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Association between lymphatic filariasis and diabetes mellitus: A systematic review and narrative synthesis

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Abbreviations

ADLA	Acute dermatolymphangioadenitis
BmA	*Brugia malayi* antigen
CFA	Circulating filarial antigen
Cox-2	Cyclooxygenase-2
CURES	Chennai Urban Rural Epidemiology Study
DEF-A1	Alpha-defensin-1
DM	Diabetes mellitus
ELISA	Enzyme-linked immunosorbent assay
FoxP3	Forkhead box P3
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon-like peptide-1
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HbA1c	Glycated haemoglobin
HO-1	Heme oxygenase-1
IDF	International Diabetes Federation
IDO	Indoleamine 2,3-dioxygenase
IFN-γ	Interferon-gamma
IgG	Immunoglobulin G
IgG4	Immunoglobulin G subclass 4
IGT	Impaired glucose tolerance
IL	Interleukin
IL-1Ra	Interleukin-1 receptor antagonist

KDM	Known diabetes mellitus
LF	Lymphatic filariasis
LMIC	Low- and middle-income country
MLTC	Multiple long-term conditions
MMDP	Morbidity management and disability prevention
MS	Metabolic syndrome
NCEP-ATP III	National Cholesterol Education Program – Adult Treatment Panel III
ND-DM	Newly diagnosed diabetes mellitus
NGT	Normal glucose tolerance
NMS	Non-metabolic syndrome
NOS	Newcastle–Ottawa Scale
NTD	Neglected tropical disease
NVBDCP	National Vector Borne Disease Control Programme
Og4C3	*Wuchereria bancrofti* antigen-capture assay
OR	Odds ratio
PAI-1	Plasminogen activator inhibitor-1
PCR	Polymerase chain reaction
PICOS	Population, Intervention, Comparator, Outcome, Study design
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
SDF-1	Stromal cell-derived factor-1
SRH	Self-rated health
STEPS	WHO STEPwise Approach to Surveillance
STH	Soil-transmitted helminths
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TGF-β	Transforming growth factor beta
Th cell	T helper cell
TLR	Toll-like receptor
TNF-α	Tumour necrosis factor alpha
Tregs	Regulatory T cells
VCRC	Vector Control Research Centre
VEGF	Vascular endothelial growth factor
WHO	World Health Organization

Abstract

Background:

Lymphatic filariasis (LF) and diabetes mellitus (DM) increasingly coexist as important health challenges in low- and middle-income countries. Chronic filarial infection induces marked immunoregulation that may influence inflammatory pathways implicated in insulin resistance, providing biological plausibility for an interaction between the two conditions. We synthesised epidemiological, immunological, endocrine, and clinical evidence on the LF–DM relationship.

Methodology/Principal Findings:

The review followed PRISMA 2020 guidance, and its protocol was prospectively registered in PROSPERO (CRD420261331823). MEDLINE and Scopus were searched for records available from database inception through 2 May 2026. Additional eligible literature was identified through Google Scholar and citation-based searching. We considered studies involving human participants in whom LF had been established using recognized diagnostic, clinical, or programme-based criteria. Studies reporting diabetes or other relevant metabolic, immunological, or clinical outcomes were eligible for inclusion. Study quality was assessed using the Newcastle-Ottawa Scale, and the certainty of the available evidence was evaluated using the GRADE approach. Variation across the included studies precluded quantitative pooling; therefore, findings were synthesized narratively. Seven studies fulfilled the eligibility criteria. All were conducted in India, with most originating from a single research network. Overall, the epidemiological evidence indicated an association between LF and lower diabetes prevalence. The largest study additionally reported lower circulating concentrations of selected pro-inflammatory cytokines among participants with LF.

Conclusions/Significance:

Evidence suggests a biologically plausible interaction between LF and DM but remains too limited and geographically concentrated for firm conclusions. The absence of studies from sub-Saharan Africa is a critical gap. Longitudinal, mechanism-focused studies across diverse LF-endemic settings are needed to clarify this relationship and inform integrated care for populations bearing dual neglected tropical disease and non-communicable disease burdens.

Keywords: lymphatic filariasis, diabetes mellitus, systematic review, immunomodulation, neglected tropical diseases, multimorbidity, helminth infection.

1 Author Summary

Lymphatic filariasis (LF) is a parasitic infection transmitted by mosquitoes and remains an important health problem in tropical regions, where it can cause severe and disfiguring limb swelling. Diabetes, a condition of persistently high blood sugar, is rising quickly in many of the same countries. Because long-term filarial infection calms the immune system, researchers have asked whether it might also influence the inflammation that contributes to diabetes. We gathered and carefully reviewed all available studies that examined both conditions in the same people. We found only seven studies, all carried out in India and most by a single research group. Together they suggest that people with diabetes tend to have less filarial infection, and that each condition may shape the body's response to the other. However, the evidence is still limited, and, strikingly, not a single study has been conducted in sub-Saharan Africa, where both diseases are common. Our review shows that this is an important and neglected question, and calls for new studies in Africa that follow people over time to understand how these two diseases interact.

2 Introduction

Diabetes mellitus (DM) comprises metabolic disorders in which impaired insulin secretion, reduced insulin sensitivity, or a combination of both results in persistently elevated blood glucose concentrations (Schleicher et al., 2022). There are two primary types of DM: type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). In T1DM, immune-mediated destruction of pancreatic beta cells results in an absolute deficiency of insulin. This loss of insulin-producing cells leads to abnormal glucose metabolism. By contrast, T2DM is primarily characterized by insulin resistance accompanied by a relative deficiency of insulin and accounts for most diagnosed diabetes cases globally (Schleicher et al., 2022).

Diabetes prevalence is increasing worldwide, with 589 million estimated cases of diabetes among adults between the ages of 20 and 79 years in 2024 (11.1% of the global adult population). This

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burden is expected to continue rising, reaching an estimated 853 million (10.9% of the global adult population) by 2050 (Magliano et al., 2025). The regional distribution of this burden is uneven, and Sub-Saharan Africa is projected to experience the greatest relative increase in diabetes cases, rising from 24.6 million to 59.5 million between 2024 and 2050 (Magliano et al., 2025).

Tanzania's national STEPS survey released in 2023 represents the most recent nationally representative, biomarker-based assessment of the disease's prevalence. It estimated that 2.9% of Tanzanian adults aged 18-69 years had DM, with 3.4% classified as having impaired fasting glycaemia (pre-diabetes) (Ministry of Health Tanzania Mainland et al., 2023). This figure is lower than modelled estimates calculated by the IDF Diabetes Atlas reporting a 9.2% crude prevalence in age group 20-79 year olds (Magliano et al., 2025). The difference likely reflects methodological differences (direct biomarker-based surveillance versus modelled estimates derived from multiple sources) and differences in the age ranges assessed.

