 0.75% higher than those without LTBI (MD 0.75; 95% CI: 0.51–0.99; p<0.00001; I^2 = 0%). Furthermore, T2DM was associated with significantly reduced Mycobacterium tuberculosis-specific IFN-γ production (SMD −1.93; 95% CI: −2.69 to −1.16; p<0.00001; I^2 = 78%). These findings indicate that T2DM substantially increases LTBI risk through hyperglycemia-associated immune dysregulation and impaired Th1-mediated IFN-γ responses. Routine LTBI screening using IGRA and optimal glycemic control should be integrated into diabetes management to reduce progression to active TB.

Keywords: *: latent tuberculosis infection, type 2 diabetes mellitus, HbA1c, interferon-gamma, meta-analysis*

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Introduction

The convergence of the tuberculosis and diabetes mellitus epidemics represents a critical public health challenge, often characterized as a syndemic in low- and middle-income countries.[1–3] The World Health Organization (WHO) estimates that approximately one-quarter of the global population harbors latent tuberculosis infection (LTBI), serving as a vast reservoir for future active tuberculosis (TB) cases.[4,5] Concurrently, the prevalence of diabetes mellitus (DM) is accelerating rapidly, with over 537 million adults currently living with the condition globally, a number projected to rise significantly in the coming decades.[6–8] Furthermore, it is well documented that nutritional and metabolic disturbances, such as chronic inflammation and malnutrition, can severely impact the clinical outcomes of TB patients by altering their immunological profiles and depleting essential lymphocyte populations.[9,10] Similar to nutritional deficits, underlying metabolic diseases like type 2 diabetes mellitus (T2DM) profoundly compromise the body's immune defense mechanisms against infectious agents.[11,12]

While the synergy between T2DM and active TB is widely documented, the epidemiological burden of LTBI among diabetic populations remains inconsistently reported. Furthermore, the precise immunological mechanisms that render diabetic patients more susceptible to *Mycobacterium tuberculosis* (Mtb) infection and reactivation are not fully elucidated, although chronic hyperglycemia and subsequent immune dysregulation are heavily implicated.[6,13] Current evidence suggests that T2DM impairs both innate and adaptive immune responses, notably altering macrophage function and reducing the protective T-helper 1 (Th1) cell cytokine cascade, primarily interferon-gamma (IFN-γ), which is essential for granuloma formation and maintenance.[14,15]

As the critical reservoir for future active TB cases, focusing on LTBI is essential to halt disease progression before clinical manifestation occurs. Furthermore, clarifying the precise immunological mechanisms underlying this vulnerability requires targeted, reliable biomarkers. In this study, HbA1c was selected as the gold standard marker of long-term glycemic control, directly reflecting metabolic stability. Concurrently, Mtb-specific IFN-γ responses, measured exclusively using interferon-gamma release assay (IGRA), were analyzed because IFN-γ is the principal cytokine responsible for macrophage activation and granuloma maintenance. This dual-marker approach provides a clear and logical framework linking T2DM-induced metabolic impairment to the failure of immune containment in LTBI.

Given the conflicting data across primary studies and the urgent need for evidence-based screening guidelines, a robust quantitative synthesis is required. Despite the known association between T2DM and active TB, the precise magnitude of LTBI risk and its relationship with glycemic and immunological markers remain inadequately synthesized. Addressing this research gap is crucial for developing targeted screening protocols. Therefore, this meta-analysis aims to provide a comprehensive four-dimensional evaluation by determining the pooled prevalence of LTBI among patients with T2DM globally, comparing the risk of LTBI between T2DM patients and healthy non-diabetic controls, assessing the direct association between glycemic control (as measured by HbA1c levels) and the risk of LTBI, and quantifying the underlying immunological impairment through the analysis of Mtb-specific IFN-γ production levels. Focusing on LTBI is essential, as it serves as the primary reservoir for future TB cases. HbA1c was selected to represent long-term glycemic stability, while IFN-γ, measured via IGRA, was used as the key cytokine for immune containment.

