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Global prevalence of diabetes-related neuropathy and vascular complications: a systematic review and meta-analysis

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ADMINISTRATIVE INFORMATION

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Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 29 September 2025 and was last updated on 29 September 2025.

INTRODUCTION

Review question / Objective Review question Among adults with diabetes worldwide, what is the pooled prevalence of diabetic peripheral neuropathy (DPN), peripheral arterial disease (PAD), and ischemic peripheral neuropathy (IPN), and how do prevalence estimates vary by diagnostic approach and study/contextual moderators?

PICOS framework
Population (P): Adults (≥18 years) with diabetes (any type; community or hospital settings; all world regions).
Intervention/Exposure/Index (I): Presence of the target complications assessed with validated approaches:
DPN: symptoms only (e.g., standardized symptom scales), signs only (e.g., nerve conduction studies, 10-g monofilament, vibration perception threshold), or combined symptoms + signs.
PAD: ankle–brachial index/toe–brachial index (ABI/TBI) or equivalent vascular assessments.
IPN: neuropathy with an ischemic/perfusion component operationalized via validated indices (including ankle–brachial index and Nerve Conduction Study definitions where applicable).
Comparator (C): Not applicable for prevalence synthesis; between-group contrasts occur across subgroups (e.g., diagnostic approach, setting, country income level, diabetes type).
Outcomes (O): Primary—pooled prevalence (event rate with 95% CI) of DPN, PAD, and IPN. Secondary—between-subgroup differences; heterogeneity (Q, I^2); small-study effects/publication bias (e.g., trim-and-fill); robustness in sensitivity analyses.
Study design (S): Observational studies (cross-sectional, cohort, case-control) reporting numerators and denominators sufficient to compute prevalence; randomized trials and animal/in-vitro studies excluded.

Objectives
1. Estimate pooled prevalence for DPN, PAD, and IPN in adults with diabetes at the global level using random-effects meta-analysis.
2. Compare prevalence by diagnostic approach (symptoms, signs, combined) and clinical/contextual factors (care setting, country income level, diabetes type).
3. Examine moderators (e.g., CKD prevalence, age, diabetes duration, HbA1c, hypertension, dyslipidemia, smoking) via subgroup analyses and meta-regression where data allow.
4. Quantify heterogeneity and small-study effects, and perform sensitivity analyses based on study quality (assessed with JBI tools) and definitional choices.

Rationale Diabetes mellitus is a leading cause of neurovascular complications that impair function, quality of life, and health-system performance. Among these, diabetic peripheral neuropathy (DPN), peripheral arterial disease (PAD), and ischemic peripheral neuropathy (IPN) are common, clinically intertwined, and often under-recognized. However, current evidence is fragmented: definitions and diagnostic tools vary across studies; estimates differ by country income level and care setting; and key clinical moderators (e.g., chronic kidney disease, age, diabetes duration, metabolic control) are rarely analyzed in a comparable way. As a result, reliable global and stratified prevalence estimates are lacking.

This review addresses these gaps by systematically synthesizing observational studies that report the prevalence of DPN, PAD, and IPN using validated criteria (e.g., symptoms, signs, or combined approaches; objective measures such as 10-g monofilament, vibration perception threshold, nerve conduction studies, and ABI/TBI). We will use random-effects meta-analysis to generate pooled prevalence with uncertainty intervals; perform predefined subgroup analyses by diagnostic approach, country income level, setting (community vs hospital), and diabetes type; and conduct meta-regression to evaluate clinical moderators. Risk of bias will be appraised with JBI tools, and small-study effects and sensitivity to study quality will be examined.

The expected contributions are:
1. Standardized, comparable global and regional prevalence estimates for DPN, PAD, and IPN;
2. Clear quantification of heterogeneity by diagnosis method and context;
3. Identification of clinical moderators that explain between-study variation; and
4. Practical evidence to guide tiered screening pathways, resource allocation, and research priorities. By including all languages and grey literature where feasible, this study aims to deliver the most complete, actionable mapping of the global burden of diabetes-related neurovascular complications.

