



SYSTEMATIC REVIEW

Association Between Angiotensin Converting Enzyme Insertion / Deletion Genotypes and Diabetic Nephropathy Defined by Urinary Albumin-to-Creatinine Ratio: A Systematic Review and Meta-Analysis

[version 1; peer review: awaiting peer review]

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Abstract

Background

Diabetic nephropathy (DN) is a major complication of type 2 diabetes mellitus (T2DM) and a leading cause of kidney failure. Evidence on the influence of ACE I/D polymorphisms in DN risk is inconsistent across populations.

Methods

A systematic review and meta-analysis was conducted following the

PRISMA 2020 guidelines. Studies published between January 1990 to February 2025 were retrieved from PubMed, EMBASE and Web of Science. Eligible observational studies reported the frequency of ACE genotypes with DN in T2DM. Independent reviewers screened studies using Rayyan software, extracted data, and assessed risk of bias using the ROBINS-E tool. Reporting on the quality of studies was determined using the STREGA guidelines. Pooled odds ratio (OR) with 95% confidence intervals (CI) were calculated using random-effects models in R version 4.4.2. Subgroup, meta-regression, and sensitivity analyses addressed heterogeneity; Egger's test assessed publication bias. Registered in PROSPERO (CRD42024577680). Funding from Fogarty International Center of the National Institutes of Health (D43TW011632).

Results

Of the 46 studies included in this review, the combined sample size was 16,322 participants. The majority of studies (29 out of 46) were conducted in Asia. Only 5 studies reported DN-related comorbidities by ACE genotypes and one assessed mortality. Twenty-five of the included 46 studies contributed data to the meta-analysis. The ACE II genotype was protective against DN; II vs. ID [OR= 0.70 (CI: 0.63–0.77)] and II vs. DD [OR= 0.68 (CI: 0.55–0.84)]; Heterogeneity was ($I^2 = 71.7\%$, $\tau^2 = 0.1776$, $p < 0.0001$). Stronger associations were observed in studies using urinary Albumin-Creatinine-Ratio over Albumin-Excretion-Rate. Egger's test showed no publication bias ($p = 0.55$).

Conclusion

The ACE II genotype is significantly protective against DN risk in T2DM. Standardization of urinary albumin measurement and further genotype-phenotype studies are needed to strengthen clinical utility of the ACE I/D polymorphisms.

Keywords

Diabetic Nephropathy, Mutations, Angiotensin Converting Enzyme Gene, Type 2 Diabetes Mellitus.



This article is included in the **Genomics and Genetics** gateway.

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Introduction

Approximately 20–50% of people with diabetes worldwide suffer from diabetic nephropathy (DN), which is among the most prevalent and costly microvascular consequences of long-term type 2 diabetes mellitus (T2DM).^{1–3} Prolonged albuminuria, decreased glomerular filtration rate, and progressive kidney damage are hallmarks of DN, which eventually results in kidney failure.⁴ While microalbuminuria, commonly assessed via the urine albumin-to-creatinine ratio (UACR), remains a widely accepted early biomarker of diabetic nephropathy (DN),⁵ several other biomarkers have demonstrated potential for early detection. These include neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), and cystatin C, which are often elevated before albumin appears in urine and may reflect early tubular injury or impaired glomerular filtration.^{6–8} Despite their clinical promise, these alternative biomarkers are not yet widely adopted in routine practice because of limitations such as high assay costs, limited availability of standardized kits, and the need for a specialized laboratory infrastructure.^{9,10} In contrast, microalbuminuria remains a practical and accessible option in most clinical settings, especially in low- and middle-income countries, owing to the affordability and availability of UACR testing.^{11–15}

The pathophysiology of DN is complex, with hyperglycemia-induced reactive oxygen species, inflammation, and genetic predispositions playing pivotal roles.^{16,17} Angiotensin-converting enzyme (ACE), a key component of the renin-angiotensin-aldosterone system (RAAS), has been implicated in the development of DN because it is involved in the regulation of blood pressure and fluid balance. ACE gene insertion/deletion (I/D) polymorphism, which results in different genotypes insertion/insertion (II), insertion/deletion (ID) and deletion/deletion (DD), has been extensively studied as a potential genetic determinant of high blood pressure and DN risk.^{18–20} Evidence suggests that the ACE DD genotype is associated with increased ACE activity, leading to higher susceptibility to DN and its complications, whereas the II genotype may have a protective effect.^{21,22}

Despite substantial research on diabetic nephropathy (DN), critical gaps remain in our understanding of the interplay between angiotensin-converting enzyme (ACE) insertion/deletion (I/D) genotypes and DN progression in type 2 diabetes mellitus (T2DM). While numerous studies have reported associations between ACE I/D polymorphisms and DN risk, the findings are inconsistent owing to variations in study design, population, and methods of microalbuminuria (UACR) measurement.^{23–26} The heterogeneity of these results could hinder the development of standardized clinical guidelines for the genetic risk assessment of DN.

Therefore, we conducted this systematic review and meta-analysis primarily to determine the association between Angiotensin Converting Enzyme (ACE) genotypes and Diabetic Nephropathy (DN) defined by Urine Albumin-to-Creatinine Ratio (UACR) in adults with Type 2 Diabetes Mellitus (T2DM). Secondary outcomes included DN-related mortality and comorbidities.

Methods

Registration and protocol

This systematic review and meta-analysis study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.²⁷ The protocol was registered with PROSPERO²⁸ under registration number CRD42024577680 and is published as a Preprint in Open science Framework (OSF) preprints.²⁹

Eligibility criteria

Studies were eligible for inclusion if they enrolled male and female participants aged 18 years or older with a confirmed diagnosis of type 2 diabetes mellitus (T2DM), and investigated angiotensin-converting enzyme (ACE) insertion/deletion (I/D) genotypes (II, ID, DD) as the primary exposure.

Diabetic nephropathy (DN) was the primary outcome, commonly defined using microalbuminuria markers such as the albumin excretion rate (AER), urine albumin-to-creatinine ratio (UACR), or albumin-to-creatinine ratio (ACR). Diagnostic thresholds for microalbuminuria were standardized across studies at 30–300 mg/day for AER and 30–300 mg/g for UACR/ACR. One study that defined DN using traditional renal function tests, including estimated glomerular filtration rate (eGFR) and serum creatinine, was also included to capture broader clinical definitions of nephropathy. This deviation from the protocol was noted but deemed valuable for completeness.

The comparator across studies was typically T2DM patients with normal UACR levels, enabling evaluation of the association between ACE genotypes and DN risk. Secondary outcomes included nephropathy-related mortality and comorbidities such as cardiovascular disease, hypertension, neuropathy, and retinopathy. Eligible studies employed observational designs (cohort, case-control, or cross-sectional) and were published between January 1990 and February 2025.

