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SYSTEMATIC REVIEW AND META-ANALYSIS

Circulating Tumour Necrosis Factor-Alpha and Interleukin-6 in Diabetic Peripheral Neuropathy: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Chronic low-grade inflammation is increasingly implicated in diabetic peripheral neuropathy (DPN). Tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) have been proposed as circulating correlates of nerve injury, yet the evidence is inconsistent, a previous synthesis addressed TNF-α alone, and no pooled estimate has ever been reported for IL-6.

Objective: To determine whether circulating TNF-α and IL-6 concentrations differ between diabetic patients with and without peripheral neuropathy, and to quantify the magnitude, precision, and consistency of any difference.

Methods: Four databases were searched for observational studies reporting serum or plasma TNF-α and/or IL-6 in diabetic patients with versus without neuropathy. Standardised mean differences (SMD, Hedges g) were pooled using a random-effects model, with Hartung–Knapp adjustment, restricted maximum-likelihood re-estimation, cluster-collapsed and leave-one-out analyses, and a prediction interval. Risk of bias used the Newcastle–Ottawa Scale and certainty the GRADE framework.

Results: Four studies (476 participants; 249 with DPN, 227 without) provided seven cytokine comparisons. The overall SMD was 0.70 (95% CI 0.22–1.18; p = 0.005; I^2 = 91%), robust across all sensitivity analyses. The effect was driven by IL-6, which was significantly and homogeneously elevated (SMD 0.65, 95% CI 0.42–0.87; I^2 = 2%). Pooled TNF-α was higher but non-significant and heterogeneous (SMD 0.71, 95% CI −0.18–1.60; I^2 = 95%), owing to one statin-treated cohort; excluding it raised the estimate to 0.88. Certainty was low for IL-6 and very low for TNF-α.

Conclusion: DPN is associated with higher circulating pro-inflammatory cytokines, with IL-6 the most consistent correlate and the first for which a pooled estimate is available. IL-6 merits prospective evaluation as a biomarker of neuropathy risk. Findings are hypothesis-generating.

1. Introduction

Diabetes mellitus is a chronic metabolic disorder defined by sustained hyperglycaemia arising from defective insulin secretion, impaired insulin action, or both. It affected an estimated 11.1% of the global adult population, corresponding to 589 million adults, and is projected to reach 853 million by 2050, with a disproportionate and growing burden in low- and middle-income countries, including those of South-East Asia.[1] As the population living with diabetes expands, so too does the population at risk of its chronic complications, of which peripheral neuropathy is among the most frequent and disabling.[2]

Diabetic peripheral neuropathy (DPN) is defined by clinical signs or symptoms of peripheral nerve dysfunction in a person with diabetes once other causes have been excluded. Its predominant phenotype is a distal symmetric sensorimotor polyneuropathy that produces sensory loss, neuropathic pain, and, in advanced disease, motor impairment. For the practising neurologist the condition poses several characteristic difficulties: its onset is frequently insidious and often asymptomatic when nerve damage first becomes detectable; nerve conduction studies, although the reference standard for large-fibre disease, are insensitive to the small-fibre injury that underlies much early and painful neuropathy; and no validated blood-based test yet identifies, ahead of overt clinical disease, the patients who will progress to painful neuropathy, foot ulceration, or amputation. The pooled global prevalence of painful diabetic neuropathy among affected patients approaches one half, underscoring the scale of the unmet need.[2]

The pathogenesis of DPN is multifactorial. Hyperglycaemia and dyslipidaemia activate several interconnected injurious cascades — the polyol, protein kinase C, advanced glycation end-product, hexosamine, and poly(ADP-ribose) polymerase pathways — which converge upon oxidative stress, mitochondrial dysfunction, and axonal degeneration.[3]

Superimposed upon these metabolic mechanisms, chronic low-grade inflammation has emerged as a central and potentially modifiable component. Immune cells, and macrophages in particular, infiltrate injured peripheral nerves and can modulate the tempo of sensory axon loss,[4] and circulating inflammatory cytokines have been causally implicated in the development of diabetic neuropathy in genetic epidemiological analyses.[5] For the purposes of this review, the term pro-inflammatory cytokine denotes a secreted immune-signalling protein, principally of monocyte or lymphocyte origin, that promotes rather than resolves the inflammatory response.

Two such cytokines have been studied most intensively. Tumour necrosis factor-alpha (TNF-α) is a monocyte-derived cytokine that promotes vascular inflammation, oxidative stress, and endothelial dysfunction, that induces downstream mediators through nuclear factor-κB signalling, and that can be directly toxic to Schwann cells; its neuro-inflammatory activity is attenuated by several disease-modifying interventions in experimental diabetic neuropathy.[6] Interleukin-6 (IL-6) is a pleiotropic cytokine that is simultaneously a principal driver of the hepatic acute-phase response and, in certain experimental contexts, a mediator with neurotrophic and reparative properties. Both are induced downstream of hyperglycaemia,[7] and both have been reported to be elevated in patients with DPN across numerous, though not entirely concordant, observational studies.