LF is caused by the filarial nematodes *Wuchereria bancrofti, Brugia malayi*, and *Brugia timori* and is transmitted to humans through mosquito bites (Al-Tameemi & Kabakli, 2019). Following the introduction of the WHO Global Programme to Eliminate Lymphatic Filariasis in 2000, the estimated number of active LF cases declined by approximately 74%, from about 199 million to 51 million by 2018 (Cromwell et al., 2020). Along with morbidity risks, LF also heavily contributes to stigma, psychosocial and economic impact such as poverty (Zeldenryk et al., 2011). The coexistence of these conditions is increasingly relevant in low- and middle-income settings, where populations continue to experience substantial burdens from both infectious and chronic diseases.

Asymptomatic chronic filarial infection is often characterized by an immunoregulatory profile involving increased anti-inflammatory cytokine activity, including IL-10 and TGF-β, together with regulatory T-cell (Treg) responses (Babu & Nutman, 2014). However, subjects with clinical disease after LF infection develop increased pro-inflammatory immune responses such as Th1 and Th17 cytokine production and reduced levels of Tregs (Babu et al., 2009). This point is important because

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insulin resistance, which plays a major role in the development of type 2 DM, has been associated with chronic inflammation caused by pro-inflammatory cytokines TNF and IL-6 (Fernández-Real & Ricart, 2003; Rehman & Akash, 2016). These contrasting immune profiles suggest that the metabolic consequences of LF may vary according to infection status and clinical phenotype

Supporting this hypothesis, observational evidence from small groups of individuals with LF and DM has suggested that chronic filarial infection may be associated with reduced inflammatory and metabolic activity relevant to diabetes (Aravindhan et al., 2010a). Experimental studies provide additional biological context, indicating that parasite-induced immune regulation can promote an anti-inflammatory environment (Hoerauf et al., 2005). In mouse models, filarial infection has been linked with protection from the development of type 1 diabetes, initially linked to expansion of regulatory T cells and type 2 immune responses (Hübner et al., 2009). Subsequent experimental work suggested that this effect may occur independently of Tregs and type 2 immunity and instead involve transforming growth factor-β (TGF-β) signalling (Hübner et al., 2012). Other mouse studies have reported improved glucose tolerance and reduced adipose-tissue inflammation following filarial infection or exposure to filarial antigens in animals with diet-induced obesity (Berbudi et al., 2016). More recent experimental evidence has also implicated IL-9 signalling, an immune pathway associated with helminth infection, in protection against obesity-related inflammation and insulin resistance (Hübner et al., 2025).

Immunometabolic effects likely vary depending on helminth species and should not be generalized. In humans, helminth infections have been shown to impact metabolic outcomes, including glucose homeostasis and risk for diabetes mellitus; however, these studies showed parasite species-specific heterogeneity in effects (Rennie et al., 2021). On the other hand, Htun et al. (2018) found a link between infection with *Taenia spp*. and diabetes mellitus, implying helminth infection is associated with poor metabolic outcomes. The potential heterogeneity by species may be particularly important for LF. Intestinal helminth infections differ from LF caused by Wuchereria bancrofti and Brugia spp.

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because LF causes chronic infection within lymphatic tissues. This comes with extended duration of host-parasite interaction and immune regulation when compared to intestinal helminth infections. As a result, these findings cannot be generalized to LF. Data specific to LF are needed to identify associations between filarial infection and metabolic outcomes such as diabetes mellitus.

A substantial proportion of the available human evidence on the LF–DM relationship comes from a research programme in southern India, which has generated much of the epidemiological, immunological, and metabolic evidence to date (Aravindhan et al., 2010a, 2010b; Sibi et al., 2021, 2022, 2025). Nevertheless, given the co-endemicity of LF and DM throughout large regions of sub-Saharan Africa and South Asia coupled with the biological plausibility of such an interaction(Hübner et al., 2009, 2025), the evidence base linking these two diseases is surprisingly limited. Furthermore, previously published reviews have focused more broadly on helminth infections and metabolic disease rather than LF specifically (Rajamanickam & Babu, 2024; Rennie et al., 2021). Therefore, the epidemiological association between LF and DM and the immunological pathways that may underlie this relationship remain poorly defined. Here, we systematically review the epidemiological, clinical, immunological, and metabolic evidence on the relationship between LF and DM and identify priorities for future research

3 Methods

3.1 Study Design

This review was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA 2020) reporting guidelines (Page et al., 2021). The protocol was registered prospectively with PROSPERO (Identification number: CRD420261331823) (S3 Appendix). Following completion of the review, the PROSPERO record was amended to note that a quantitative meta-analysis was not performed because of an inadequate number of eligible studies and important clinical and methodological discrepancies across studies precluded meaningful statistical pooling. Results from the eligible studies were therefore synthesized narratively.

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3.2 Eligibility criteria

Eligibility criteria were established before conducting this systematic review and were structured around the PICOS (Population, Intervention/Exposure, Comparator, Outcomes, Study design) framework.

3.2.1 Population

Studies were included if they involved human participants of any age from both LF-endemic and non-endemic settings.

3.2.2 Intervention/Exposure

Studies were eligible if LF status was established using recognized clinical, laboratory, or epidemiological criteria. Laboratory-based confirmation included circulating filarial antigen (CFA) tests, microscopic detection of microfilariae, or molecular assays, including polymerase chain reaction (PCR). Where clinical or epidemiological ascertainment was used, the potential for misclassification was considered in the risk-of-bias assessment.

3.2.3 Comparator

Studies with or without a comparator group were eligible. Where available, comparator groups consisted of LF-negative individuals.

3.2.4 Outcomes

The primary outcome was DM status. DM status was defined based on diagnostic criteria using fasting plasma glucose, glycated haemoglobin (HbA1c), oral glucose tolerance testing, or clinical diagnosis. The reported diabetes category (type 1 or type 2 diabetes mellitus) was also collected and considered when interpreting the findings. Secondary outcomes included immunological, inflammatory, metabolic, and endocrine outcomes. These included cytokines with known pro- or anti-inflammatory activity (e.g., tumour necrosis factor alpha [TNF-α], interleukins [IL-6, IL-1β, IL-

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10], transforming growth factor-beta [TGF-β], and interleukin-1 receptor antagonist [IL-1Ra]), chemokines, adipokines (e.g., leptin and adiponectin), and other metabolic or endocrine biomarkers

3.2.5 Study Design

Eligible studies used observational designs, including cross-sectional, case-control, and cohort approaches.