Articles with missing data on key study variables or those that did not explore the ACE I/D-DN relationship were excluded. Non-English articles whose abstracts were available in English were included in the initial screening; however, those whose full texts were not available for retrieval were eventually excluded. Abstracts, unpublished studies, and grey literature were not included in this review, and no direct contact was made with study authors for clarification or additional data. Discrepancies were resolved through discussion, ensuring consistency and minimizing bias, although formal blinding and interrater reliability statistics were not applied.

Information sources

We conducted a comprehensive search on across multiple electronic databases (PubMed, Web of Science, and EMBASE) to identify studies relevant to the research objectives. Additional studies were retrieved from Google Scholar and reference lists of the included articles to ensure broad coverage.

Search strategy

The search strategy was designed to capture studies assessing the relationship between angiotensin-converting enzyme (ACE) insertion/deletion (I/D) genotypes and diabetic nephropathy (DN). The search included studies published from 1st January 1, 1990, to 28th February 28, 2025, without language restrictions. Keywords and medical subject headings (MeSH) related to “ACE I/D genotypes,” “diabetic nephropathy,” and “microalbuminuria” were combined with Boolean Operators “OR” and “AND” “AND” and truncated where applicable to optimize retrieval. The search strings used are listed in [Table 1](#).

Table 1. Search strategy and database hits for the systematic review and meta-analysis on ACE I/D genotypes and diabetic nephropathy.

Database	Search date	Search string	#Hits
PubMed	28 th February, 2025	((“Type 2 Diabetes Mellitus” OR “T2DM” OR “Diabetes Mellitus, Type 2”[tiab]) AND (“Diabetic Nephropathies” OR “Diabetic Nephropathy” OR “DN” OR “Nephropathy” OR “Kidney Disease”) AND (“Angiotensin-Converting Enzyme” OR “ACE” OR “ACE I/D” OR “ACE Insertion/Deletion Polymorphism” OR “ACE Genotypes”) AND (“Urine Albumin-to-Creatinine Ratio” OR “UACR” OR “Microalbuminuria” OR “Albuminuria”) AND (“Mortality” OR “Comorbidities” OR “Complications”) AND (“Genetic Markers” OR “Polymorphism, Genetic” OR “Biomarkers”))	48
EMBASE	28 th February, 2025	((“Type 2 Diabetes Mellitus” or T2DM or “Diabetes Mellitus Type 2”) and (“Diabetic Nephropathies” or “Diabetic Nephropathy” or DN or Nephropathy or “Kidney Disease”) and (“Angiotensin-Converting Enzyme” or ACE or “ACE I/D” or “ACE Insertion/Deletion Polymorphism” or “ACE Genotypes”) and (“Urine Albumin-to-Creatinine Ratio” or UACR or Microalbuminuria or Albuminuria) and (Mortality or Comorbidities or Complications) and (“Genetic Markers” or Polymorphism or Genetic or Biomarkers)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	15
Web of Science	28 th February, 2025	TS = ((“Type 2 Diabetes Mellitus” OR T2DM OR “Diabetes Mellitus Type 2”) AND (“Diabetic Nephropathy” OR “Diabetic Nephropathies” OR DN OR Nephropathy OR “Kidney Disease”) AND (“Angiotensin-Converting Enzyme” OR ACE OR “ACE I/D” OR “ACE Insertion/Deletion Polymorphism” OR “ACE Genotypes”) AND (“Urine Albumin-to-Creatinine Ratio” OR UACR OR Microalbuminuria OR Albuminuria) AND (Mortality OR Comorbidities OR “Hypertension” OR “Cardiovascular Disease”) AND (“Genetic Markers” OR Polymorphism OR Genetic OR Biomarkers) AND TS = (Cohort OR “Case-Control” OR “Cross-Sectional” OR “Observational Study” OR “Randomized Controlled Trial” OR RCT) AND TS = (Adult OR “18 years and above”) NOT TS = (“Type 1 Diabetes” OR “Gestational Diabetes” OR Prediabetes OR “Case Report” OR Review OR Editorial OR “Animal Study”))	13

This table presents the detailed search strategy used to retrieve relevant studies for inclusion in the study. Searches were conducted on February 28, 2025, across three major databases: PubMed, EMBASE, and Web of Science. The search strings combined terms related to diabetes, nephropathy, ACE genotypes, urinary albumin-to-creatinine ratio (UACR), genetic polymorphisms, and DN-related outcomes such as mortality and comorbidities. Boolean operators (AND/OR) and truncation were used to maximize retrieval. The table includes the exact search strings and the number of articles retrieved (#Hits) from each database.

Abbreviations: ACE – Angiotensin-Converting Enzyme; DN – Diabetic Nephropathy; I/D – Insertion/Deletion; T2DM – Type 2 Diabetes Mellitus; UACR – Urine Albumin-to-Creatinine Ratio; RCT – Randomized Controlled Trial; TS – Topic Search; mp – Multi-purpose fields.

Two independent experienced information retrieval specialists (AAK and ML), in consultations with the lead reviewer (RK), independently conducted the database searches and verified the inclusion of additional studies from alternative sources such as Google Scholar and reference lists. Discrepancies in the search results were resolved through consensus discussion. The systematic review process was organized using Rayyan,³⁰ a web-based platform that facilitates the filtering and assessment of papers based on predetermined requirements for inclusion and exclusion.

Selection process

Two reviewers, RK and JT, independently assessed the titles and abstracts of the studies according to the inclusion criteria using Rayyan software. Full-text articles were retrieved from studies that met the eligibility requirements. Any disagreements regarding inclusion were resolved through a consensus between the two reviewers. Full-text articles were retrieved from eligible studies, and the selection process is shown in [Figure 1](#).