The existing evidence is nonetheless incompletely synthesised. A previous meta-analysis pooled studies of TNF-α and reported significantly higher serum concentrations in type 2 diabetic patients with neuropathy than in those without,[8] but that synthesis did not evaluate IL-6, for which no pooled estimate has ever been reported, and it did not incorporate several informative studies published subsequently. A clinically relevant evidence gap therefore persists concerning the two most frequently measured pro-inflammatory cytokines, and in particular concerning IL-6.

The novelty of this study lies in providing the first quantitative meta-analytic estimate of the association between circulating IL-6 and diabetic peripheral neuropathy, in updating the pooled evidence for TNF-α with more recent studies, and in comparing the two mediators within a single, internally consistent analytical framework that formally accounts for cohorts contributing more than one cytokine. The aim of this study was to determine whether circulating TNF-α and IL-6 concentrations differ between diabetic patients with and without peripheral neuropathy, to quantify the magnitude, precision, and consistency of any difference, and to identify the sources of heterogeneity so that the clinical and mechanistic implications can be appraised.

2. Methods

2.1. Protocol, reporting, and review question

This systematic review and meta-analysis was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement. The review question was framed using the PECO structure: the population comprised adults with diabetes mellitus; the exposure was the presence of diabetic peripheral neuropathy, encompassing distal sensorimotor polyneuropathy and both painful and painless forms; the comparator was diabetic patients without neuropathy; and the outcome was the circulating serum or plasma concentration of TNF-α and IL-6. Because the constituent studies employed several overlapping terms, the exposure was operationalised as any physician-diagnosed or instrument-ascertained peripheral neuropathy attributable to diabetes, and the manner of ascertainment in each study was recorded. Painful and painless cases were combined into a single neuropathic arm for the primary analysis.

2.2. Search strategy and eligibility

PubMed, Scopus, the Cochrane Central Register of Controlled Trials, and Google Scholar were searched. The core Boolean string was: (“diabetic peripheral neuropathy” OR “distal sensorimotor polyneuropathy” OR “diabetic neuropathy”) AND (“tumor necrosis factor” OR “TNF-alpha” OR “interleukin-6” OR “IL-6” OR “pro-inflammatory cytokine”) AND (“serum” OR “plasma” OR “circulating” OR “level”). The string was adapted to each database, and equivalent Medical Subject Heading terms were incorporated in PubMed. No language restriction was imposed; records whose group-level data could not be reliably verified were not carried into the quantitative synthesis, a decision noted as a potential source of language bias. Reference lists of retrieved articles and of the previous TNF-α meta-analysis were hand-searched. Studies were eligible if they were observational investigations of adults with diabetes that measured serum or plasma TNF-α and/or IL-6 and reported these concentrations separately for neuropathic and non-neuropathic diabetic patients as a mean with standard deviation or a median with interquartile range. Reviews, animal or in-vitro experiments, comparisons against healthy non-diabetic controls only, and studies reporting cytokines solely as per-standard-deviation risk estimates were excluded; the direction of the latter was examined qualitatively so that their evidence was not lost.

2.3. Data extraction, risk of bias, and certainty

For each included study the first author, year, country, design, method of neuropathy ascertainment, diabetes type, group sample sizes, and the mean and standard deviation of each cytokine were extracted and verified against the source, and each study was confirmed to possess a valid digital object identifier. Where a study reported the outcome by severity strata or pain status, the subgroups were combined into a single neuropathic arm using the Cochrane group-combination formula. Where medians and interquartile ranges were

reported, means and standard deviations were reconstructed using the method of Wan and colleagues, and the influence of this reconstruction was tested by sensitivity analysis. Because all eligible studies were observational, methodological quality was appraised with the Newcastle–Ottawa Scale across selection, comparability, and outcome or exposure ascertainment; the Cochrane risk-of-bias tool (RoB 2.0) specified in the analytic template applies only to randomised trials and was therefore not applicable, and this deliberate deviation is recorded on the corresponding figure. The certainty of evidence for each cytokine was rated using the GRADE framework.

2.4. Statistical analysis

The effect measure was the standardised mean difference expressed as Hedges g, chosen to harmonise the different assays and units used across studies; the small-sample correction of Hedges was applied. A standardised mean difference is a unitless measure of the separation between two groups relative to their pooled standard deviation and cannot be translated into a diagnostic threshold. Effect sizes were pooled using a random-effects model with the DerSimonian–Laird estimator of between-study variance (τ^2). Because two cohorts contributed both a TNF-α and an IL-6 estimate, three measures accommodated the resulting non-independence: a Hartung–Knapp adjustment, reported as the primary interval; a restricted maximum-likelihood re-estimation of τ^2 as a cross-check; and a cluster-collapsed analysis in which each cohort was reduced to a single averaged effect. Heterogeneity was quantified with the I^2 statistic and the χ^2-based Q test, with I^2 above 75% regarded as substantial, and a prediction interval was calculated. Subgroup analysis was pre-planned by cytokine, robustness was examined by leave-one-out analysis, and the influence of the median-reconstructed study was tested by its removal. Because fewer than ten estimates were pooled, formal small-study-effect testing was not appropriate and publication bias was assessed by visual inspection of the funnel plot. Analyses were performed in Python (NumPy and SciPy) and R (packages meta and metafor); a two-sided p-value below 0.05 was considered significant.