Condition being studied Diabetic peripheral neuropathy (DPN), peripheral arterial disease (PAD), and ischemic peripheral neuropathy (IPN) are common and consequential neurovascular complications of diabetes that impair mobility, precipitate foot ulceration and amputation, and diminish quality of life. Yet, global prevalence estimates remain uncertain due to wide variability across world regions and care settings, as well as heterogeneity in diagnostic approaches. Studies variously rely on symptoms, signs, or combined criteria for DPN; vascular indices such as ABI/TBI for PAD; and operational definitions of IPN that capture ischemic or perfusion components. These methodological differences, together with variation in population characteristics (age, diabetes duration, glycaemic control) and comorbid conditions (e.g., chronic kidney disease), hinder comparability and limit the translation of evidence into practice and policy.

This review addresses these gaps by synthesizing observational evidence to derive pooled global prevalence estimates for DPN, PAD, and IPN, while explicitly assessing heterogeneity and examining moderators related to diagnostic approach, care setting, country income level, diabetes type, and key clinical correlates. By mapping how measurement choices and contextual factors shape prevalence, the study will produce robust, generalizable estimates that can inform risk-based screening strategies, prioritize preventive foot care, and support service planning in both resource-limited and resource-rich settings. In addition, the findings can guide harmonization of case definitions and surveillance metrics for diabetes-related neurovascular complications worldwide.

METHODS

Search strategy

Databases and coverage
We will search MEDLINE (via PubMed), Embase (via Elsevier), Scopus, and Web of Science Core Collection from inception to 28 February 2025. We will also screen Google Scholar (first ~200 hits sorted by relevance) and the Indonesian GARUDA portal for grey literature. No language, document type, or publication status limits will be applied at the search stage. Reference lists of included

studies and relevant reviews will be hand-searched to identify additional records.

Population/Condition and outcomes of interest
Adults (≥18 years) with diabetes (any type), reporting prevalence (or data enabling prevalence calculation) of diabetic peripheral neuropathy (DPN), peripheral arterial disease (PAD), or ischemic peripheral neuropathy (IPN) measured with validated approaches (e.g., symptoms/signs/combined for DPN; ABI/TBI for PAD; operational definitions for IPN capturing ischemic/perfusion components).

Search concepts (blocks)
1. Diabetes
2. Target complications: DPN, PAD, IPN (and synonyms)
3. Measurement terms (diagnostic instruments/indices commonly used)
4. Prevalence/epidemiology
5. Observational study designs
(Concepts combined with AND; synonyms within each concept combined with OR.)

De-duplication and management
All records will be exported to EndNote 21 for de-duplication, then screened in a two-stage process (title/abstract, full text) by two independent reviewers.

Keywords: diabetes mellitus OR hyperglycemia AND peripheral arterial disease OR peripheral arterial disease OR peripheral neuropathy OR peripheral nervous system diseases OR ischemic peripheral neuropathy AND prevalence OR prevalence OR incidence OR incidence OR event rate.

Participant or population

Patient/Participant/Population
Target group: Adults (≥18 years) with diabetes (any type: type 1 or type 2) as defined by study authors using accepted criteria (e.g., WHO/ADA).
Settings & geography: Any setting (community, outpatient, inpatient) and all world regions; no restrictions by sex, ethnicity, or country income level.
Comorbidities: Common comorbid conditions (e.g., hypertension, CKD, CVD) are permitted and may be examined as moderators.
Outcome linkage: Studies must report prevalence (or provide sufficient data to compute it) for at least one target complication measured with validated approaches:
DPN: symptoms, signs (e.g., NCS, 10-g monofilament, VPT), or combined criteria.
PAD: vascular indices (e.g., ABI/TBI, Doppler/duplex where reported).
IPN: operational definitions capturing ischemic/perfusion components.
Mixed samples: Eligible if data for participants with diabetes are separately extractable (or if ≥80% of the sample has diabetes).
Exclusions: Pediatric populations (<18 years), gestational diabetes, prediabetes/isolated hyperglycemia without diabetes, non-human/in-vitro studies, and cohorts where neuropathy/arterial disease is primarily non-diabetic unless diabetic-specific data are separable.