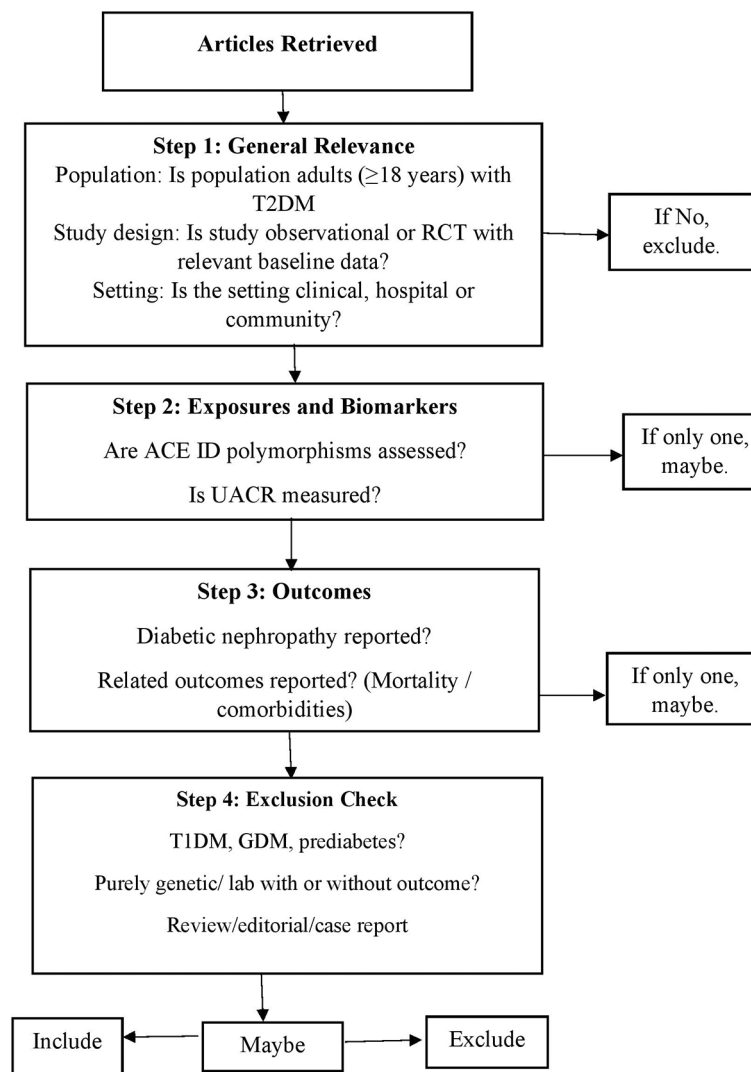


Figure 1. Schematic diagram of article selection process for inclusion in the systematic review. This flowchart illustrates the stepwise criteria used to screen and select articles for inclusion in the systematic review. The selection process involved four major steps: (1) assessing general relevance based on population, study design, and setting; (2) evaluating the presence of key exposures and biomarkers (i.e., ACE I/D polymorphisms and UACR); (3) confirming the reporting of diabetic nephropathy and related outcomes (e.g., mortality, comorbidities); and (4) applying exclusion criteria such as type 1 diabetes (T1DM), gestational diabetes (GDM), prediabetes, purely genetic/laboratory studies lacking clinical outcomes, and non-original articles (e.g., reviews or editorials). Articles were classified as "Include," "Maybe," or "Exclude" depending on how fully they met the criteria.

Abbreviations: T1DM – Type 1 diabetes mellitus; T2DM – Type 2 diabetes mellitus; GDM – Gestational diabetes mellitus; ACE – Angiotensin-converting enzyme; I/D – Insertion/deletion; RCT – Randomized Controlled Trial; UACR – Urine albumin-to-creatinine ratio.

Data collection process

Data extraction was performed independently by two authors, RK and JT, using a standardized data extraction form in Microsoft excel. The extracted data included study characteristics (author, year, population, and design, age, sex and clinical characteristics such as glycated hemoglobin levels, blood pressure, T2DM duration, body mass index), exposure details (ACE I/D genotypes), comparators (UACR measurement methods), outcomes (DN, mortality, and comorbidities), and statistical measures such as the frequency counts were also retrieved and computed in to Odds ratio with confidence intervals. Discrepancies were resolved through discussion with GNK and RA.

Data items

The data extraction captured a broad range of information including details on study design such as case control, cross-sectional or cohort, sample size and distribution between males and females, age, genotyping methods such as PCR, UACR or other DN diagnostic approaches, and outcome reporting. Genotype frequencies were entered in Excel, and odds ratio (OR) with 95% confidence intervals (CI) were calculated using R software version 4.4.2. Secondary outcomes such as comorbidities and mortality were recorded as binary variables (Yes/No) based on whether a particular study explicitly reported on them. No missing data were encountered during the meta-analysis, as only studies with complete and extractable data were included in the quantitative synthesis. Studies lacking sufficient data, as identified during visual inspection of the compiled Excel sheet, were excluded from meta-analysis and instead included in the narrative synthesis.

Risk of bias assessment

The risk of bias in individual studies was assessed using the ROBINS-E tool,³¹ which evaluates bias across key domains: confounding, selection bias, classification of interventions, and outcome assessment. Confounding was assessed as part of the ROBINS-E risk of bias evaluation, where considerations were made on whether studies appropriately controlled for potential confounders such as age, sex, duration of diabetes, and comorbidities. Where studies reported such adjustments or stratifications, these were documented and factored into the overall bias assessment. Studies were assigned an overall remark of either a low, moderate or some concerns, or high risk of bias. The risk of the bias assessments as depicted by the robvis tool³² are shown in Figure 2. The results of the bias assessment are available as Extended data. The ROBINS-E risk of bias assessment was conducted independently by CNB and SPR.

Effect measures

We included 25 studies in the meta-analysis to assess the association between ACE I/D genotypes and diabetic nephropathy risk. For the primary outcome, diabetic nephropathy (DN) assessed using urine albumin to creatinine ratio or renal function tests, odds ratio (OR) with 95% confidence intervals (CI) were used as the effect measure to compare the risk of DN across ACE I/D genotypes (II vs. ID and II vs. DD). This binary outcome metric was selected due to the categorical nature of the genotype data and the case or non-case definition of DN. Odds ratio OR were calculated using genotype frequency data. Secondary outcomes such as comorbidities (hypertension, cardiovascular disease) and mortality were synthesized narratively, and their presence (Yes) or absence (No) was recorded per study.

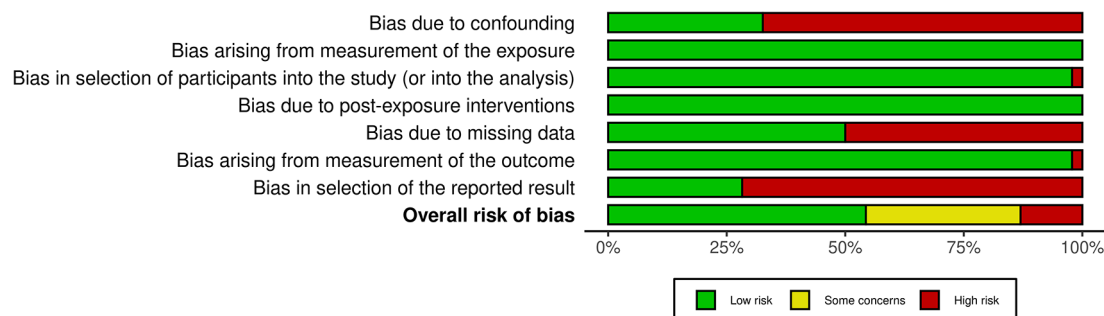


Figure 2. Bar plot summary of domain-level risk of bias judgements using the ROBINS-E tool. This bar plot illustrates the proportion of studies judged at each level of risk of bias across the seven ROBINS-E domains and overall, using the robvis tool. Most domains had a high proportion of low-risk ratings, particularly for confounding, exposure measurement, and participant selection. However, bias due to missing data and selective outcome reporting were the most frequent high-risk areas. In the "Overall risk of bias" domain, the bar plot shows approximately 60% of studies as low risk, which aligns with the actual count of 25 out of 46 studies (54%) that were included in the meta-analysis based on their low-risk rating.