Materials and methods

Study Design and Protocol

This meta-analysis was conducted in strict adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (Figure 1).[16] The study protocol was registered prospectively with PROSPERO (CRD420251241731).

Search Strategy and Data Sources

A comprehensive literature search was executed across three major databases: ScienceDirect, PubMed, and ProQuest, covering the period from inception up to March 2026. The search strategy utilized a combination of Medical Subject Headings (MeSH) and free-text terms, including: "Type 2 Diabetes Mellitus", "T2DM", "Latent Tuberculosis", "LTBI", "Interferon-gamma Release Assay", "IGRA", "QuantiFERON", "T-SPOT", "HbA1c", and "Interferon-gamma". Boolean operators (AND/OR) were employed to appropriately combine and refine the search strings.

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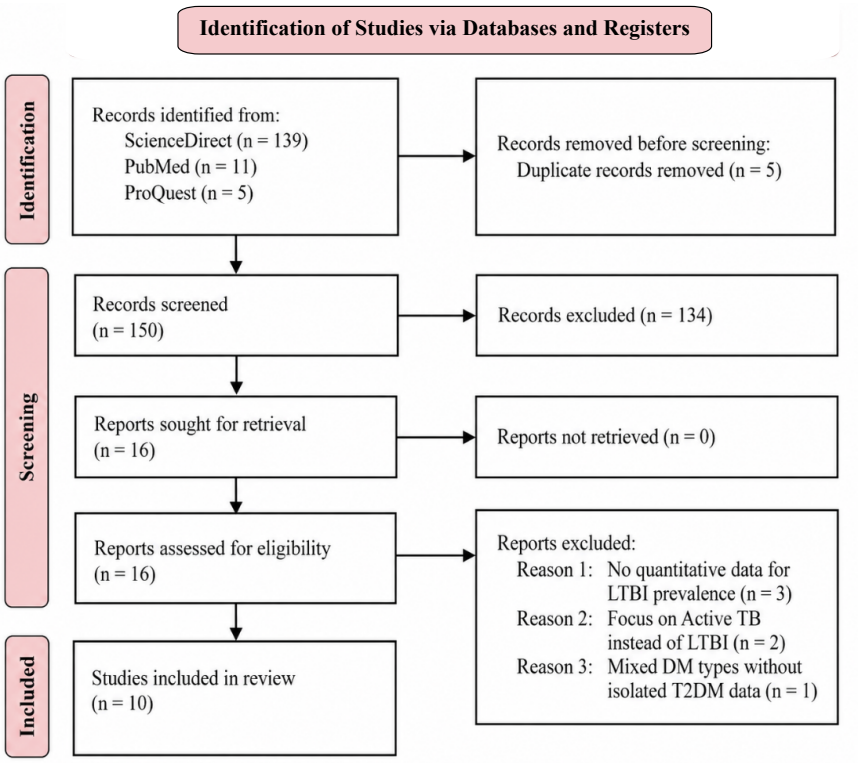


Figure 1. The results of the article screening are based on the PRISMA protocol.

Eligibility Criteria

Studies were considered eligible if they fulfilled the following criteria: (1) observational study designs (cross-sectional, cohort, or case-control); (2) adult populations specifically diagnosed with T2DM, alongside healthy non-DM control groups where applicable; (3) utilization of blood-based IGRA, such as QuantiFERON or T-SPOT. TB, as the definitive diagnostic modality for LTBI; and (4) provision of sufficient quantitative data to calculate at least one of our predefined endpoints (prevalence rates, odds ratios, or continuous data for HbA1c and IFN-γ levels). Studies were strictly excluded if they focused solely on active TB, utilized the tuberculin skin test (TST) without IGRA confirmation, involved Type 1 DM or mixed DM populations without isolated data for T2DM, or were non-original research articles (e.g., reviews, case reports, editorials).