3. Results

3.1. Study selection

The database search identified 288 core PubMed records together with additional records retrieved from the remaining registers. After removal of duplicates, 168 records were screened on title and abstract, of which 141 were excluded as reviews, animal or in-vitro experiments, records without a comparison between diabetic patients with and without neuropathy, or records reporting other outcomes. Twenty-seven full texts were assessed for eligibility and fifteen were excluded at the full-text stage: the largest group because cytokine concentrations were reported only as per-standard-deviation odds or hazard ratios rather than group means, as in the population-based cohort analyses; others because only medians without usable dispersion measures were presented, because the comparison was against healthy non-diabetic controls, or because group-level data could not be verified. Twelve studies were retained for qualitative synthesis, of which four provided extractable group-level means and standard deviations and entered the quantitative meta-analysis, contributing seven cytokine-specific effect estimates. The selection process, with exact counts at each stage, is shown in Figure 1.

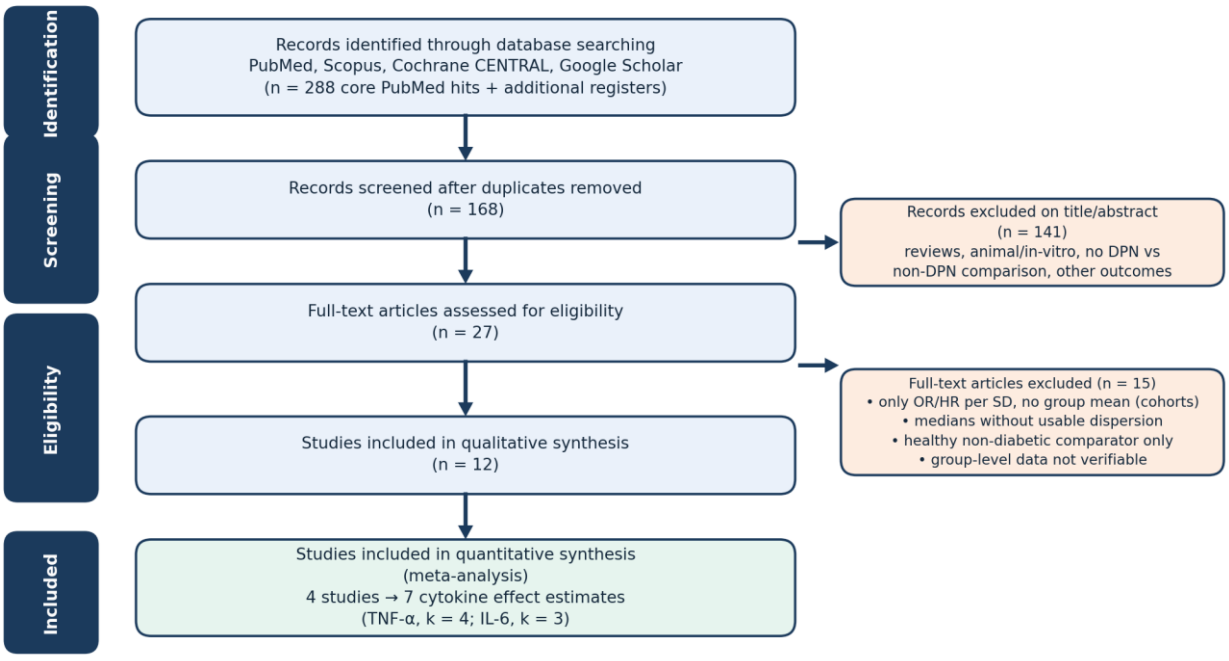

Figure 1. PRISMA 2020 flow diagram of study identification, screening, eligibility, and inclusion.

3.2. Study characteristics and risk of bias

The four studies contributing to the quantitative synthesis comprised 476 participants, of whom 249 had diabetic peripheral neuropathy and 227 did not.[9–12] Two were cross-sectional, one was a case-control study, and one contributed baseline data from a five-year prospective cohort. Neuropathy was ascertained by nerve conduction studies with a clinical score in one study, by the Michigan Neuropathy Screening Instrument in two, and by a validated clinical diagnosis in one; this variation in case definition, spanning objective electrophysiology and clinical screening, is a source of clinical heterogeneity considered below. Cytokines were measured by chemiluminescence, multiplex immunoassay, or flow cytometry. The full characteristics of each study are summarised in Table 1.

Table 1. Characteristics of the studies included in the quantitative synthesis.

Study	Country	Design	Neuropathy ascertainment	Cytokine(s)	n DPN / non-DPN	Assay
Li 2017	China	Cross-sectional	Nerve conduction studies + TCSS	TNF-α, IL-6	30 / 40	Chemiluminescence
Zheng 2021	China	Cohort (baseline)	MNSI	TNF-α, IL-6	63 / 43	Multiplex (Luminex)
Abdulrhaman 2024	Iraq	Case-control	Clinical DPN diagnosis	TNF-α	70 / 70	ELISA
Huang 2025	China	Cross-sectional	MNSI severity nomogram	TNF-α, IL-6	86 / 74	Flow cytometry

DPN, diabetic peripheral neuropathy; ELISA, enzyme-linked immunosorbent assay; IL-6, interleukin-6; MNSI, Michigan Neuropathy Screening Instrument; TCSS, Toronto Clinical Scoring System; TNF-α, tumour necrosis factor-alpha.