Intervention Not applicable. This review is a prevalence-focused systematic review and meta-analysis of observational studies. We do not evaluate therapeutic or preventive interventions. Instead, we synthesize the prevalence of diabetic peripheral neuropathy (DPN), peripheral arterial disease (PAD), and ischemic peripheral neuropathy (IPN) among adults with diabetes and compare estimates across diagnostic approaches (e.g., symptoms, signs such as NCS/10-g monofilament/VPT, combined criteria; ABI/TBI for PAD) and contextual moderators (care setting, country income level, diabetes type, and clinical factors). If the form requires an entry, please record: “No intervention observational prevalence synthesis.”

Comparator Not applicable. This review does not assess therapeutic interventions. It synthesizes prevalence estimates from observational studies. There is no active comparator arm. Where contrasts are reported, they are analytical subgroups (e.g., diagnostic approach, care setting, country income level, diabetes type) rather than comparators. If the form requires text, enter: “No comparator observational prevalence synthesis; subgroup contrasts only.”

Study designs to be included Observational studies reporting prevalence with extractable numerators/denominators: cross-sectional, cohort (baseline/prevalence data), and case-control (if prevalence calculable).Exclude: randomized/experimental trials, case reports/series without a denominator, reviews, editorials, conference abstracts without data, and animal/in-vitro studies.

Eligibility criteria Eligibility criteria (additional to PICOS):

Inclusion
– Adults ≥18 years with diabetes (any type) per study-defined accepted criteria (e.g., WHO/ADA).
– Reports prevalence (or data to compute it: numerator & denominator) for Diabetic Peripheral

Neuropathy (DPN), Peripheral Arterial Disease (PAD), or Ischemic Peripheral Neuropathy (IPN) using validated methods/indices/questionnaires (e.g., DPN: symptoms/signs/combined; PAD: ABI/TBI; IPN: ischemic/perfusion-based operationalization).
– Observational design (cross-sectional, cohort, case-control).
– Any setting (community/outpatient/inpatient) and region; no language/date restrictions at inclusion stage.
– Unique dataset (when multiple reports use the same cohort, include the most complete/recent with non-overlapping data).

Exclusion
– Pediatric populations (<18 y), gestational diabetes, prediabetes/isolated hyperglycemia without diabetes.
– Populations where neuropathy/arterial disease is primarily non-diabetic (e.g., chemotherapy-induced neuropathy) unless diabetic-specific data are separable.
– Randomized/experimental trials, case reports/series without a denominator, reviews, editorials, letters, protocols, and conference abstracts without sufficient extractable data.
– Animal/in-vitro studies.
– Studies with insufficient/unclear outcome definition or unvalidated measures for DPN/PAD/IPN after author contact.
– Duplicate/overlapping publications without additional, non-overlapping data.

Information sources

Electronic databases (from inception to 28 February 2025):
MEDLINE (via PubMed), Embase (Elsevier), Scopus, and Web of Science Core Collection. Searches will combine controlled vocabulary (MeSH/Emtree) and free-text terms for diabetes, target complications (DPN, PAD, IPN), and epidemiological terms (e.g., prevalence/incidence). No language or date limits at the search stage.

Grey literature and local sources:
Google Scholar and Indonesia's GARUDA portal. Preprints may be screened when methodological detail is sufficient for prevalence estimation.

Supplementary identification:
Backward and forward citation chasing of all included studies and relevant reviews using Scopus/Web of Science/Google Scholar.
Handsearching key journals or special issues identified during screening as needed.

Contact with study authors (≥1 email attempt) to obtain full texts, clarify methods/outcomes, or retrieve missing numerators/denominators.
Management and deduplication:
All records will be exported to EndNote 21 for de-duplication before two-stage screening (titles/abstracts, then full text).

Updating policy:
If new, potentially eligible records emerge during screening or citation chasing, database searches will be re-run using the same strategy before final data extraction to ensure currency.