Data Extraction

Data extraction was conducted independently by two reviewers using a standardized, pilot-tested template to ensure high fidelity. Any discrepancies or disagreements between the two reviewers during the screening and extraction phases were systematically resolved through consensus, or when necessary, through consultation with a third independent reviewer. Extracted baseline variables included study characteristics (primary author, publication year, country, and study design), participant demographics (sample sizes and mean age), and the specific IGRA modality used. For the quantitative meta-analytical synthesis, we systematically extracted data across four distinct dimensions: (a) the total number of evaluated T2DM patients and the number of positive LTBI events to calculate the pooled prevalence; (b) dichotomous data (events and totals) in both T2DM and non-DM control groups for comparative risk assessment; (c) continuous data (mean, SD, and sample size) of HbA1c percentages comparing LTBI-positive versus LTBI-negative T2DM patients; and (d) continuous data (mean, SD, and sample size) of quantitative Mtb-specific IFN-γ production levels (e.g., IU/mL or pg/mL) comparing T2DM patients with LTBI against non-DM patients with LTBI.

Quality Assessment and Critical Appraisal

The methodological quality of the included studies was rigorously appraised using the Joanna Briggs Institute (JBI) Critical Appraisal Tools.[17] In this study, a score of >80% was categorized as 'Low' risk of bias, 50–80% as 'Moderate' risk, and <50% as 'High' risk. These thresholds were used to determine the strength of evidence provided by each study and to ensure that the meta-analysis reflects high-quality clinical data. The literature search was conducted from February 1 to March 15, 2026, by two independent reviewers. Disagreements were resolved through consensus or adjudication by a third reviewer.

Statistical Analysis

All meta-analytical calculations were performed using RevMan Web (Cochrane Collaboration). To account for the expected clinical and methodological heterogeneity across studies from different geographical regions, a random-effects model utilizing the restricted maximum-likelihood (REML) estimator was applied for all analyses.

For the first outcome, the pooled prevalence of LTBI and its 95% confidence interval (CI) were calculated using the generic inverse variance method. For the second outcome, the comparative risk of LTBI between T2DM and non-DM groups was evaluated by calculating the pooled odds ratio (OR) with 95% CI using the inverse variance method. For continuous outcomes, the mean difference (MD) was used to analyze the difference in HbA1c levels between LTBI-positive and LTBI-negative T2DM patients. Due to variations in the laboratory measurement units of cytokines across studies (e.g., pg/mL vs. IU/mL), the standardized mean difference (SMD) was utilized to pool the quantitative data of IFN-γ production.

Statistical heterogeneity was assessed using the I^2 statistic, where $I^2 > 50\%$ indicated substantial heterogeneity. Statistical significance was set at a p-value<0.05. Finally, in accordance with Cochrane guidelines, publication bias was visually evaluated using a funnel plot for outcomes comprising 10 or more studies.

Results

Study Selection

Through the PRISMA-guided database search, 155 records were initially identified. After the removal of duplicates and rigorous screening of titles, abstracts, and full texts against the eligibility criteria, a total of 10 observational studies met the final inclusion criteria for this meta-analysis. These studies encompassed 1,740 patients with T2DM and their respective non-DM control groups (Table 1).[1,4,6,13–15,18–21] The studies were geographically diverse, covering populations in Asia, Africa, and the Americas. All included studies utilized the IGRA as the primary diagnostic modality for LTBI, ensuring high diagnostic specificity.

Quality Assessment

A rigorous appraisal of the included literature confirmed a high standard of methodological quality across the majority of the studies (Table 2). The analysis, based on the JBI criteria, identified that most cohorts, exhibited a low risk of bias with perfect or near-perfect scores.[1,20] Only study was identified as having a moderate risk of bias, which was carefully accounted for during the quantitative synthesis.[21]

Estimated Prevalence of LTBI Among Individuals with T2DM

Data extraction from the 10 included studies yielded 513 LTBI events among 1,740 T2DM patients. Using a random-effects model with the generic inverse variance method, the overall pooled prevalence of LTBI in the T2DM population was 27% (95% CI: 23%–32%) (Figure 2). Significant heterogeneity was observed across the studies ($I^2 = 76\%$, $p<0.00001$), reflecting the varied baseline TB endemicity in the distinct geographical regions where the studies were conducted.