Synthesis methods

Study selection and eligibility for synthesis

Studies were deemed eligible for synthesis if they included adult patients with T2DM, assessed ACE I/D polymorphisms and reported DN outcomes using laboratory-based criteria. The review included studies that assessed DN using albumin excretion rate (AER) or microalbuminuria, albumin-to-creatinine ratio (ACR), or renal function markers such as serum creatinine and estimated glomerular filtration rate (eGFR). These criteria allowed for flexible yet clinically relevant definitions of nephropathy. Study characteristics and outcome definitions were tabulated to determine synthesis eligibility. Studies without sufficient genotype data or outcome definitions were excluded.

Data preparation and conversion

Data preparation involved standardizing genotype frequency data across included studies. Frequencies for ACE I/D genotypes were extracted and used to calculate odds ratio (OR) with corresponding 95% confidence intervals (CI). For meta-analysis, all effect sizes were transformed into log odds ratios and back-transformed for interpretation. Secondary outcomes such as comorbidities and mortality were recorded as binary variables (reported vs. not reported) in Excel spreadsheets.

Reporting study outcomes

For the primary outcome, diabetic nephropathy (DN), the standardized metric used was the odds ratio (OR) with corresponding 95% confidence intervals (CI), comparing DN prevalence across ACE I/D genotypes (II, ID, DD). OR were chosen because they are appropriate for summarizing associations in observational studies. Genotype frequencies from individual studies were extracted into Microsoft Excel, and OR were calculated using R software (version 4.4.2). These OR were log-transformed for meta-analysis to stabilize variance and ensure normality assumptions. The pooled estimates were then back-transformed to the original OR scale.

For secondary outcomes, such as mortality, cardiovascular disease, hypertension, neuropathy, and retinopathy, data were extracted into Excel as binary indicators (Yes/No) depending on whether each study reported on the specific outcome.

Statistical models

The primary effect measure used was the odds ratio (OR) for the association between ACE I/D genotypes and DN. Random-effects models were used for all meta-analyses to account for between-study heterogeneity in population, study design, and UACR diagnostic methods. Statistical significance was determined at $p < 0.05$. Heterogeneity was assessed using the I^2 and τ^2 statistics. Meta-regression was performed to explore heterogeneity sources, particularly differences in urinary albumin measurement methods (ACR vs. AER). All statistical estimates were generated using R software (version 4.4.2).

Presentation of results

Forest plots were generated to visually present pooled OR and 95% CI. Individual study estimates and weights were shown. Funnel plots and Egger's regression tests assessed publication bias. All statistical visualizations and analyses were produced in R software. Reporting bias was examined via funnel plots and Egger's test; no significant asymmetry was detected.

Subgroup and sensitivity analyses

To explore sources of heterogeneity, subgroup analyses were conducted based on urinary albumin measurement methods (ACR vs. AER) of the included studies. Meta-regression was used to assess the potential influence of these study-level characteristics on effect size estimates.

Sensitivity analyses were conducted using a leave-one-out approach, in which each study was sequentially removed from the meta-analysis to evaluate the robustness and stability of the pooled effect estimates.

Reporting bias assessment

Selective outcome reporting and qualitative assessments were done through quality appraisal of the studies conducted using the STREGA reporting guidelines. KR and DT assessed adherence, with discrepancies resolved by ENO and BBA.

Studies were rated as fair, good, very good, or excellent. Excellent studies provided thorough methodological and genotyping details; very good ones had minor gaps; good studies had moderate reporting deficiencies; and fair studies lacked core STREGA elements. The full results of STREGA appraisal are provided in the Extended data.

Certainty assessment

We did not apply the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework,³³ which is best suited for intervention studies. Instead, we appraised the certainty of evidence by triangulating risk of bias (via ROBINS-E), reporting quality of studies (via STREGA), consistency, precision of pooled estimates, and the direction of effects across studies.

Results

Study selection

The initial search across PubMed, EMBASE, Web of Science, Google Scholar, and reference lists yielded 968 records. After 189 duplicates were removed, 779 unique records were screened for eligibility. During the screening process,