3.3 Information Sources and Search Strategy

We searched MEDLINE (via PubMed) and Scopus from database inception through 2 May 2026 to identify relevant articles. The search strategy combined MeSH vocabulary with keywords relating to LF and DM. Search terms included "lymphatic filariasis", "*Wuchereria bancrofti*", *"filariasis*", "diabetes mellitus", "diabetes", "hyperglycaemia", "inflammation", "cytokines", and "immune response". Complete search strategies can be found in S2 Appendix. Forward citation searching of eligible studies and supplementary searches of Google Scholar were also performed to find out possibly suitable studies not retrieved through the primary database searches. No extra eligible studies were identified through these supplementary searches. No date restrictions were applied to the search strategy. Only English-language studies involving humans were eligible for inclusion.

3.4 Study Selection

After records were retrieved, they were imported into Rayyan, and duplicates were removed (Ouzzani et al., 2016). Titles and abstracts were screened by two reviewers separately in two stages. The first stage entailed determining eligibility. The second stage consisted of full-text articles of studies deemed eligible by either reviewer. If discrepancies occurred, they were settled by consensus or by consulting a third reviewer.

3.5 Data extraction

Data extraction and management were performed using Rayyan (Ouzzani et al., 2016). The extracted data consisted of study characteristics (author, year of publication, country, study design), participant characteristics (sample size), the diagnostic methods used to assess LF exposure status and DM outcomes as well as reported immunological, inflammatory, metabolic and endocrine markers of interest (included cytokines and adipokines). Two reviewers independently extracted the data and cross-checked for accuracy. Differences were resolved through discussion and when required by consensus with a third reviewer.

3.6 Risk of Bias Assessment

Risk of bias was assessed with the Newcastle-Ottawa Scale (NOS) scale. NOS evaluates quality based on three main perspectives; how the groups were selected for the study, if they are comparable, and how the exposures or outcomes were assessed (Lo et al., 2014). Possible biases included measurement bias and diagnostic bias. Variations in LF diagnostic among included studies were considered when determining risk of bias and drawing conclusions. Each study could have been scored up to 9, with corresponding low, moderate, or high risk of bias categories based on the score (Lo et al., 2014). Two reviewers independently evaluated each study using the NOS tool. Any disagreements were resolved by discussion or with a third reviewer. Results of the risk-of-bias assessment are shown in Table 2.

3.7 Certainty of Evidence Assessment

We applied the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework to rate evidence certainty across main outcomes (Schünemann et al., 2019). Ratings accounted for risk of bias, inconsistency, indirectness, imprecision, and potential publication bias (Kirmayr et al., 2021). Because we included observational evidence, baseline certainty started as low; however, scores were adjusted upward or downward depending on effect size, dose-response

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trends, or residual confounding factors (Schünemann et al., 2019; Yousefifard & Shafiee, 2023). Following GRADE guidelines, the final evidence certainty for every outcome was categorized as high, moderate, low, or very low.

3.8 Data Synthesis

Because only a small number of epidemiological studies were available and the studies showed substantial clinical and methodological heterogeneity, quantitative pooling was not considered appropriate. The findings were therefore synthesized narratively across the main outcome domains, including epidemiological associations between LF and DM, immuno-inflammatory responses, endocrine and metabolic pathways, clinical outcomes, and multimorbidity. Study characteristics, including study design, population characteristics, diabetes phenotype, LF assessment methods, outcome definitions, as well as the strength and direction of these links, were compared across studies

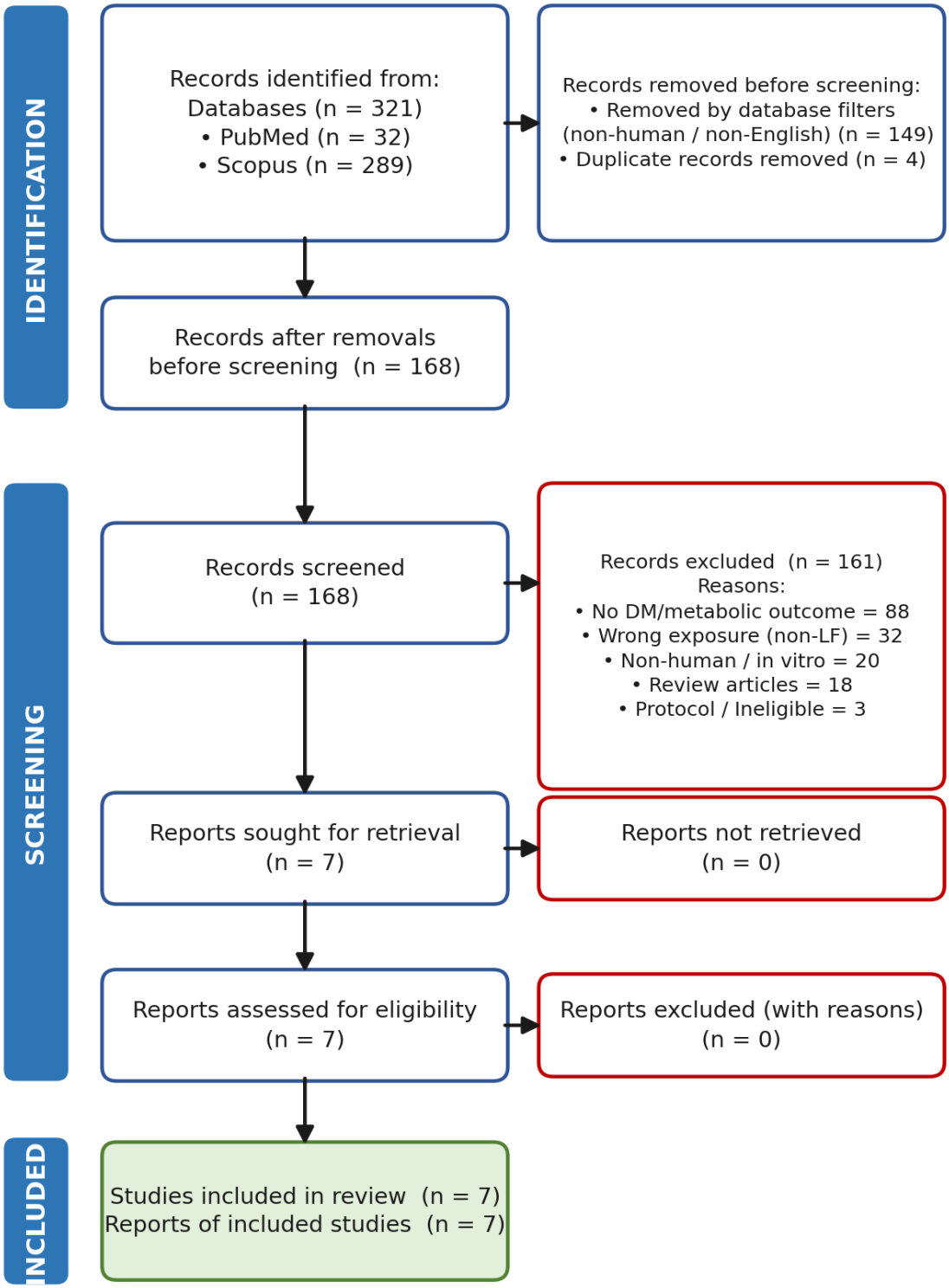
4 Results

4.1 Study selection

The database searches retrieved 321 records overall, comprising 32 from MEDLINE via PubMed and 289 from Scopus. Before screening, 149 records were removed by the prespecified database filters and four duplicate records were removed, leaving 168 unique records that were screened by title and abstract, of which 161 were excluded; the most common reasons were absence of a diabetes/metabolic outcome and wrong exposure. The study selection process is summarised in Fig 1. The remaining seven records were retrieved for full-text assessment, and all met the predefined eligibility criteria. All seven studies (six cross-sectional and one case-control) were included in the narrative synthesis.