Increased Risk of LTBI in Patients with T2DM

Six studies provided sufficient dichotomous data to compare the risk of LTBI between T2DM patients and healthy non-DM controls.[1,6,14,18,19,21] The meta-analysis revealed that patients with T2DM had a significantly higher risk of acquiring LTBI compared to individuals without diabetes. The pooled Odds Ratio was 1.86 (95% CI: 1.41–2.45; $p<0.0001$) (Figure 3). Notably, this specific comparison demonstrated zero heterogeneity ($I^2 = 0\%$, $p=0.54$), indicating a highly consistent pattern across all evaluated populations that T2DM definitively amplifies LTBI susceptibility.

Higher HbA1c Levels in T2DM Patients with LTBI

To investigate the role of glycemic control, continuous data of HbA1c levels from five studies were analyzed.[1,4,13,15,19] The synthesis demonstrated that T2DM patients who tested

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Table 1. Baseline characteristics of included studies.

Author, Year	Country	Study Design	Sample Size (N)*	LTBI Prevalence in T2DM (%)	Immune Response (IFN-γ/Cytokines) Findings
Ssekamatte *et al*., 2025 [1]	Uganda	Cross-sectional	164	31.50%	T2DM significantly decreased Mtb-specific IFN-γ, TNF, and IL-12 secretion, indicating impaired Th1 and macrophage responses due to hyperglycemia.
Cheng *et al*., 2025 [4]	Taiwan	Cross-sectional	112	24.10%	T2DM patients with LTBI showed Aryl Hydrocarbon Receptor (AhR) dysregulation, which correlated with altered IFN-γ release.
Abdul-Ghani *et al*., 2024 [6]	Yemen	Cross-sectional	150	22.00%	Demonstrated a strong correlation between poor glycemic control (elevated HbA1c) and an increased risk of IGRA positivity.
Huang *et al*., 2023 [13]	Taiwan	Cross-sectional	128	27.30%	Uncontrolled T2DM triggered gut microbiota alterations, which negatively impacted T-cell capacity for optimal IFN-γ production.
Aravindhan *et al*., 2022 [14]	India	Cross-sectional	88	29.50%	T2DM patients with LTBI exhibited a significant decrease in anti-inflammatory cytokines (e.g., IL-38), indicating a chronic hyper-inflammatory state.
He *et al*., 2022 [15]	China	Cohort	210	20.40%	Quantitative IFN-γ responses fluctuated more in T2DM; excessively high IGRA values correlated with an increased risk of LTBI progression.
Restrepo *et al*., 2021 [19]	USA/ Mexico	Cross-sectional	94	35.10%	Monocyte-derived macrophages (MDMs) in T2DM showed abnormal polarization upon Mtb antigen exposure, failing to clear bacilli effectively.
Agha *et al*., 2020 [21]	Egypt	Cross-sectional	150	18.60%	The mean quantitative IFN-γ levels in T2DM patients with LTBI were significantly lower compared to the non-DM control group.
Koesoemadinata *et al*., 2017 [20]	Indonesia	Cross-sectional	530	38.90%	Highlighted a high burden of LTBI in the T2DM population within an endemic area, indicating immunological vulnerability due to metabolic comorbidities.
Kumar *et al*., 2015 [18]	India	Cross-sectional	114	26.30%	T2DM comorbidity was associated with a drastic reduction in circulating levels of the IL-20 subfamily of cytokines

Sample size (N) represents the number of patients within the T2DM group evaluated for LTBI and/or immune responses. T2DM = Type 2 Diabetes Mellitus; LTBI = Latent Tuberculosis Infection; IFN-γ = Interferon-gamma; Mtb = *Mycobacterium tuberculosis*; IGRA = Interferon-Gamma Release Assay.