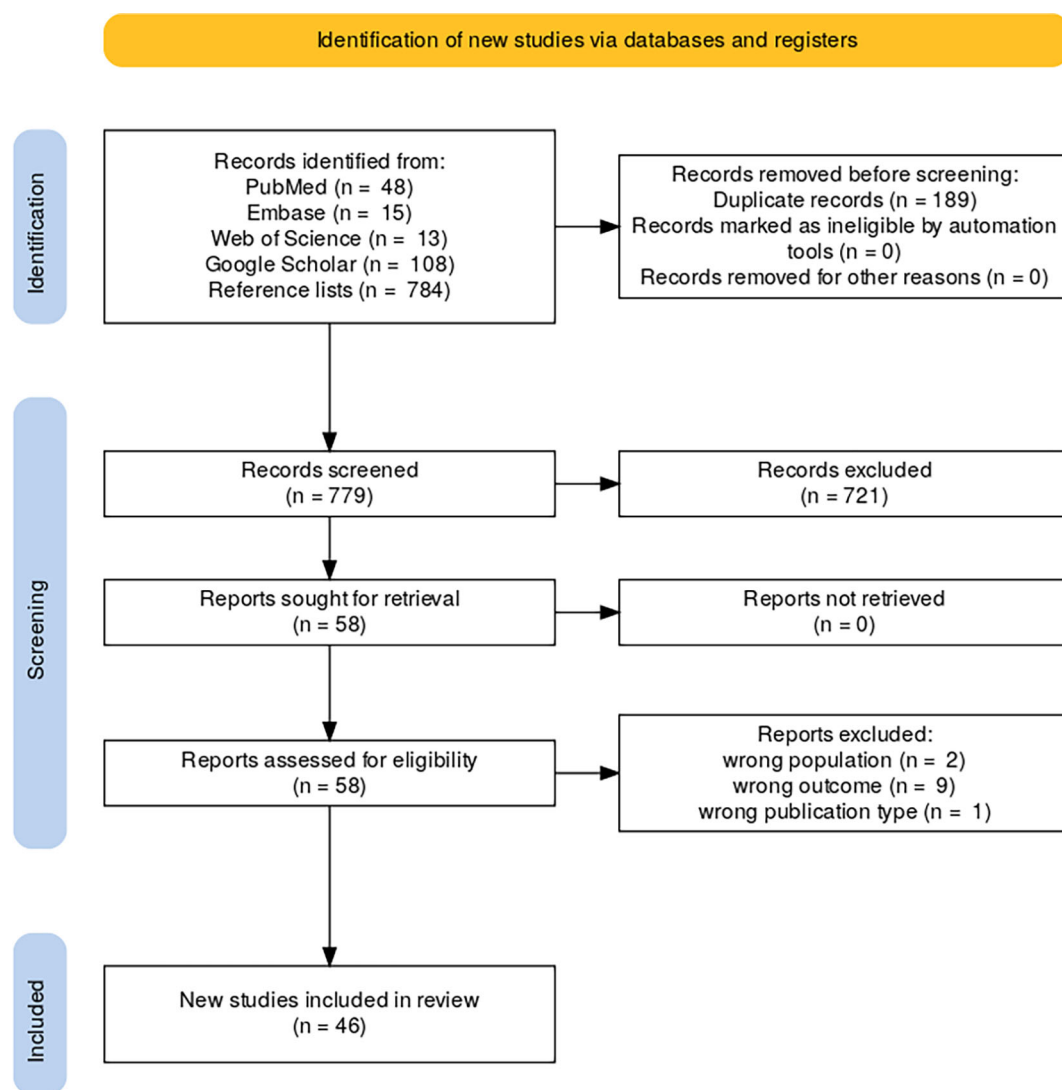


Figure 3. PRISMA 2020 flow diagram for study selection. This flow diagram outlines the process of identifying, screening, and including studies in the review. A total of 968 records were identified through database searches and reference lists: PubMed (n = 48), Embase (n = 15), Web of Science (n = 13), Google Scholar (n = 108), and reference lists (n = 784). After removing 189 duplicates, 779 records were screened. Of these, 721 were excluded based on title and abstract screening, and 58 full-text reports were assessed for eligibility. Twelve reports were excluded due to; wrong population (n = 2), wrong outcome (n = 9), or wrong publication type (n = 1). Ultimately, 46 studies were included in the final review.

721 records were excluded based on the title and abstract review. A total of 58 full-text articles were retrieved, all of which were successfully accessed. After full-text assessment, 12 studies were excluded due to incorrect population ($n = 2$), wrong outcome ($n = 9$), or wrong publication type ($n = 1$). Ultimately, 46 studies met the inclusion criteria and were included in this systematic review and meta-analysis. The complete screening and selection process is summarized in the PRISMA 2020 flowchart³⁴ as shown in [Figure 3](#).

Exclusion of ineligible studies

After full-text review, 12 studies that initially appeared to meet inclusion criteria were excluded for the following reasons: a) Wrong publication type ($n = 1$): Panagiotopoulos et al.,³⁵ was a narrative review rather than a primary research study. b) Wrong outcome ($n = 9$): These studies, including Wong et al.,³⁶ investigated ACE polymorphisms however, interest was with macroangiopathy and not type 2 diabetes mellitus associated nephropathy; Ahluwalia et al.,³⁷ and Pai et al.,³⁸ assessed ACE polymorphisms not as insertion/deletion SNPs. Fujisawa et al.,³⁹ presented ACE I/D polymorphisms data in relation to retinopathy and myocardial infarction but not diabetic nephropathy (DN). Taha et al.,⁴⁰ assessed ACE polymorphisms in type 2 diabetes mellitus patients but did not stratify them into nephropathy cases and controls. Araz et al.,⁴¹ ACE ID, DD, II were not distributed across UACR/albuminuric groups. Canani et al.,⁴² ACE DD and ID genotypes were not reported independently. Wong et al.,⁴³ distribution of ACE I/D across different DN categories determined by UACR/Microalbuminuria/AER was not done. Draman et al.,⁴⁴ microalbuminuria/UACR was not measured. c) Wrong Population ($n = 2$): Pontremoli et al.,⁴⁵ focused on essential Hypertension and Al-Harbi et al.,⁴⁶ in the methods section of the full text did not specify the population as type 2 diabetes mellitus (T2DM) but unrelated adult patients. These studies were excluded to ensure consistency with our predefined Population Exposure Comparator Outcome (PECO) criteria and focus on clinically relevant DN outcomes in adults with T2DM.

Study characteristics

We followed the Centre for Reviews and Dissemination (CRD) approach⁴⁷ and the Synthesis Without Meta-analysis (SWiM) guidelines⁴⁸ due to their detailed and structured framework. Forty-six (46) observational studies investigating the association between ACE I/D polymorphisms and DN in patients with T2DM were examined. The total sample size across all studies was 16,322 participants, with individual study populations ranging from 50 to 3744 participants. The combined mean of mean age in the studies was 58.11 (± 4.30). The combined median of mean numbers of males was 90.5 (IQR: 62.75-171.5) and that of females was 105.5 (IQR: 57.0-183.75). Most studies were conducted in Asia (29/46), Europe (8/46), Middle East (6/46) and Africa (5/46) reflecting a diverse geographical representation. Studies were grouped based on outcome assessment methods (ACR vs. AER), study design (case-control, cross-sectional, or cohort), and genotype comparisons (II vs. DD, II vs. ID), to account for methodological and clinical heterogeneity and to enable meaningful synthesis of effect estimates across similar contexts. Most studies assessed the primary outcome of DN using either ACR^{23,25,49–70} or AER,^{71–91} whereas only one study used traditional renal function tests⁹² (serum creatinine, eGFR, and urea levels). Genotyping for ACE I/D polymorphism was primarily conducted using polymerase chain reaction (PCR) methods, including conventional PCR, PCR-RFLP, high-resolution melting, and sequencing approaches. While all studies reported ACE I/D genotype distributions and DN outcomes, only five studies (10.7% of 46) explored associations with comorbidities, and one (2.2% of 46) reported on mortality. The majority identified either the D allele or DD genotype as being associated with increased DN risk, although several (40/46) reported null or population-specific findings.

The geographical distributions of the studies included in this review are shown in [Figure 4](#).

Examining ACE I/D polymorphism in relation to diabetic nephropathy and comorbidities

Due to the limited number of studies addressing ACE I/D polymorphism in relation to diabetic nephropathy and associated comorbidities, the included studies were synthesized narratively rather than statistically. The summary of findings examining ACE I/D polymorphism in relation to diabetic nephropathy and comorbidities is presented in [Table 2](#).