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PRISMA 2020 FLOW DIAGRAM



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Fig. 1. Flow of records through the screening and selection stages of this systematic review of the association between lymphatic filariasis and diabetes mellitus.

4.2 Characteristics of Included Studies

All seven included studies were conducted in India, predominantly in South India (Chennai and Puducherry), with one community-based study from Odisha. Six studies employed cross-sectional designs, while one used a case-control design. Collectively, the studies investigated epidemiological associations between LF and DM, immunological and cytokine responses, endocrine and metabolic pathways, clinical outcomes, and multimorbidity among individuals with LF (Aravindhan et al., 2010a, 2010b; Kubal et al., 2025; Sibi et al., 2021, 2022, 2025; Sinha et al., 2025).

The studies included both community and hospital-based populations and demonstrated substantial methodological diversity. Heterogeneity was observed in participant characteristics, diabetes phenotypes (type 1 diabetes, type 2 diabetes, and metabolic syndrome), LF diagnostic methods, sample size, and outcome definitions. These differences precluded quantitative synthesis and informed the narrative approach adopted in this review. A detailed summary of study characteristics is presented in **Table 1**.

Table 1. Characteristics of Included Studies

Study (Author, Year)	Country	Study Design	Sample Size	Population / Setting	Diabetes Type	LF Diagnosis	Outcomes Assessed	Key Findings
Aravindhan et al., 2010b (Am J Trop Med Hyg)	India	Cross-sectional	n=762 T1DM=200 NGT=562	T1DM patients and normoglycaemic controls from a tertiary diabetes centre, Chennai	Type 1 DM	*W. bancrofti* Og4C3 antigen-capture ELISA (TropBio)	LF prevalence; filarial antigen-specific IgG and IgG4 antibody levels	LF prevalence 0% in T1DM vs 2.6% in NGT (p=0.026); IgG4 seropositivity lower in T1DM (2%) vs NGT (14%); IgG comparable, suggesting similar

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Study (Author, Year)	Country	Study Design	Sample Size	Population / Setting	Diabetes Type	LF Diagnosis	Outcomes Assessed	Key Findings
								exposure but lower active infection in T1DM
Aravindhan et al., 2010a — CURES 83 (PLoS NTD)	India	Cross-sectional (population-based)	n=1,416 NGT=943 IGT=154 ND-DM=158 KDM=161	Representative urban population from CURES cohort (normoglycaemic, pre-diabetic, T2DM), Chennai	Type 2 DM	*W. bancrofti* Og4C3 antigen-capture ELISA (TropBio)	LF prevalence; filarial antigen load; anti-filarial IgG and IgG4; serum cytokines (TNF-α, IL-6, GM-CSF, IFN-γ, IL-10, IL-13, TGF-β)	LF prevalence decreased from NGT (10.4%) to KDM (4.3%); antigen load and IgG lower in KDM; IL-6 and GM-CSF significantly reduced in DM+LF+ vs DM+LF−
Sibi et al., 2021 (Front Immunol)	India	Cross-sectional (immunological)	n=20 NGT-LF+=8 DM-LF+=12	Asymptomatic LF+ individuals with and without T2DM, tertiary diabetes clinic, Chennai	Type 2 DM	*W. bancrofti* Og4C3 antigen-capture ELISA (TropBio)	TLR2/TLR4-induced cytokines and chemokines; BmA-induced adaptive immune responses; Th polarisation; T-cell activation; Cox-2, HO-1, IDO, p47Phox expression	Diabetes augmented TLR-induced IL-27, IL-1Ra, IL-12, IL-33, IL-9, SDF-1, Cox-2 and IDO; increased Th9 polarisation; inflammatory markers unexpectedly upregulated rather than suppressed under comorbidity
Sibi et al., 2022 (Front Endocrinol)	India	Cross-sectional (with 10-year follow-up data)	n=88 NMS-LF−=22 NMS-LF+=22 MS-LF−=21 MS-LF+=23	Individuals with and without metabolic syndrome (LF+ and LF−) from CURES cohort, Chennai	Metabolic syndrome (NCEP-ATP III)	*W. bancrofti* Og4C3 antigen-capture ELISA (TropBio; ≥128 units)	Pancreatic hormones (insulin, glucagon); incretins (ghrelin, GIP, GLP-1); adipokines (adiponectin, leptin, resistin, adipsin, PAI-1, visfatin); 10-year follow-up profiles	Active LF increased glucagon, ghrelin, GIP, GLP-1 and reduced adipsin in MS-LF+ subjects; effects were transient and absent at follow-up when all LF+ had cleared infection; insulin and most adipokines unaffected
Sibi et al., 2025 (Sci Rep)	India	Cross-sectional (immunological)	n=45 Control=12 LF=8 DM=12 DM-LF=13	Asymptomatic LF+ and LF− individuals with and without T2DM, aged 30–50 years, tertiary	Type 2 DM	*W. bancrofti* Og4C3 antigen-capture ELISA (TropBio)	Innate and adaptive immune cytokines (TNF-α, IL-6, IL-1β, IL-10, IL-1Ra, TGF-β, IL-27, DEF-A1, IL-12,	Diabetes selectively reduced IL-1β, IL-1Ra, DEF-A1, IL-8, and lipid peroxidation in