On the Newcastle–Ottawa Scale the studies scored between six and eight of nine stars, indicating low to moderate risk of bias; the principal limitation was incomplete adjustment for confounders in the two smaller studies, as detailed in Figure 2.

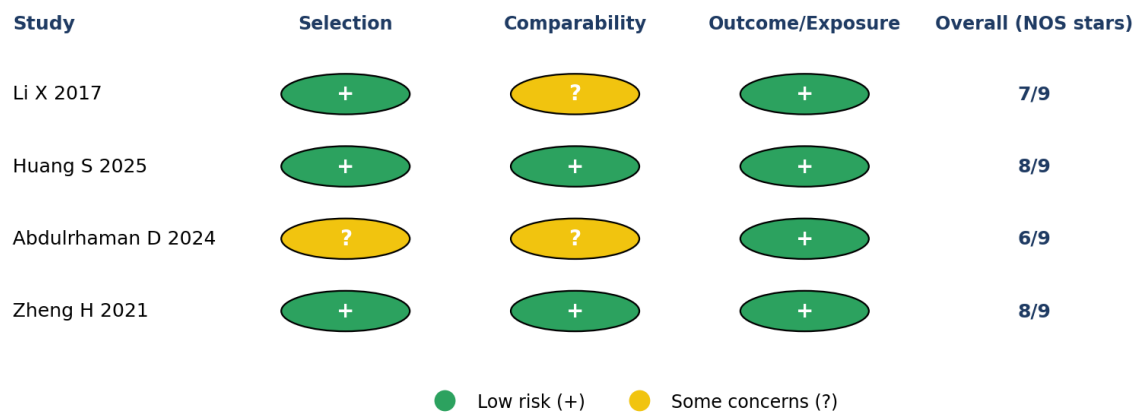

Figure 2. Risk-of-bias summary (Newcastle–Ottawa Scale). The Cochrane RoB 2.0 tool was not applicable because all included studies were observational; the substitution is a deliberate methodological deviation.

3.3. Cytokine-specific analyses

Consistent with the divergent behaviour of the two mediators, the cytokine-specific estimates are presented first, and both are displayed with the overall summary in Figure 3. For IL-6, based on three estimates, the pooled standardised mean difference was 0.65 (95% CI 0.42 to 0.87; $p < 0.001$) with negligible heterogeneity (I^2 = 2%, τ^2 = 0.001); the Hartung–Knapp interval likewise excluded the null (0.15 to 1.14; p = 0.030). Every IL-6 estimate was positive and of similar magnitude, indicating a consistent elevation of circulating IL-6 in neuropathic patients.[9–12] An effect of this size implies that a substantial majority of neuropathic patients had IL-6 concentrations above the median of the non-neuropathic group. For TNF-α, based on four estimates, the pooled standardised mean difference was 0.71 (95% CI −0.18 to 1.60; p = 0.12) but with extreme heterogeneity (I^2 = 95%). Three of the four TNF-α estimates were strongly positive, whereas one cross-sectional study reported lower TNF-α in the neuropathic group (SMD −0.37, 95% CI −0.69 to −0.06);[12] this single discordant dataset accounts for the wide confidence interval and for the failure of the pooled TNF-α estimate to reach significance. The test for a difference between the two cytokine subgroups was not significant.

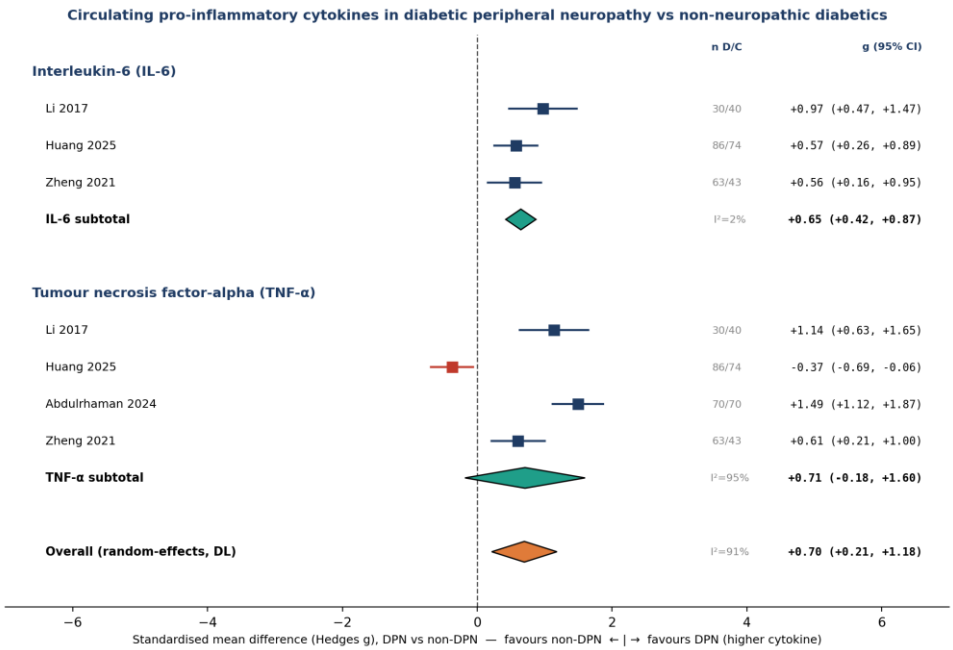

Figure 3. Forest plot of standardised mean differences (Hedges g) in circulating IL-6 and TNF-α between diabetic patients with and without peripheral neuropathy. Squares denote individual estimates (the red marker flags the single discordant TNF-α estimate); diamonds denote random-effects subtotals and the overall estimate.