Table 1. Methodological quality assessment of included studies using JBI Critical Appraisal Tools.

Author, Year	Study Design	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	(%) Yes	Risk
Ssekamatte *et al*., 2025[1]	Cross-sectional	√	√	√	√	√	√	√	√	100	Low
Cheng *et al*., 2025[4]	Cross-sectional	√	√	√	√	√	U	√	√	87.5	Low
Abdul-Ghani *et al*., 2024[6]	Cross-sectional	√	√	√	√	√	√	√	√	100	Low
Huang *et al*., 2023[13]	Cross-sectional	√	√	√	√	U	√	√	√	87.5	Low
Aravindhan *et al*., 2022[14]	Cross-sectional	√	√	√	√	√	√	√	√	100	Low
He *et al*., 2022[15]	Cohort*	√	√	√	√	√	U	√	√	87.5	Low
Restrepo *et al*., 2021[19]	Cross-sectional	√	√	√	√	√	√	√	√	100	Low
Agha *et al*., 2020[21]	Cross-sectional	√	√	√	√	U	U	√	√	75.0	Moderate
Koesoemadinata *et al*., 2017[20]	Cross-sectional	√	√	√	√	√	√	√	√	100	Low
Kumar *et al*., 2015[18]	Cross-sectional	√	√	√	√	U	√	√	√	87.5	Low

The baseline cross-sectional data of the cohort study was appraised using the JBI cross-sectional tool for consistency in prevalence evaluation.[15] Q1: were the criteria for inclusion in the sample clearly defined?; Q2: were the study subjects and the setting described in detail?; Q3: was the exposure measured in a valid and reliable way?; Q4: were objective, standard criteria used for measurement of the condition?; Q5: were confounding factors identified?; Q6: were strategies to deal with confounding factors stated?; Q7: were the outcomes measured in a valid and reliable way?; Q8: was appropriate statistical analysis used?. Abbreviations:√ = yes; U = unclear.

positive for LTBI had significantly worse glycemic control compared to their LTBI-negative counterparts. The pooled mean difference in HbA1c was 0.75% (95% CI: 0.51–0.99; p<0.00001) (Figure 4). Similar to the risk analysis, this finding showed remarkable consistency with an I^2 of 0%, confirming that elevated HbA1c is a direct and robust predictor of LTBI in diabetic populations.

Reduced Mtb-Specific IFN-γ Responses in T2DM Patients with LTBI

To provide a pathophysiological basis for the increased susceptibility, quantitative Mtb-specific IFN-γ production data from four studies were synthesized using the standardized mean difference (SMD).[1,15,19,21] The analysis revealed a profound immunological deficit; T2DM patients with LTBI exhibited significantly lower levels of IFN-γ production compared to non-DM patients with LTBI. The pooled SMD was -1.93 (95% CI: -2.69 to -1.16; $p < 0.00001$; I^2=78%) (Figure 5). This substantial negative effect size empirically confirms the presence of DM-induced immune dysregulation and suppressed Th1 responses.

Publication Bias

Visual inspection of the funnel plot for the primary outcome (overall pooled prevalence of LTBI), which comprised 10 studies, revealed a generally symmetrical distribution of the effect estimates around the pooled effect size. This symmetry suggests the absence of significant publication bias within the synthesized literature (Figure 6).