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Study (Author, Year)	Country	Study Design	Sample Size	Population / Setting	Diabetes Type	LF Diagnosis	Outcomes Assessed	Key Findings
				diabetes clinic, Chennai			IFN-γ, and others); chemokines; hormones; lipid peroxidation; Tregs; exhausted T cells; FoxP3	LF+ subjects; VEGF elevated in DM-LF; adaptive immune markers largely unaffected; limited downregulatory effect on innate anti-filarial immunity
Sinha et al., 2025 (BMC Public Health)	India	Cross-sectional (community-based)	n=584 (LF patients)	LF patients ≥18 years, Cuttack district, Odisha; multistage random sampling via NVBDCP registries; predominantly rural and deprived	Not specified	Clinical history of LF via NVBDCP registries; no laboratory confirmation†	Prevalence and patterns of MLTCs; multimorbidity clusters; self-rated health (SRH) by number of chronic conditions; sociodemographic correlates	MLTC prevalence 68.8%; hypertension most common (29.3%), then peptic ulcer (26.9%) and diabetes (14.1%); most common triad: LF + hypertension + diabetes (1.5%); per-unit decline in SRH with each additional condition
Kubal et al., 2025 (PLoS NTD)	India	Case-control	n=166 Diabetic=79 Non-diabetic=87	Filarial lymphoedema patients attending ICMR-VCRC clinic, Puducherry; lymphoedema ≥2 years; within 25 km of clinic	Type 2 DM	Clinical diagnosis; lymphoedema severity graded per Dreyer's 7-stage system; DM confirmed via self-report and records	ADLA frequency (1-year and 2-year); ADLA severity; lymphoedema grade; MMDP adherence; predictors of ADLA (logistic regression)	Diabetes not significantly associated with ADLA frequency or severity; lymphoedema severity (grades 3–4) and intertrigo were the strongest independent predictors; home-based care associated with more frequent ADLA episodes (p=0.037)

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4.3 Risk of Bias

We evaluated methodological quality using the Newcastle–Ottawa Scale (NOS) (Lo et al., 2014). For cross-sectional designs, this appraisal focuses on three main criteria: selection, comparability, and outcome or exposure measurement, with scores capped at nine stars (Carra et al., 2025). Out of seven evaluated papers, six demonstrated low risk of bias (NOS scores 7-9), performing especially well in subject selection and outcome/exposure measurement (Table 2). A single study showed moderate risk of bias (NOS score 6), primarily because LF exposure relied on medical records and registries rather than lab testing, and all outcomes were self-reported without a comparison group (Sinha et al., 2025).

Across the immunological studies, the comparability domain represented the principal source of potential bias because important metabolic confounders, including age, sex, obesity, and antidiabetic treatment, were not consistently adjusted for (Sibi et al., 2021, 2025). Due to the small number of included studies, we did not formally test for publication bias. A summary of the risk-of-bias assessment is presented in **Table 2**.

Table 2: Risk of Bias Assessment (Newcastle-Ottawa Scale)

Study (Author, Year)	Study Design	Selection (max 4)	Comparability (max 2)	Outcome / Exposure (max 3)	Total (max 9)	Risk of Bias
Aravindhan et al., 2010b (T1DM)	Cross-sectional	4	1	3	8	Low
Aravindhan et al., 2010a CURES 83	Cross-sectional	4	2	3	9	Low
Sibi et al., 2021	Cross-sectional	3	1	3	7	Low
Sibi et al., 2022	Cross-sectional	4	1	3	8	Low
Sibi et al., 2025	Cross-sectional	3	1	3	7	Low
Sinha et al., 2025	Cross-sectional	3	2	1	6	Moderate
Kubal et al., 2025	Case-control	4	2	3	9	Low

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4.4 Certainty of Evidence

The certainty of evidence for each major outcome domain was assessed using the GRADE framework (Kirmayr et al., 2021; Yousefifard & Shafiee, 2023). Five outcome domains were evaluated: epidemiological association between LF and DM, immuno-inflammatory markers, endocrine and metabolic markers, clinical outcomes related to acute dermatolymphangioadenitis (ADLA), and multimorbidity.

The certainty of evidence for the epidemiological association between LF and DM was rated as low, based on two cross-sectional studies (Aravindhan et al., 2010a, 2010b). Although risk of bias and inconsistency were not considered serious concerns, the certainty of evidence was downgraded for indirectness because both studies were conducted within the same geographic setting and for imprecision because only two studies were available. The certainty of evidence for immuno-inflammatory markers was rated as very low, based on two cross-sectional studies (Sibi et al., 2021, 2025). Downgrading reflected substantial heterogeneity in immune markers and outcome definitions, indirectness arising from evidence generated within a single geographic region, and very serious imprecision due to small sample sizes.

The certainty of evidence for endocrine and metabolic markers was rated as very low, based on a single cross-sectional study (Sibi et al., 2022), with downgrading for indirectness (evidence from a single geographic region) and very serious imprecision (small sample size).

Evidence for both clinical outcomes related to ADLA (Kubal et al., 2025) and multimorbidity (Sinha et al., 2025) was rated as very low**,** as each outcome was informed by a single study. The ADLA study was downgraded because of indirectness and very serious imprecision, whereas the multimorbidity study was additionally downgraded for risk of bias, as LF was ascertained without laboratory confirmation and outcomes were self-reported features inherent to its large-scale community-based design. Formal testing for publication bias was omitted given the small study sample size. Overall, the certainty of evidence ranged from low to very low across all outcome

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domains, with downgrading primarily reflecting indirectness, imprecision, and the observational nature of the available evidence. The complete GRADE assessment is presented in Table 3.

Table 3. Certainty of evidence assessment using the GRADE approach for outcomes evaluating the association between lymphatic filariasis and diabetes mellitus

Outcome	No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Certainty
Epidemiological association between LF and DM	2 (Aravindhan et al., 2010a, 2010b)	Observational	Not serious	Not serious	Serious	Serious	Not assessed	**Low**
Immuno-inflammatory markers	2 (Sibi et al., 2021, 2025)	Observational	Not serious	Serious	Serious	Very serious	Not assessed	**Very Low**
Endocrine and metabolic markers	1 (Sibi et al., 2022)	Observational	Not serious	Not applicable	Serious	Very serious	Not assessed	**Very Low**
Clinical outcomes (ADLA episodes)	1 (Kubal et al., 2025)	Observational	Not serious	Not applicable	Serious	Very serious	Not assessed	**Very Low**
Multimorbidity outcomes	1 (Sinha et al., 2025)	Observational	Serious	Not applicable	Serious	Very serious	Not assessed	**Very Low**

4.5 Qualitative Synthesis

Because the included studies differed substantially in methodology, populations, and clinical focus, findings were synthesised narratively across five outcome domains: epidemiological associations between LF and DM, immuno-inflammatory responses, endocrine and metabolic effects, clinical outcomes related to acute dermatolymphangioadenitis (ADLA), and multimorbidity.

4.5.1 Evidence from Epidemiological Studies

Two cross-sectional studies evaluated the relationship between LF and DM, and both found lower LF prevalence among participants with diabetes than among comparison groups (Aravindhan et al., 2010a, 2010b). In the CURES 83 study, LF prevalence was significantly lower among participants with T2DM than among normoglycaemic controls, and LF-positive participants with diabetes also showed reduced circulating pro-inflammatory cytokine responses (Aravindhan et al., 2010a). A second study involving individuals with T1DM similarly found no LF cases among participants with

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T1DM, compared with an LF prevalence of 2.6% among normoglycaemic controls. The diabetic group also had significantly lower concentrations of filaria-specific IgG4 (Aravindhan et al., 2010b).