Main outcome(s)

Primary outcome:
Pooled prevalence (event rate, % with 95% CI) of each target complication among adults (≥18 years) with diabetes:
1. Diabetic peripheral neuropathy (DPN)
2. Peripheral arterial disease (PAD)
3. Ischemic peripheral neuropathy (IPN).

Additional outcome(s) Secondary/analytic outcomes (to contextualize prevalence):
1. Between-subgroup differences in prevalence by diagnostic approach, care setting (community vs. hospital), country income level, and diabetes type.
2. Meta-regression results for continuous moderators (e.g., age, % male, diabetes duration, HbA1c, CKD prevalence) when data permit.
3. Heterogeneity (Q, I^2) and small-study effects/publication bias (e.g., trim-and-fill–adjusted prevalence).

Data management Search results from all databases will be exported and imported into EndNote 21 for duplicate removal using the software's de-duplication function. After de-duplication, records will undergo two-stage screening titles/abstracts followed by full texts by two independent reviewers. For records with unavailable full texts, the original authors will be contacted at least once via email.

Data will be extracted by two independent authors using the predesigned extraction form specified in the Methods. Extracted items include:
1. Participant characteristics: age, percentage male, body mass index (BMI), and diabetes duration.
2. Study characteristics: author, publication year, country, study design, and sample size.
3. Risk factors/comorbidities: percentages with hypertension, chronic kidney disease, cardiovascular disease, smoking, and alcohol.
4. Laboratory data: mean HbA1c, low-density lipoprotein cholesterol, and triglycerides.

5. Outcome data: measurement tools and criteria used for DPN, PAD, IPN, plus numerators/denominators enabling prevalence calculation.
Where data are unclear or unavailable, study authors will be emailed at least once to obtain or clarify information. Disagreements at any stage will be resolved by consensus.

Methodological quality will be appraised with the JBI critical appraisal tools appropriate to design, with item ratings recorded as Yes/No/Unclear/Not applicable and converted to a percentage score to classify studies as good (≥70%), moderate (50–69%), or poor (<50%) quality.

For quantitative synthesis, a working dataset will be prepared with event rates (cases/total) for DPN, PAD, and IPN from each study. These data will be analyzed using Comprehensive Meta-Analysis (CMA) v3.0 as outlined in the Statistical Analysis section.

Quality assessment / Risk of bias analysis Methodological quality of primary studies will be appraised using the Joanna Briggs Institute (JBI) critical appraisal tools matched to study design. For cross-sectional studies, the 9-item checklist covers: participant selection, exposure and outcome measurement, confounding, and appropriateness of statistical analysis. For case-control studies, the 10-item checklist assesses group comparability/matching, case/control definition, exposure and outcome measurement, confounding, exposure duration, and statistical analysis.

Two reviewers will independently rate each item as "Yes" (1 point), "No" (0), "Unclear" (0), or "Not applicable" (excluded from the denominator). For each study, a percentage score will be calculated as: (number of "Yes" items / total applicable items) × 100%. Based on this score, studies will be classified as good quality (≥70%), moderate quality (50–69%), or poor quality (<50%). Discrepancies will be resolved by discussion with a third reviewer.

All item-level judgments and final category assignments will be recorded and used for sensitivity analyses (e.g., excluding poor-quality studies) as specified in the Statistical Analysis section.

Strategy of data synthesis For each primary study, we will compute the event rate (prevalence = number of cases divided by total sample) separately for diabetic peripheral neuropathy, peripheral arterial disease, and ischemic peripheral neuropathy. Meta-analyses will be conducted in Comprehensive Meta-Analysis (version 3.0) using random-effects models to derive pooled prevalence estimates with 95% confidence intervals for each of the three complications analyzed independently.

Subgroup analysis Subgroup analyses will be conducted to explore sources of between-study heterogeneity in the prevalence of diabetic peripheral neuropathy, peripheral arterial disease, and ischemic peripheral neuropathy. In accordance with the Methods, categorical moderators will be limited to the following prespecified factors:
1. Study setting: community versus hospital.
2. Type of diabetes: type 1 diabetes, type 2 diabetes, or mixed cohorts.
3. Study country/region: country-level or aggregated regional groupings as reported.