Quantitative synthesis of ACE I/D polymorphism in diabetic nephropathy

From the 46 studies, only those with a low overall score on the ROBINS E assessment were included in the quantitative synthesis. We conducted a meta-analysis, meta-regression, subgroup analysis, sensitivity analysis, and publication bias assessment on 25 studies to evaluate the association between ACE I/D polymorphisms and diabetic nephropathy (DN) in the study population.

Meta-analysis

This was conducted in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines,⁹³ and the corresponding checklist was completed to ensure comprehensive and transparent reporting. The included studies were deemed appropriate for assessing the hypothesis as they reported on ACE I/D genotypes and diabetic nephropathy outcomes in adult T2DM populations. Data were selected and coded based on sound clinical

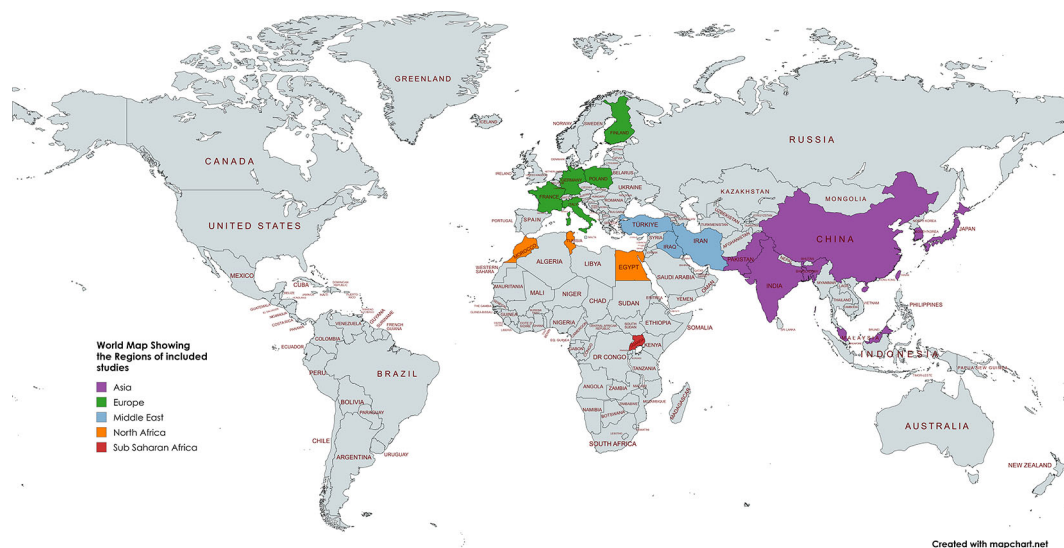


Figure 4. Geographical distribution of studies included in the review. This world map illustrates the countries where the 46 studies included in the systematic review were conducted. The studies are distributed across several regions, including Asia (China, Japan, South Korea, India, Pakistan, Taiwan, Bangladesh, Malaysia), the Middle East (Iran, Iraq), Europe (Finland, France, Germany, Italy, Poland, Turkey), and Africa (Egypt, Morocco, Tunisia, Uganda). Countries are color-coded to reflect regional groupings. The map was generated using [MapChart.net](#).

principles, prioritizing studies that clearly defined diabetic nephropathy using established albuminuria or renal function markers and reported ACE I/D genotype distributions relevant to the study objectives. Data classification and coding were performed independently by two reviewers using a standardized extraction template. Most included studies used standardized measures of albuminuria to define nephropathy, ensuring relevance to the primary outcome and alignment with the review objective. Data classification and coding were performed independently by two reviewers (RK and JT) using a standardized extraction template. Discrepancies were resolved through discussion with another reviewer; EAO, ensuring consistency and minimizing bias, although formal blinding and interrater reliability statistics were not applied.

Random-effects models using the DerSimonian–Laird method⁹⁴ were used to estimate the pooled odds ratios (ORs) and 95% confidence intervals (CIs) across genotype comparisons to account for expected heterogeneity in study populations and methodologies across the included observational studies. Genotype II was associated with a lower risk of developing DN. The random-effects models showed a significant protective effect of the homozygous insertion (II) genotype, with pooled odds ratio (OR) of 0.70 (95% CI: 0.63–0.77) versus heterozygous insertion/deletion (ID) and 0.68 (95% CI: 0.55–0.84) versus homozygous deletion (DD). Heterogeneity across studies was moderate to substantial ($I^2 = 71.7\%$, $\tau^2 = 0.1776$, $p < 0.0001$), suggesting variability in the effect estimates, possibly due to methodological or population differences. A forest plot summarizing the pooled estimates and heterogeneity is shown in [Figure 5](#).

Meta-regression

Meta-regression was performed to explore the sources of heterogeneity in the association between ACE I/D genotypes and diabetic nephropathy (DN) risk. In the crude model ($k = 25$; DerSimonian–Laird estimator), the residual heterogeneity was $\tau^2 = 0.1100$ (SE = 0.0917; $\tau = 0.3317$), with $I^2 = 52.3\%$ ($p = 0.0141$) and $R^2 = 38.06\%$. The test for residual heterogeneity was significant (QE(12) = 25.16, $p = 0.0141$), while the test for moderators was not (QM(12) = 16.56, $p = 0.17$), indicating limited explanatory power overall. However, the form of UACR measurement was a significant individual predictor ($\beta = 0.57$, SE = 0.19, $p = 0.0033$; 95% CI: 0.19–0.95), suggesting that variations in measurement methods contributed meaningfully to heterogeneity in DN risk estimates. In the adjusted model, which included additional moderators, the residual heterogeneity increased ($\tau^2 = 0.1253$, SE = 0.0692; $\tau = 0.3540$), with $I^2 = 63.0\%$ ($p < 0.0001$) and $R^2 = 29.45\%$. The overall test for residual heterogeneity remained significant (QE(23) = 62.21, $p < 0.0001$). The test of moderators was significant (QM(1) = 5.79, $p = 0.016$), confirming that the form of UACR measurement remained a key source of heterogeneity ($\beta = 0.40$, SE = 0.17, $p = 0.016$; 95% CI: 0.07–0.72). The results are summarized in [Table 3](#).

Subgroup analysis

Subgroup analyses were based on the methods used to assess the primary outcome which is DN and these included; ACR, AER and RFTs. They revealed differences in the strength of associations between ACE I/D genotypes and diabetic

Table 2. Summary of included studies examining ACE I/D polymorphism in relation to diabetic nephropathy and comorbidities.