4.5.2 Immuno-inflammatory Responses.

Three cross-sectional studies described immuno-inflammatory findings from experimental assessments in LF and DM comorbidity using whole-blood stimulation with toll-like receptor (TLR) ligands or filarial antigens and/or measurement of circulating inflammatory mediators (Aravindhan et al., 2010a; Sibi et al., 2021, 2025).

Aravindhan et al. *(2010a)* assessed differences in inflammatory profiles between LF-positive and LF-negative participants with diabetes, while Sibi et al. (2021, 2025) assessed antifilarial immune responses among LF-positive participants with and without diabetes.

In general, diabetes–LF comorbidity was associated with changes in inflammatory and immune parameters across the three studies; however, the direction and magnitude of effects differed according to the biomarkers assessed, immune compartments, and experimental conditions. These findings are summarized in Table 4.

Sibi et al. (2021, 2025) alone were used for the GRADE evidence evaluation because these studies directly assessed the effect of diabetes on antifilarial immune responses among LF-positive participants. Aravindhan et al. *(2010a)* was included in the narrative summary because it provided supplementary information on inflammatory differences by LF status among participants with diabetes.

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Table 4. Main findings of immunological and inflammatory studies under LF and DM comorbidity

Study	Design	Population	Key Immune Markers Assessed	Main Finding
Aravindhan et al., 2010a (CURES 83) (Aravindhan et al., 2010a)	Cross-sectional	T2DM with/without LF, South India (n=1,416)	Serum cytokines: IL-6, TNF-α, GM-CSF, TGF-β, IL-10,IL-13.	Serum IL-6 and GM-CSF significantly reduced in LF-positive versus LF-negative diabetic subjects; TGF-β raised in diabetic subjects overall but did not differ by LF status.
Sibi et al., 2021 (Sibi et al., 2021)	Cross-sectional	LF-positive subjects with/without T2DM, South India	TLR-induced and antigen-induced cytokines, chemokines, defensins, Th polarization, Cox-2/IDO expression	Diabetes augmented TLR-mediated IL-10, IL-1Ra, IL-9, IL-33, SDF-1 and Cox-2/IDO expression; enhanced Th9 polarization in DM-LF group
Sibi et al., 2025 (Sibi et al., 2025)	Cross-sectional	LF-positive subjects with/without T2DM, South India	Plasma innate/adaptive cytokines, chemokines, redox markers, Tregs, exhausted T-cells	Diabetes specifically reduced circulating IL-1β, IL-1Ra, DEF-A1, IL-8, and lipid peroxidation; increased VEGF; most adaptive immune markers unaffected by diabetes co-morbidity

4.5.3 Endocrine and metabolic effects

One cross-sectional study evaluated endocrine and metabolic parameters among individuals with metabolic syndrome and active lymphatic filariasis (LF) (Sibi et al., 2022). Compared with uninfected individuals with metabolic syndrome, active LF infection was associated with altered concentrations of incretins, adipokines, and other metabolic hormones. These endocrine differences were no longer observed at the 10-year follow-up after all previously LF-positive participants had cleared their infection, indicating that the observed endocrine changes were associated with active rather than resolved infection. A detailed summary of the endocrine and metabolic findings is presented in **Table 5**.

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Table 5. Main findings of the endocrine and metabolic assessment study under LF and DM comorbidity

Study	Design	Population	Biomarkers Assessed	Comparison Groups	Main Finding
Sibi et al., 2022 (Sibi et al., 2022)	Cross-sectional (baseline and 10-year follow-up)	Metabolic syndrome subjects with/without LF, South India (n=88)	Pancreatic hormones: insulin, glucagon; Incretins: ghrelin, GIP, GLP-1; Adipokines: adiponectin, leptin, adipsin, resistin, visfatin, PAI-1	MS-LF+ vs MS-LF− at baseline and 10-year follow-up	Active LF infection associated with elevated ghrelin, GIP, and GLP-1 and reduced adipsin in MS-LF+ compared to MS-LF- at baseline, whereas insulin and glucagon were elevated in metabolic syndrome irrespective of LF status; all effects were absent at 10-year follow-up after infection clearance, indicating that the LF-associated changes are dependent on active infection

4.5.4 Clinical and multimorbidity outcomes.

No significant association was observed between diabetes and the frequency or severity of acute dermatolymphangioadenitis (ADLA) among patients with filarial lymphoedema. Instead, lymphoedema severity (grade 3/4) and the presence of intertrigo were identified as the strongest predictors of ADLA risk, whereas diabetes showed a non-significant trend towards fewer and less frequent ADLA episodes (Kubal et al., 2025). In a separate community-based study involving 584 individuals with LF, the overall prevalence of multiple long-term conditions (MLTC) was 68.8%. Diabetes commonly clustered with hypertension and peptic ulcer disease, and increasing numbers of chronic conditions were associated with progressively poorer self-rated health (Sinha et al., 2025).

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5 Discussion

5.1 Epidemiological associations

The main epidemiological observation from this review was an inverse relationship between LF and diabetes. This relationship was observed in the two human studies for which data were adequate to examine this outcome. Both cross-sectional studies from southern India found that study participants with diabetes had a lower prevalence of LF compared with individuals without diabetes (Aravindhan et al., 2010a, 2010b). Among participants in the CURES 83 study, LF prevalence was lower among participants with newly diagnosed or established diabetes than among age- and sex-matched participants without diabetes. In the same study, LF was associated with reduced proinflammatory cytokine responses among diabetic participants compared with diabetic participants without LF, providing complementary evidence of differences in inflammatory responses between these groups (Aravindhan et al., 2010a).

Findings among participants with T1DM were suggestive of a similar phenomenon. Aravindhan et al. (2010b) reported zero cases of LF among 200 participants with T1DM, compared with 14 of 562 participants with normal glucose tolerance (2.6%). Positivity for filaria-specific IgG4 was substantially lower among participants with T1DM than controls, whereas antifilarial IgG levels, interpreted as a marker of previous exposure, did not differ significantly between groups. These findings provide epidemiological evidence for an inverse relationship between LF and T1DM, while the accompanying serological findings suggest that the difference was more closely related to current LF infection than to previous exposure (Aravindhan et al., 2010b).

Overall, the two studies raise the possibility that the relationship between LF and diabetes extends to both T1DM and T2DM. Whether the biological processes underlying this relationship are shared between diabetes phenotypes cannot yet be determined from these two studies alone. Additionally, the association between LF and diabetes should not be interpreted as evidence that LF protects against diabetes or vice versa. Both epidemiological studies included in this review were cross-

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sectional; therefore, the temporal order of infection and disease diagnosis could not be ascertained. Differences between participant groups in characteristics such as infection status, diabetes phenotype, and other unmeasured factors may also have contributed to the observed differences. The available evidence therefore supports an epidemiological association between LF and diabetes, but does not establish causality.