Within each subgroup, pooled prevalence and 95% confidence intervals will be estimated using random-effects models. Subgroup analyses will be performed only when at least two studies contribute data to a given level to ensure minimum analytic stability. When a study provides data for more than one eligible subgroup (e.g., separate estimates by setting), each estimate will be treated as a distinct subgroup entry provided that double-counting of participants is avoided.

Between-subgroup differences will be evaluated using the Q-between statistic from mixed-effects models, and corresponding p-values will be reported. Forest plots stratified by subgroup will be used to visualize patterns of prevalence across categories. Sensitivity checks will be performed, where feasible, by (a) excluding studies at poor methodological quality based on the Joanna Briggs Institute appraisal and (b) re-estimating pooled prevalence after removing subgroups represented by only two studies to assess robustness.

All subgroup procedures will be applied consistently and independently to diabetic peripheral neuropathy, peripheral arterial disease, and ischemic peripheral neuropathy.

Sensitivity analysis Sensitivity analysis: Not planned. Results will be explored using prespecified subgroup analyses and meta-regression only.

Language restriction No. We will not impose language limits; all languages will be eligible, with translation performed as needed during screening and data extraction.

Country(ies) involved Indonesia, Thailand, Taiwan.

Other relevant information Full details are provided in the Supplementary: Tables S1–S12 and Figures S1–S3. Table S1 lists the complete database strategies (PubMed, Embase, Scopus, Web of Science) with the last search on 28 February 2025 and the record yields per database. Table S2 documents excluded studies with specific reasons. For each outcome, we have standardized extraction frameworks: participant characteristics (S3 DPN; S6 PAD; S9 IPN), comorbidities and risk factors (S4; S7; S10), and prevalence numerators/denominators with diagnostic methods and cut-points exactly as reported by each study (S5 DPN; S8 PAD; S11 IPN). Diagnostic approaches captured include common DPN tools (e.g., symptoms/signs batteries, VPT, monofilament, NCS), PAD measures (ABI/TBI with thresholds), and IPN criteria as reported in primary studies. Risk-of-bias results for all included studies are summarized in Table S12 (JBI format). Forest plots of pooled prevalence for DPN (Figure S1), PAD (Figure S2), and IPN (Figure S3) are compiled from these extractions. This Supplementary package also serves as the audit trail for selection (with reasons), data items, thresholds used across studies, and analytic inputs for the meta-analysis.

Keywords diabetes mellitus; diabetic neuropathies; ischemic peripheral neuropathy; meta-analysis; peripheral arterial disease; prevalence.

Dissemination plans Peer-reviewed publication: Submit the completed systematic review and meta-analysis (reported per PRISMA 2020) to an international journal in diabetes/vascular epidemiology.

Registration links: Maintain this INPLASY record and update it with the article citation/DOI.
Supplementary materials: Publish the search strategies, screening flow, data-extraction form, JBI appraisal summaries, and meta-analysis outputs (figures/tables) as supplementary files with the article.

Conference sharing: Present findings as oral/poster presentations at relevant scientific meetings on diabetic complications, peripheral neuropathy, and peripheral arterial disease.

Stakeholder summary: Prepare a brief, plain-language summary highlighting pooled prevalence estimates and implications for screening and service planning for clinicians and educators.

Contributions of each author

Author 1 - Asmat Burhan - Conceptualization, Methodology, Protocol drafting, Search (database strategy & execution) Screening (title/abstract, full text) Data curation (extraction, management) Formal analysis (CMA v3.0) Writing – original draft Visualization (figures/tables).
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Author 2 - Ramida Subpaiboonkit - Validation: critical appraisal of study quality (JBI).
Email: d432112019@tmu.edu.tw
Author 3 - Huang Hui-Chuan - Supervision, Methodology oversight Validation (eligibility, data, risk of bias) Adjudication (disagreement resolution) Writing – review & editing Interpretation (results, implications) Project administration Final approval (submitted version).
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