Discussion

This meta-analysis provides a holistic and robust evaluation of the burden of LTBI in patients with T2DM. By synthesizing data from 10 high-quality studies

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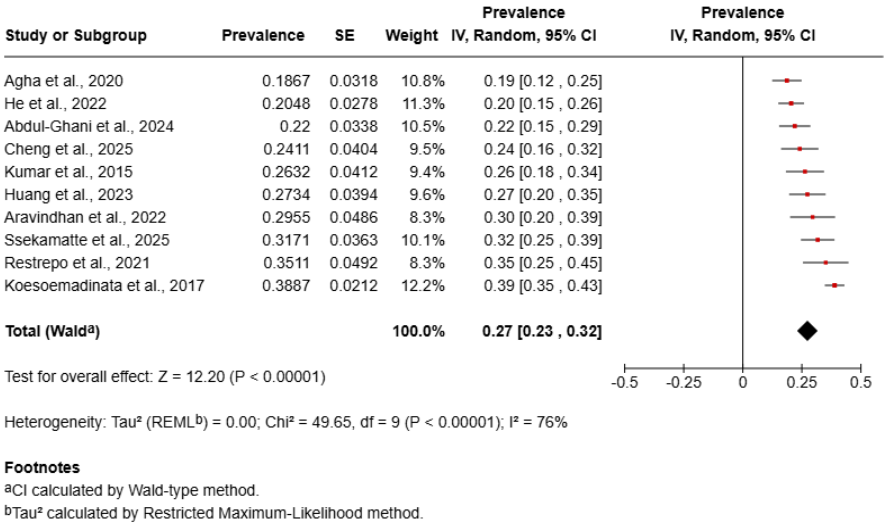


Figure 2. Forest plot of the pooled prevalence of LTBI among patients with DM.

encompassing 1,740 T2DM patients, we established that the global pooled prevalence of LTBI in this vulnerable population is 27%. More importantly, our comparative analysis definitively demonstrates that T2DM patients have an 86% higher risk (OR 1.86) of harboring LTBI compared to healthy non-DM individuals. The remarkable consistency of this finding across diverse geographic regions ($I^2 = 0\%$) underscores T2DM as a universal, independent risk factor for Mtb infection.[1,6,14,21]

A key strength of this study is the integration of clinical parameters and immunological biomarkers to explain the elevated risk. A highly significant, dose-dependent association between poor glycemic control and susceptibility to LTBI was observed. T2DM patients with LTBI had an average HbA1c level 0.75% higher than those without LTBI. Chronic hyperglycemia is known to facilitate a pro-oxidative state and the accumulation of advanced glycation end-products (AGEs), which subsequently impair phagocytosis, chemotaxis, and the bactericidal capacity of alveolar macrophages.[4,13,19,22] This metabolic impairment is often accompanied by an exacerbated pro-inflammatory state and the disruption of regulatory T cell functions, which

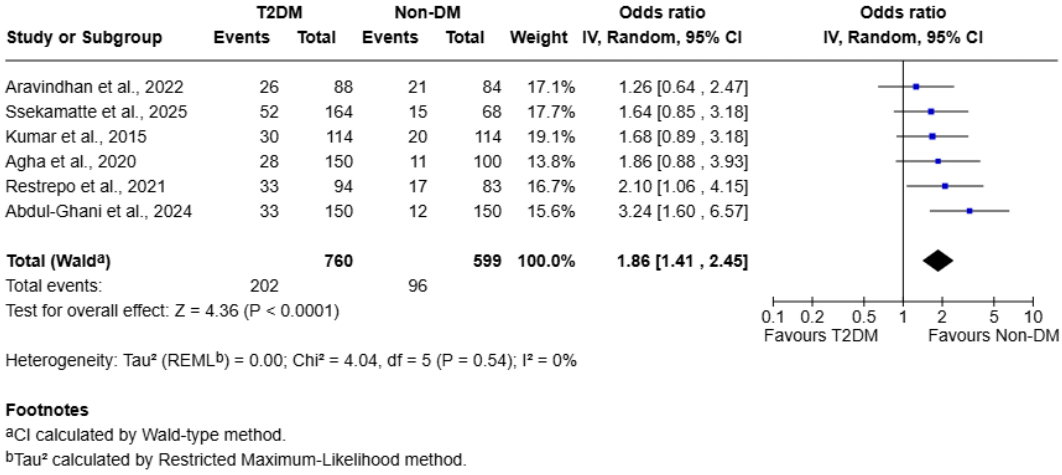


Figure 3. Forest plot comparing the risk of LTBI between DM patients and non-DM controls.