5.2 Potential Immunological Mechanisms

While epidemiological evidence supporting this hypothesis is currently sparse, immunological findings provide a plausible biological basis for an interaction between LF and metabolic disease. Persistent filarial infection induces regulatory immune responses characterised by expansion of Tregs, increased IL-10 and TGF-β production, attenuation of pro-inflammatory effector responses, and changes in Th1, Th2, and regulatory immune responses (Hoerauf et al., 2005; Rajamanickam & Babu, 2025). These immunomodulatory pathways likely reflect host adaptation that limits pathology during chronic filarial infection. Thus, it is biologically plausible that regulatory processes activated during chronic filarial infection also influence inflammation relevant to insulin resistance or type 2 diabetes, although this has not yet been demonstrated conclusively (Fernández-Real & Ricart, 2003; Rehman & Akash, 2016; Rennie et al., 2021).

The human studies did not show a consistent pattern of immune suppression among people with LF and DM comorbidity. Aravindhan et al. *(2010a)* found significantly lower circulating IL-6 and GM-CSF among LF-positive than LF-negative participants with diabetes, suggesting a less pro-inflammatory circulating profile among LF-positive participants. (Sibi et al., 2021) found a different pattern, with enhanced immune responses to TLR stimulation, greater Th9 polarisation, and increased expression of IL-9, IL-33, SDF-1, Cox-2, and IDO among LF-positive participants with diabetes. (Sibi et al., 2025) identified yet another pattern, with lower circulating IL-1β, IL-1Ra, DEF-

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A1, and IL-8 and higher VEGF in the diabetes–LF group, while most measured adaptive immune markers did not differ significantly by diabetes status. Differences according to diabetes status were therefore observed across these studies, suggesting that diabetes may affect some but not all components of the immune response to filarial infection or exposure rather than uniformly shifting LF-positive individuals towards inflammatory or regulatory immunity (Aravindhan et al., 2010a; Sibi et al., 2021, 2025).

Variation between these studies may relate partly to biological and methodological factors that can shape immune profiles. Immune activity was assessed in different sample sizes and participant populations, across different immune compartments, using different stimulation approaches and panels of immune biomarkers. Aravindhan et al. *(2010a)* measured circulating cytokines in a large epidemiological study population. In contrast, (Sibi et al., 2021) examined cellular responses following stimulation with TLR ligands and selected filarial antigens. (Sibi et al., 2025) measured innate and adaptive immune markers, redox parameters, regulatory T cells, and exhausted T cells in circulation. Because these studies did not measure identical immune parameters, comparisons were necessarily based on subsets of the available data. Differences between their findings may therefore reflect differences in experimental and biological context rather than direct contradiction. Additional studies will be required to determine whether these findings are reproducible across populations and settings.

Experimental studies provide additional support for immune regulation during LF infection or exposure, although they cannot demonstrate that these mechanisms apply to individuals with LF and diabetes. Experimental filarial infection or filarial antigen exposure was associated with improved glucose tolerance and reduced autoimmune diabetes in mouse models (Berbudi et al., 2016; Hübner et al., 2009, 2012, 2025). Mechanisms explored in these models include expansion of Tregs, TGF-β signalling, altered regulation of adipokines, and IL-9-mediated immunomodulation (Berbudi et al.,

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2016; Hübner et al., 2009, 2012, 2025). Thus, multiple interacting mechanisms may contribute to metabolic effects associated with helminth infection, although the specific components operating in humans have not been established. Observational research from broader helminth epidemiology has associated helminth infection with lower fasting glucose and reduced prevalence of metabolic syndrome (Hays, 2018; Pham et al., 2023)**.** However, whether helminth infection has a sufficient effect on glucose metabolism to provide meaningful protection from diabetes in humans remains unclear.

Endocrine activity provides another biologically plausible pathway linking active LF infection with metabolic regulation. Ghrelin, glucose-dependent insulinotropic polypeptide (GIP), glucagon-like peptide-1 (GLP-1), and adipsin concentrations differed between participants with metabolic syndrome who had LF infection and those with metabolic syndrome who did not, according to (Sibi et al., 2022)**.** These differences were no longer detectable at the 10-year follow-up, when the previously LF-positive participants had cleared their infection, suggesting that the observed endocrine differences were more closely associated with active infection than with prior exposure (Sibi et al., 2022). Treatment of other helminth infections has also been reported to influence metabolic hormones, including GIP, GLP-1, insulin, and leptin, indicating that active helminth infection may influence metabolic regulation (Pham et al., 2023; Tahapary et al., 2017).

Several limitations are relevant to the interpretation of these findings.Sibi et al. (2022) used circulating filarial antigen as a measure of active infection. Metabolic hormones and adipokines can also be influenced by body composition, sex, diet, physical activity, and other metabolic factors that were not consistently accounted for in the analysis (Sibi et al., 2022). Additionally, this study was conducted within the same South Indian research programme as several other studies included in this review. Findings from other populations are therefore needed to determine whether the observed endocrine associations are reproducible. Although suggestive of a mechanism through which active

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LF infection may modify metabolism, the findings from (Sibi et al., 2022) are not definitive. Taken together with the immunological findings from human and experimental research, the available evidence supports the possibility that LF-associated immunomodulation and endocrine changes may influence metabolic activity in a context-dependent manner, but does not establish a causal mechanism. Longitudinal and experimental studies in larger and more diverse populations are necessary to test this hypothesis.

5.3 Clinical Outcomes and Multimorbidity

Evidence on clinical outcomes was available from two studies, although each addressed a different aspect of LF–DM comorbidity. In patients with filarial lymphoedema, Kubal et al. (2025) found no significant association between diabetes and either the frequency or severity of ADLA episodes. By comparison, higher lymphoedema grade and intertrigo showed stronger associations with ADLA risk than diabetes status. This finding places greater emphasis on management of lymphoedema severity and skin-barrier complications, including intertrigo, within MMDP care.

In a separate community-based study, Sinha et al. (2025) found that multimorbidity was common among people affected by LF, with 68.8% reporting multiple long-term conditions. Diabetes was among the conditions contributing to the observed multimorbidity patterns, including clusters with hypertension and peptic ulcer disease. The number of coexisting chronic conditions was also associated with progressively poorer self-rated health, indicating that the clinical burden in LF-affected populations extends beyond the manifestations of filarial disease itself. Taken together, these findings indicate that clinical management of LF should consider coexisting chronic conditions, particularly where diabetes and other non-communicable diseases contribute to multimorbidity.

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5.4 Strengths and Limitations

The review followed PRISMA 2020 guidance (Page et al., 2021) and was prospectively registered with PROSPERO. Multiple bibliographic databases were searched, and established methods were used for study selection, data extraction, risk-of-bias assessment, and certainty-of-evidence evaluation. By bringing together epidemiological, immunological, endocrine, and clinical evidence on LF and DM, this review integrates findings from different areas of investigation and provides a broader synthesis of the available evidence.