First author, year	Study design	Method of ACE I/D genotyping	Diabetic nephropathy assessment	Results/conclusion	Reported ACE I/D polymorphism and mortality/comorbidities in DN
Araz et al., 2001	Cross-sectional	Polymerase chain reaction	Albumin-creatinine ratio	No link found between ACE I/D polymorphism and DN or DR in Turkish T2DM patients.	Yes
Arfa et al., 2008	Case-control	Polymerase chain reaction	Albumin Excretion rate	Preliminary findings show no association between ACE I/D polymorphism, T2DM, or DN in Tunisians.	No
Grzeszczak et al., 1998	Case-control	Polymerase chain reaction	Albumin-creatinine ratio	No association found between ACE I/D, PstI polymorphisms and nephropathy in NIDDM.	No
Gupta et al., 2023	Cross-sectional	Polymerase chain reaction	Albumin-creatinine ratio	VEGF D allele linked to DR in DN patients, highlighting VEGF's role in retinopathy.	Yes
Kiconco et al., 2024	Cross-sectional	PCR	Microalbuminuria	ACE I/D affects metabolic markers, not nephropathy.	No
Luo et al., 2019	Case-control	PCR with sequencing	Albumin Excretion rate	ACE gene at the rs4646994 locus may increase the risk of developing DN.	No
Parchwani et al., 2013	Case-control	Polymerase chain reaction	Albumin Excretion rate	ACE DD variant linked to higher DN risk, not severity, in T2DM.	No
Uddin et al., 2007	Case-control	PCR	Albumin Excretion rate	Percentage of DD genotype and D allele was significantly higher in DN compared to controls.	No
Viswanathan et al., 2001	Case-control	PCR	Albumin-creatinine ratio	D allele linked to nephropathy; no ID/DD distribution difference.	No
Yahya et al., 2024	Cross-sectional	PCR	Albumin-creatinine ratio	DD genotype linked to 2× DN risk; AGT1R A1166C not associated with DN in Iraqi T2DM.	No
Yahya et al., 2024	Cross-sectional	HRM-RT and PCR-RFLP	Albumin-creatinine ratio	ID and AC genotypes linked to lower ACE1/2, lower ACR, better ACEI response.	No

This table provides a summary of selected. It includes details on study design, methods of ACE I/D genotyping, approaches used to assess DN (albumin-to-creatinine ratio, albumin excretion rate, or microalbuminuria), main findings or conclusions, and whether mortality or comorbid conditions (such as retinopathy, cardiovascular disease) related to ACE I/D polymorphism were reported. Most studies employed polymerase chain reaction (PCR) techniques for genotyping and utilized albumin-based measures to assess nephropathy. While several studies reported a significant association between the D allele or DD genotype and DN, comorbidity and mortality data were less frequently examined or reported.

Note: The full Table 2 is available as Extended Data.

Abbreviations: ACE, angiotensin-converting enzyme; ACEI, angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; AGT, angiotensinogen; AGT1R, angiotensin II type 1 receptor; ALR2, aldose reductase 2; DD, homozygous deletion genotype; DN, diabetic nephropathy; DR, diabetic retinopathy; HRM-RT, high-resolution melt real-time; ID, heterozygous insertion/deletion genotype; I/D, insertion/deletion; NIDDM, non-insulin-dependent diabetes mellitus; PCR, polymerase chain reaction; PCR-RFLP, polymerase chain reaction–restriction fragment length polymorphism; T2DM, type 2 diabetes mellitus; VEGF, vascular endothelial growth factor.

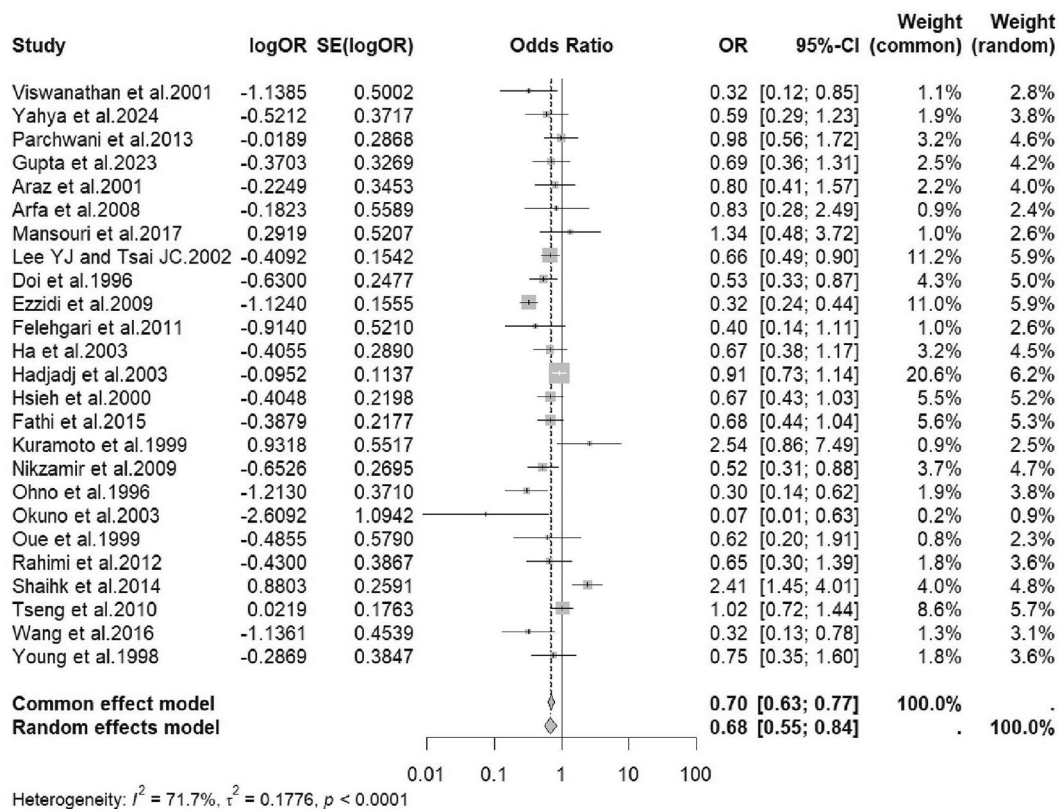


Figure 5. Forest plot of pooled odds ratios from meta-analysis of ACE I/D polymorphism and diabetic nephropathy risk. This forest plot presents the individual and pooled odds ratio (OR) with corresponding 95% confidence intervals (CIs) for studies included in the meta-analysis assessing the association between ACE I/D polymorphism and the risk of diabetic nephropathy. Each horizontal line represents the confidence interval for a single study, with the square marker indicating the point estimate of the OR. The size of each square reflects the weight assigned to the study in the random-effects model. The diamond at the bottom of the plot represents the overall pooled OR, with a value of 0.68 (95% CI: 0.55–0.84). The heterogeneity among studies was moderate ($I^2 = 71.7\%$, $p < 0.0001$).