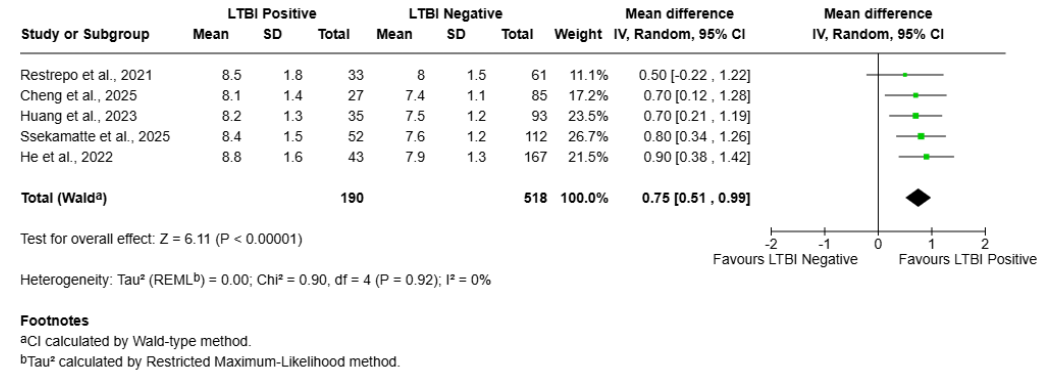


Figure 4. Forest plot of the association between glycemic control (HbA1c) and LTBI risk.

fail to maintain an adequate anti-inflammatory response during prolonged hyperglycemia.[23] The interplay between elevated glucose levels and systemic metabolic syndrome heavily dictates the severity of immune cell dysregulation, increasing the vulnerability to subsequent Mtb survival.24 Our finding empirically validates that strict glycemic control is not merely a metabolic goal, but a critical infectious disease prevention strategy.

Furthermore, we provided definitive quantitative evidence of T2DM-induced immune dysregulation. The hallmark of host defense against Mtb is a robust Th1-mediated cellular immune response, centrally orchestrated by IFN-γ, which activates macrophages to contain the bacilli within granulomas. Our analysis revealed a profound and statistically significant reduction in Mtb-specific IFN-γ production (SMD -1.93) in T2DM patients compared to non-DM controls.[1,15,19] This suppression of IFN-γ effectively explains the pathogenesis of why patients with T2DM are not only more easily infected by Mtb but also face a dramatically higher risk of LTBI reactivation progressing into active, cavitary pulmonary tuberculosis.[15,21] Similar systemic immune dysfunctions, such as a skewed neutrophil-to-lymphocyte ratio, have been identified as crucial indicators of disease severity and cavitation in pulmonary TB, further highlighting how broader immune disruptions exacerbate TB outcomes.[25]

From a clinical and public health perspective, these findings carry significant implications. The substantial prevalence (27%) and the nearly twofold increased risk of LTBI highlight an urgent need to integrate routine TB screening protocols within diabetic care clinics, particularly in TB-endemic regions. The exclusive use of IGRA in our