Nevertheless, there are a number of limitations that should be considered when interpreting the results of this review. Firstly, the body of evidence included in this review was small, consisting of seven studies from India, of which five were from the same South Indian programme. Despite these studies providing important data on the epidemiological and biological links between LF and diabetes, the fact that they are concentrated within a single endemic setting limits confidence that the findings can be generalised to other settings. Studies from independent populations living in other endemic areas are required to corroborate the results observed in this review.

None of the included studies were interventional in design. As such, causal relationships between LF and DM cannot be inferred from observational data, and the evidence may be susceptible to residual confounding or selection bias. Heterogeneity in participant characteristics, LF/DM case definitions, laboratory methods, and biomarker panels also limited comparability between studies and contributed to the low certainty of evidence. Furthermore, most studies assessed LF status using detection of circulating filarial antigen (CFA). Although CFA detection is useful for determining current infection status, it cannot differentiate between previously infected individuals and those who have never been infected with LF. Nor can CFA differentiate between microfilaraemic and amicrofilaraemic infection. This could have led to some misclassification of exposure status.

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Diabetes case definition also varied between studies. The majority of included studies used glycated haemoglobin (HbA1c), which cannot independently distinguish between type 1 and type 2 diabetes. However, the principal studies additionally used both C-peptide and glutamic acid decarboxylase (GAD) autoantibody assays to help classify diabetes type and thereby reduce this limitation. Therefore, some uncertainty may remain around outcomes for which HbA1c was the sole classification criterion.

Finally, no eligible studies were identified from sub-Saharan Africa. Given the substantial burden of both LF and diabetes in the region, the absence of evidence represents an important geographical gap. It therefore remains unclear whether findings from predominantly South Asian populations can be generalised to other LF-endemic settings. Studies assessing LF status and diabetes in sub-Saharan Africa are needed to evaluate the generalisability of the current evidence.

5.5 Research and Public Health Implications

Several research and practice priorities emerge from these findings. First, studies from India have identified an inverse association between LF and diabetes; however, this finding should be explored in other endemic populations, particularly in sub-Saharan Africa and Southeast Asia. Prospective studies with standardised definitions and assessments of LF infection and metabolic outcomes, alongside immunological and endocrine biomarkers where possible, are needed to determine whether the epidemiological association is reproducible and whether biological alterations observed in individual studies are consistent across populations and settings.

Longitudinal research would also allow investigation of whether metabolic and immune alterations differ according to the presence or clearance of active LF infection. Undertaking such work concurrently with LF elimination efforts and mass drug administration campaigns could help determine whether changes in infection status are accompanied by changes in markers of immune

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regulation, endocrine function, and glycaemic status. Findings from such studies would provide stronger evidence regarding temporality than can be obtained from the primarily cross-sectional studies included in this review.

Integrated approaches to care may also be relevant based on these clinical findings. The reported high prevalence of multimorbidity among LF-affected populations, alongside the identification of diabetes as one of several conditions contributing to these multimorbidity patterns, suggests that chronic disease care should be considered alongside LF morbidity services. If resources allow, diabetes screening and management could be integrated into lymphoedema care packages, while diabetes services in endemic settings could consider the relevance of LF screening and management for patients diagnosed with diabetes. Implementation studies are needed to evaluate the feasibility, impact, and effectiveness of such strategies.

In a broader context, delineation of the relationship between LF and diabetes may shed light on how persistent helminth infections interact with metabolic and immune mechanisms. At present, the evidence base is too limited to determine whether these alterations are clinically meaningful or whether they differ according to infection status or diabetes phenotype.

Conclusion

In this systematic review, a small, geographically concentrated evidence base was identified regarding the association between LF and DM. Seven eligible studies were included, all of which were performed in India. Available epidemiological evidence indicated an inverse association between LF and diabetes, including both T1DM and T2DM. Immunological and endocrine findings provided biological plausibility for these observations and indicated that active filarial infection may alter inflammatory, regulatory, innate immune, and metabolic pathways. Among people with filarial lymphoedema, diabetes was not associated with the frequency or severity of ADLA, whereas

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multimorbidity was common among people affected by LF. Findings from the available evidence should nevertheless be interpreted cautiously. Included studies were limited by observational study design, the available evidence was geographically restricted to India, and certainty was low to very low across outcomes. Important uncertainties therefore remain regarding causality, the mechanisms underlying the observed associations, and generalizability to other LF-endemic populations. The small number of studies and absence of eligible evidence from sub-Saharan Africa further restrict the generalizability of the findings. Future research should assess whether epidemiological associations identified in this review can be reproduced in other endemic settings and whether active LF infection is associated with longitudinal changes in immune, endocrine, and glycaemic outcomes. Prospective and mechanistic studies including participants from diverse LF-endemic populations, particularly in sub-Saharan Africa, are needed to address these uncertainties and determine whether the observed association between LF and diabetes is reproducible and clinically meaningful.

Declarations

Ethics approval and consent to participate

Not applicable. This study was a systematic review and did not involve the collection of new data from human participants or animals.

Consent for publication

Not applicable.

Availability of data and materials

The data extracted and analysed during this systematic review are available from the corresponding author upon reasonable request.

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Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Abdallah A. Ngenya conceived and led the systematic review, developed the review protocol, coordinated the review process, conducted the literature review and data synthesis, and drafted the manuscript. **Said S. Aboud, Inge Kroidl, and Indulekha Karunakaran** contributed to the conceptualisation, methodological development, supervision, interpretation of findings, and critical revision of the manuscript. **Emanuel A. Mpolya** provided overall doctoral supervision, contributed to the scientific direction of the review, and critically reviewed the manuscript. **Abdallah Yusuph and Jonathan Akyoo** independently screened the identified articles and assessed eligibility against the prespecified criteria.

Joseph Boniface Nkuba served as the third reviewer and resolved disagreements between the first and second screeners. **Marc P. Hübner, Akili Kalinga, Bettina Pitter, Ute Klarmann-Schulz, Achim Hoerauf, and Benjamin Lenz** critically reviewed successive drafts and contributed to the refinement of the manuscript. All authors reviewed and approved the final manuscript.

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Use of AI-assisted tools

QuillBot Microsoft Word Add-in (version 1.3.57) was used for language editing, sentence refinement, grammar and readability. Quillbot was not used to make decisions regarding study eligibility, nor to generate study results, perform statistical analyses, or generate figures. Study eligibility decisions were conducted by human reviewers based on prespecified criteria and conflicts were resolved by consulting a third reviewer. Authors are responsible for the accuracy, originality, interpretation and integrity of the manuscript.

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7 Supporting information

S1 Checklist. PRISMA 2020 Checklist.

S2 Appendix. Full search strategies and reasons for exclusion.

S3 Appendix. PROSPERO registration record (review protocol).

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