3.4. Overall pooled effect

Across all seven estimates, circulating pro-inflammatory cytokine concentrations were significantly higher in patients with peripheral neuropathy than in those without. The overall random-effects pooled standardised mean difference was 0.70 (95% CI 0.22 to 1.18; p = 0.005), a moderate-to-large effect, with substantial heterogeneity (I^2 = 91%, τ^2 = 0.38, Q = 65.4, degrees of freedom = 6, p < 0.001). This estimate proved robust to every safeguard applied: the Hartung–Knapp interval remained above the null (0.15 to 1.25; p = 0.021); restricted maximum-likelihood re-estimation gave a near-identical result (0.70, 95% CI 0.25 to 1.15); and the cluster-collapsed analysis produced a materially identical estimate (0.79, 95% CI 0.20 to 1.39). The prediction interval for the overall effect was wide (−1.02 to 2.41), an honest reflection of the between-study dispersion. All pooled estimates with their heterogeneity and robustness analyses are consolidated in Table 2.

Table 2. Pooled estimates, heterogeneity, and robustness analyses.

Analysis	k	SMD (Hedges g)	95% CI	I^2 (%)	p
IL-6 (DerSimonian–Laird)	3	0.65	0.42 to 0.87	2	<0.001
IL-6 (Hartung–Knapp)	3	0.65	0.15 to 1.14	2	0.030
TNF-α (DerSimonian–Laird)	4	0.71	−0.18 to 1.60	95	0.12
Overall (DerSimonian–Laird)	7	0.70	0.22 to 1.18	91	0.005
Overall (Hartung–Knapp)	7	0.70	0.15 to 1.25	91	0.021
Overall (REML cross-check)	7	0.70	0.25 to 1.15	—	—
Overall (cluster-collapsed, 4 studies)	4	0.79	0.20 to 1.39	94	0.009
Overall omitting median-reconstructed study	5	0.75	0.05 to 1.45	94	0.036
Overall omitting discordant TNF-α cohort	6	0.88	0.55 to 1.21	74	<0.001

CI, confidence interval; IL-6, interleukin-6; k, number of effect estimates; REML, restricted maximum likelihood; SMD, standardised mean difference; TNF-α, tumour necrosis factor-alpha.

3.5. Sensitivity analyses, severity gradient, and publication bias

The overall estimate was robust to the sequential omission of individual estimates: leave-one-out pooled standardised mean differences ranged from 0.56 to 0.88, and the lower confidence bound remained above zero in every iteration. As shown in Table 2, removal of the single discordant TNF-α estimate reduced overall heterogeneity from I^2 = 91% to 74% and increased the pooled effect to 0.88 (95% CI 0.55 to 1.21), while removal of the median-reconstructed study left the result essentially unchanged (0.75, 95% CI 0.05 to 1.45). A descriptive examination of the one study reporting cytokines across graded neuropathy severity showed that IL-6 was similar across the absent, mild,

and moderate categories (approximately 6.1, 4.8, and 6.0 pg/mL) but was markedly elevated in the severe category (approximately 25.7 pg/mL); the elevation was therefore confined to the severe stratum rather than following a graded rise across severity, and TNF-α likewise did not increase monotonically.[12] Because fewer than ten estimates were available, a formal Egger regression test was not performed; the funnel plot in Figure 4 is presented for completeness only and did not reveal gross asymmetry, though the small number of estimates precludes firm inference.

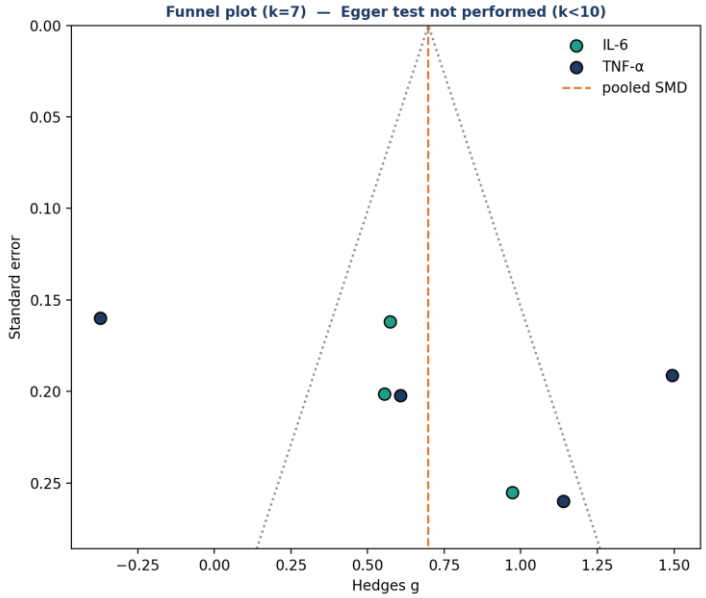

Figure 4. Funnel plot of the seven cytokine effect estimates. No formal small-study-effect test was undertaken because fewer than ten estimates were available.