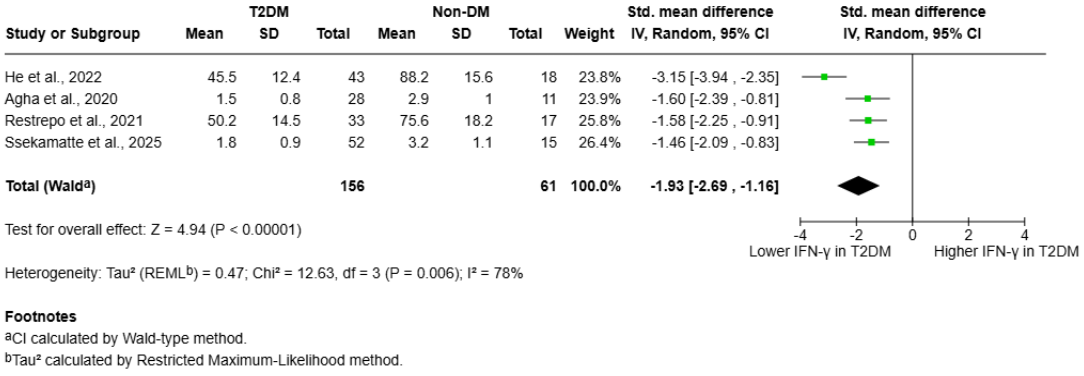


Figure 5. Forest plot of quantitative IFN-γ levels (Standardized Mean Difference) in DM patients.

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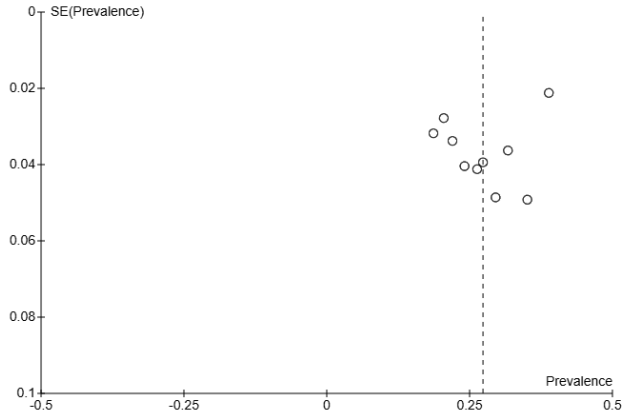


Figure 6. Funnel plot assessing publication bias for the overall pooled prevalence of latent tuberculosis infection (LTBI) among patients with T2DM.

included studies reinforces the reliability of these results, as IGRA is not confounded by prior BCG vaccination, a critical advantage over the traditional TST.[18,20] Preventive therapy for LTBI should be strongly considered for T2DM patients, especially those exhibiting chronic poor glycemic control.

This study has several limitations that should be acknowledged. First, the significant heterogeneity observed in the prevalence analysis suggests variations in baseline TB endemicity and diverse diagnostic protocols across different study regions. Second, the reliance on observational study designs precludes the establishment of definitive causal relationships between glycemic fluctuations and immune suppression. Finally, the limited number of studies providing quantitative IFN-γ data emphasizes the need for larger, prospective cohorts to validate our immunological findings.

Conclusion

This meta-analysis provides compelling, multi-dimensional evidence that T2DM significantly increases the burden of Latent Tuberculosis Infection. T2DM is associated with a 27% LTBI prevalence and an 86% higher risk of infection compared to non-diabetic populations. This heightened susceptibility is pathophysiologically driven by poor glycemic control (elevated HbA1c) and marked immune dysregulation, characterized by a profound suppression of protective IFN-γ responses. Routine IGRA screening and aggressive glycemic management are critical interventions required to mitigate the risk of LTBI and prevent its progression to active TB in diabetic patients. The primary novelty of this study lies in its targeted quantification of the dual mechanism: unlike previous research focusing on active TB, we provide a synthesized quantitative link demonstrating how chronic hyperglycemia directly suppresses Mtb-specific IFN-γ responses, thereby elucidating the specific immunological failure that facilitates latent infection in T2DM.

Authors' Contributions

In order to qualify for authorship of the submitted manuscript, every of the listed authors should have made substantial intellectual contributions both to the research and to its preparation. MZI conceptualized the study design, conducted the systematic search, performed data extraction and statistical analysis, and wrote the initial draft of the manuscript. DWF and AE provided critical insights for data interpretation, contributed significantly to the intellectual content, and comprehensively reviewed the manuscript. All authors discussed the findings, participated in the final revisions, and approved the final version of the manuscript for publication.

Ethical Statement

This article is based exclusively on the review and analysis of previously published literature. No primary data were collected, and no human participants, human biological materials, or animals were involved in this study. Therefore, ethical approval from an institutional review board or ethics committee was not required.

Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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