3.6. Qualitative synthesis and certainty of evidence

The studies that could not be pooled were broadly concordant with the meta-analysis. Population-based cohort data indicated that higher circulating inflammatory burden preceded and predicted incident distal sensorimotor polyneuropathy,[13] and composite inflammatory indices such as the neutrophil-to-lymphocyte ratio were independently associated with prevalent DPN in large clinical series.[14] Several case-control and cross-sectional studies reported elevated TNF-α or IL-6 in neuropathic or advanced-complication patients,[15,16] while a minority found the TNF-α association attenuated after adjustment or absent in statin-treated populations. Applying the GRADE framework, the certainty of evidence for the IL-6 association was rated low — observational evidence not further downgraded for inconsistency or imprecision, the principal residual concern being confounding — whereas the certainty for TNF-α was rated very low, downgraded further for serious inconsistency and imprecision.

4. Discussion

This systematic review and meta-analysis yielded three principal findings. First, taken together, TNF-α and IL-6 were significantly higher in diabetic patients with peripheral neuropathy than in those without, corresponding to a moderate-to-large standardised mean difference of 0.70 that was robust across every sensitivity analysis. Second, and most importantly, this overall signal was driven by IL-6, which showed a consistent, precise, and homogeneous elevation (SMD 0.65, I^2 = 2%) and for which this analysis provides the first pooled quantitative estimate. Third, the pooled TNF-α estimate, although numerically positive and strongly elevated in three of four datasets, did not reach significance and was extremely heterogeneous, a result attributable to a single discordant cohort.[12]

4.1. Interpretation and biological plausibility

The associations are biologically coherent. IL-6 is a central mediator of the acute-phase response, induced downstream of TNF-α through nuclear factor-κB signalling, and circulating inflammatory cytokines have been causally linked to diabetic neuropathy in genetic epidemiological analyses.[5] A mechanistic explanation for why IL-6 behaved more consistently is instructive: IL-6 is a comparatively stable, downstream, integrative marker whose circulating concentration is relatively robust to short-term fluctuation, whereas TNF-α has a short half-life, is secreted in a pulsatile manner, and is more sensitive to sampling conditions, assay platform, and concomitant medication. IL-6 also possesses a recognised functional duality, driving systemic inflammation while, in some experimental settings, supporting nerve conduction. TNF-α, for its part, promotes endothelial dysfunction, microvascular ischaemia, and Schwann-cell toxicity, and its neuro-inflammatory activity is attenuated by disease-modifying interventions in experimental models;[6] these mechanistic strands are consistent with the recognition that immune-cell infiltration and axonal bioenergetic failure act together to produce nerve injury in diabetes.[3,4]

4.2. Comparison with the previous meta-analysis

The most directly comparable prior work pooled fourteen studies and reported significantly higher serum TNF-α in type 2 diabetic patients with neuropathy (SMD 1.20, 95% CI 0.80 to 1.61).[8] The present TNF-α estimate (0.71) points in the same direction but is smaller and non-significant. Three factors reconcile these results: the earlier synthesis included more than three times as many TNF-α datasets and had far greater power; it predated the discordant statin-enriched cohort that widened the present interval;[12] and the stricter requirement here for a directly extractable diabetic non-neuropathic comparator excluded several studies that the earlier work incorporated. When the discordant cohort was removed, the TNF-α-inclusive overall estimate rose to 0.88 with markedly reduced heterogeneity, approaching the earlier figure. The present work extends this literature by incorporating more recent studies and, above all, by providing the first pooled estimate for IL-6, and it should be read as one component of a broader effort to characterise the inflammatory signature of diabetic neuropathy that also encompasses adhesion molecules, C-reactive protein, and composite haematological indices.[14-16]

4.3. Heterogeneity and the case definition of neuropathy

Overall heterogeneity was substantial but its source was clearly localised. The IL-6 subgroup was essentially homogeneous (I^2 = 2%), whereas virtually all heterogeneity resided in the TNF-α subgroup (I^2 = 95%) and was attributable to the single discordant cohort, in which a high proportion of patients received statins and renin–angiotensin-system inhibitors — agents known to lower circulating TNF-α — and in which the authors themselves reported that TNF-α, unlike IL-6, did not differ by neuropathy status.[12] A comparable attenuation of the TNF-α signal in patients receiving metabolic therapy has been described elsewhere.[17] Beyond this, between-study variability is explicable by differences in assay platform, in the definition and severity of neuropathy, in diabetes type and duration, and in background pharmacotherapy. The differing case definitions deserve emphasis: two studies used the Michigan Neuropathy Screening Instrument, which detects a broad and comparatively mild spectrum of disease, whereas others used nerve conduction studies or a formal clinical diagnosis; pooling such definitions introduces clinical heterogeneity that the small number of studies did not permit to be examined formally.

4.4. Painful versus painless neuropathy

The project from which this review arose was originally motivated by the role of interleukins in neuropathic pain, and painful diabetic neuropathy affects nearly half of patients with established DPN.[2] Several included studies specifically examined painful neuropathy.[18] In the present analysis, painful and painless cases were combined into a single neuropathic arm because too few studies reported the two phenotypes separately to permit a stratified synthesis; this leaves open the possibility that the inflammatory profile of painful neuropathy differs from that of painless disease. Interleukin-17, prominent in the originating narrative review, was not meta-analysed because too few studies reported it in a poolable comparison. These are priorities for future work.

4.5. Clinical implications

For the practising neurologist these findings reinforce the concept of diabetic peripheral neuropathy as an inflammatory as well as a metabolic and microvascular disorder, and they identify IL-6 as the more consistent circulating correlate. A stable, widely available marker reproducibly elevated in neuropathic patients is an attractive candidate to complement, rather than replace, clinical screening instruments and nerve conduction studies, particularly for the early or small-fibre disease that electrophysiology detects poorly. It must be stated plainly, however, that no diagnostic threshold can be derived from these data, and the predominantly cross-sectional design means the direction of causation is unknown. Any suggestion that IL-6 could be used clinically, or that anti-inflammatory or immunomodulatory therapy — or the incidental cytokine-lowering effect of established metabolic agents — might prevent or attenuate neuropathy, must be regarded strictly as a hypothesis for future research,[6] and not every immunomodulatory strategy alters systemic cytokine concentrations, underscoring the need for direct evaluation rather than extrapolation.[19]

4.6. Generalisability, strengths, and limitations

The included populations were predominantly East Asian and Middle Eastern, and no South-East Asian cohort contributed to the pooled estimate; since the authors practise in Indonesia and the journal serves a South-East Asian readership, regional studies are needed before these estimates can be assumed to apply locally. The strengths of this review include a focused and clinically meaningful question, the exclusive use of primary-source-verified data with confirmed digital object identifiers, assay harmonisation through the standardised mean difference, and conservative safeguards including the Hartung–Knapp adjustment, restricted maximum-likelihood re-estimation, a cluster-collapsed analysis, a prediction interval, and a formal certainty appraisal. Several limitations must be acknowledged. Only four studies provided extractable group-level data and could be pooled, so the synthesis is small and, for TNF-α, underpowered; informative population-based cohorts could not be incorporated because they reported only per-standard-deviation risk estimates, although their direction of effect was concordant.[13,14] The reconstruction of means from medians for one study introduces approximation without material effect on the result. Residual confounding by glycaemic control, obesity, and concomitant medication was incompletely controlled, the case definition of neuropathy varied, and small-study effects could not be formally tested.

5. Conclusion

Diabetic peripheral neuropathy is associated with higher circulating concentrations of pro-inflammatory cytokines, with an overall standardised mean difference of 0.70 that remained stable across Hartung–Knapp, restricted maximum-likelihood, cluster-collapsed, and leave-one-out sensitivity analyses. The dominant and most reliable contributor was interleukin-6, which was significantly and homogeneously elevated in neuropathic patients and for which this study provides the first pooled quantitative estimate; a descriptive severity analysis further suggested that the IL-6 elevation is confined to severe neuropathy rather than rising progressively across severity strata. Tumour necrosis factor-alpha was numerically higher and strongly elevated in three of four datasets, but the pooled estimate did not reach significance owing to a single cohort in which extensive statin and antihypertensive use plausibly suppressed circulating TNF-α; when this dataset was excluded, the association strengthened and became more homogeneous, aligning with the earlier and larger meta-analysis of TNF-α. Graded as low certainty for IL-6 and very low for TNF-α, the findings support a genuine inflammatory contribution to the pathogenesis of diabetic neuropathy and identify IL-6 as the more consistent circulating correlate. Circulating IL-6 warrants prospective evaluation as a candidate biomarker to complement existing screening instruments and electrophysiological testing, while recognising that no diagnostic threshold can yet be defined and that causation remains unproven. Because the evidence base is small, dominated by cross-sectional designs, geographically restricted, and susceptible to pharmacological confounding, these conclusions are hypothesis-generating, and the clear priority is a set of adequately powered, prospectively designed cohort studies with standardised assays, uniform electrophysiological neuropathy definitions, separate reporting of painful and painless phenotypes, careful adjustment for confounders, and the deliberate inclusion of South-East Asian populations.

6. Declarations

6.1. Ethics approval and consent to participate

Ethical approval and patient consent were not required. This study is a systematic review and meta-analysis of previously published, de-identified aggregate data and did not involve any new collection of individual patient data or identifiable material. Each included study had obtained ethical approval and informed consent as reported in its original publication.

6.2. Consent for publication

Not applicable; no identifiable individual patient data or images are presented.

6.3. Availability of data and materials

All data analysed in this review were extracted from previously published studies, each of which is cited in the reference list. The extracted dataset, the analysis code, and the risk-of-bias assessments are available from the corresponding author on reasonable request.

6.4. Competing interests

The authors declare no conflict of interest.

6.5. Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

6.6. Author contributions

All authors contributed to the conception and design of the review. DC performed the literature search, study selection, and data extraction and drafted the manuscript. IPEW supervised the analysis and critically revised the manuscript for important intellectual content. AAAM contributed to data interpretation and manuscript revision. All authors approved the final version and agree to be accountable for the work.

6.7. Acknowledgements

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References

1. Genitsaridi I, Salpea P, Salim A, et al. 11th edition of the IDF Diabetes Atlas: global, regional, and national diabetes prevalence estimates for 2024 and projections for 2050. Lancet Diabetes Endocrinol. 2025;14(2):149–56. doi:10.1016/S2213-8587(25)00299-2.
2. Tao Y, Zhang HY, MacGilchrist C, et al. Prevalence and risk factors of painful diabetic neuropathy: a systematic review and meta-analysis. Diabetes Res Clin Pract. 2025;222:112099. doi:10.1016/j.diabres.2025.112099.
3. Chen C, Zhu L, Li W, et al. Hyperglycemia promotes SIRT3-mediated deacetylation of SARM1 to exacerbate diabetic peripheral neuropathy in mice. Proc Natl Acad Sci U S A. 2026;123:e2517110123. doi:10.1073/pnas.2517110123.
4. Hakim S, Jain A, Adamson SS, et al. Macrophages protect against sensory axon loss in peripheral neuropathy. Nature. 2025;640:182–91. doi:10.1038/s41586-024-08535-1.
5. Guo N, Li Q, Wang H, et al. Exploring the role of immune cell traits and circulating inflammatory cytokines in the development of diabetic neuropathy. Cytokine. 2025;194:156985. doi:10.1016/j.cyto.2025.156985.
6. Lee SO, Kuthati Y, Huang WH, et al. Semaglutide ameliorates diabetic neuropathic pain by inhibiting neuroinflammation in the spinal cord. Cells. 2024;13(22):1857. doi:10.3390/cells13221857.
7. Bagher AM. Intraplantar β-caryophyllene alleviates pain and inflammation in streptozotocin-induced diabetic peripheral neuropathy via CB2 receptor activation. Int J Mol Sci. 2025;26(9):4430. doi:10.3390/ijms26094430.
8. Mu ZP, Wang YG, Li CQ, et al. Association between tumor necrosis factor-α and diabetic peripheral neuropathy in patients with type 2 diabetes: a meta-analysis. Mol Neurobiol. 2017;54(2):983–96. doi:10.1007/s12035-016-9702-z.
9. Li X, Zhu J, Liu N, et al. TNF-alpha in peripheral neuropathy patients with impaired glucose regulation. J Diabetes Res. 2017;2017:7024024. doi:10.1155/2017/7024024.

10. Zheng H, Sun W, Zhang Q, et al. Proinflammatory cytokines predict the incidence of diabetic peripheral neuropathy over 5 years in Chinese type 2 diabetes patients: a prospective cohort study. EClinicalMedicine. 2021;31:100649. doi:10.1016/j.eclinm.2020.100649.
11. Abdulrhaman D, Fahad H, Khalil N. Association of serum biomarkers level transforming growth factor-β and tumor necrosis factor-α with diabetic neuropathy. Hum Antibodies. 2024;32(4):193–9. doi:10.3233/HAB-240031.
12. Huang S, Lan Y, Zheng C, et al. Association between low-grade inflammation and distal sensorimotor polyneuropathy in type 2 diabetes: a cross-sectional study. BMC Neurol. 2025;25(1):378. doi:10.1186/s12883-025-04379-y.
13. Huemer MT, Spagnuolo MC, Maalmi H, et al. Phenotype-based clusters, inflammation and cardiometabolic complications in older people before the diagnosis of type 2 diabetes: KORA F4/FF4 cohort study. Cardiovasc Diabetol. 2025;24(1):83. doi:10.1186/s12933-025-02617-8.
14. Li J, Wang X, Jia W, et al. Association of the systemic immuno-inflammation index, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio with diabetic microvascular complications. Front Endocrinol (Lausanne). 2024;15:1367376. doi:10.3389/fendo.2024.1367376.
15. Zaib S, Ahmad S, Khan I, et al. An evaluation of inflammatory and endothelial dysfunction markers as determinants of peripheral arterial disease in those with diabetes mellitus. Sci Rep. 2024;14(1):15348. doi:10.1038/s41598-024-65188-w.
16. Sangeeta S, Siripuram C, Konka S, et al. Biomarkers of inflammation, oxidative stress, and endothelial dysfunction in early detection of diabetic foot ulcers. Cureus. 2025;17(4):e82174. doi:10.7759/cureus.82174.
17. Sakyi SA, Laing EF, Mantey R, et al. Profiling immuno-metabolic mediators of vitamin B12 deficiency among metformin-treated type 2 diabetic patients in Ghana. PLoS One. 2021;16(3):e0249325. doi:10.1371/journal.pone.0249325.
18. Hassan AB, Al-Dosky AHA. Vitamin D status and its association with inflammatory markers among Kurdish type 2 diabetic patients with painful diabetic peripheral neuropathy. Steroids. 2023;199:109289. doi:10.1016/j.steroids.2023.109289.
19. Okdahl T, Kufaishi H, Kornum D, et al. Transcutaneous vagus nerve stimulation has no anti-inflammatory effect in diabetes. Sci Rep. 2024;14(1):21042. doi:10.1038/s41598-024-72139-y.