nephropathy (DN) risk. Studies using albumin-to-creatinine ratio (ACR) showed the strongest protective effect of the II genotype, with pooled odds ratio (OR) of 0.59 (95% CI: 0.47–0.75) under the random-effects model and 0.59 (95% CI: 0.51–0.67) under the common-effect model. For studies using the albumin excretion rate (AER), the association was weaker (random-effects OR = 0.71, 95% CI: 0.55–0.92; common-effect OR = 0.77, 95% CI: 0.66–0.90). The weakest association was observed in the study using renal function tests (RFTs), with a random-effects OR of 0.68 (95% CI: 0.55–0.84) and a common-effect OR of 0.70 (95% CI: 0.63–0.77). Heterogeneity varied across subgroups: $I^2 = 60.3\%$ ($p = 0.0019$) for ACR and $I^2 = 58.3\%$ ($p = 0.0102$) for AER; no heterogeneity was detected in the RFT-based subgroup. These results suggested that the method used to assess DN may influence the estimated association between ACE I/D polymorphisms with DN risk. The full summary of subgroup results is presented in Table 4.

Sensitivity analyses

Leave-one-out sensitivity analysis was conducted to assess the robustness of the findings and the influence of individual studies on the pooled effect estimates. One study was excluded at a time, and the overall odds ratio (OR) and 95% confidence interval (CI) were calculated. The pooled log OR ranged from -0.34 to -0.45, with minimal variation across iterations. The confidence intervals remained narrow and did not cross the null, suggesting consistent associations. The exclusion of Shaihk et al.⁹² produced the most marked change (log OR = -0.4474; 95% CI: -0.6255 to -0.2692), followed by Kuramoto et al.⁸¹ and Tseng et al.,⁶⁶ though none altered the overall interpretation. These results indicated that no single study had a disproportionate impact on the association between ACE I/D genotypes and diabetic nephropathy in the meta-analysis. The full results are shown in Table 5 and visualized in Figure 6.

Table 3. Meta-Regression of Study-Level covariates on the association between ACE I/D polymorphism and diabetic nephropathy risk.

Covariate	Estimate	SE	z-value	p-value	CI lower	CI upper	Interpretation
Mean Age	-0.0533	0.0347	-1.5335	0.1251	-0.1214	0.0148	Older populations may trend toward lower effect sizes; not significant
Mean SBP (mmHg)	-0.0287	0.0278	-1.0342	0.3011	-0.0832	0.0257	Higher SBP may be weakly associated with lower effect, but not significant
Mean DBP (mmHg)	0.0348	0.0401	0.8673	0.3858	-0.0438	0.1134	Higher DBP shows a non-significant positive trend
Mean HbA1c (%)	-0.0775	0.1558	-0.4973	0.619	-0.3828	0.2279	Higher HbA1c not significantly associated with effect size
BMI (Kg/m ²)	0.033	0.0465	0.7097	0.4779	-0.0581	0.1241	BMI does not significantly influence the association
Mean T2D duration (years)	0.0267	0.0414	0.6441	0.5195	-0.0544	0.1077	Duration of diabetes not a significant moderator
Hypertension (Yes/No)	0.4198	0.3045	1.3788	0.168	-0.1769	1.0165	Non-significant trend toward stronger effect in hypertensive populations
Cardiovascular Disease (Yes/No)	-0.7762	0.4844	-1.6022	0.1091	-1.7256	0.1733	Suggestive but non-significant inverse association in CVD populations
Stroke (Yes/No)	1.0204	0.8991	1.135	0.2564	-0.7417	2.7825	No significant association with stroke prevalence
Retinopathy (Yes/No)	0.0338	0.2426	0.1395	0.889	-0.4416	0.5093	Retinopathy status not associated with effect size
Neuropathy (Yes/No)	0.3655	0.6829	0.5352	0.5925	-0.973	1.704	Neuropathy not significantly associated with pooled effect
Form of UACR measured	0.57	0.194	2.938	0.0033*	0.1898	0.9503	Significant moderator - quantitative UACR methods associated with stronger genotype-DN associations

This table summarizes the results of a meta-regression analysis evaluating potential moderators of the association between ACE I/D polymorphism and diabetic nephropathy (DN) across included studies. For each covariate, the regression estimate, standard error (SE), z-value, p-value, and 95% confidence interval (CI) are presented, along with an interpretation. While most clinical and demographic variables (age, blood pressure, HbA1c, T2D duration) were not statistically significant moderators, the form of UACR measurement (ACR, AER, RFTs) was significantly associated with effect size ($p = 0.0033$).

Abbreviations: BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; DBP, diastolic blood pressure; DN, diabetic nephropathy; HbA1c, glycated hemoglobin A1c; OR, odds ratio; SBP, systolic blood pressure; SE, standard error; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio; ACR, albumin-to-creatinine ratio; AER, albumin excretion rate; RFTs, renal function tests.

Table 4. Subgroup meta-analysis of ACE I/D polymorphism and diabetic nephropathy risk by biomarker type (ACR, AER, and RFT).

Study/Sub-Group (Heterogeneity testing)	logOR	SE (logOR)	OR	95% confidence Intervals	Weight (Common)	Weight (Random)
ACR (Heterogeneity: $I^2 = 60.3\%$, $t^2 = 0.0931$, $p = 0.0019$)						
Araz et al. 2001	-0.2249	0.3453	0.80	[0.41 – 1.57]	2.2	4.0
Doi et al. 1996	-0.6300	0.2477	0.53	[0.33 – 0.87]	4.3	5.0
Ezzidi et al. 2009	-1.1240	0.1555	0.32	[0.24 – 0.44]	11.0	5.9
Felehgari et al. 2011	-0.9140	0.5210	0.40	[0.14 – 1.11]	1.0	2.6
Gupta et al. 2023	-0.3703	0.3269	0.69	[0.36 – 1.31]	2.5	4.2
Ha et al. 2003	-0.4055	0.2890	0.67	[0.38 – 1.17]	3.2	4.5
Lee YJ and Tsai JC 2002	-0.4092	0.1542	0.66	[0.49 – 0.90]	11.2	5.9
Mansouri et al. 2001	0.2919	0.5207	1.34	[0.48 – 3.72]	1.0	2.6
Oue et al. 1999	-0.4855	0.5790	0.62	[0.20 – 1.91]	0.8	2.3
Rahimi et al. 2012	-0.4300	0.3867	0.65	[0.30 – 1.39]	1.8	3.6
Teng et al. 2010	0.0219	0.1763	1.02	[0.72 – 1.44]	8.6	5.7
Viswanathan et al. 2001	-1.1385	0.5002	0.32	[0.12 – 0.85]	1.1	2.7
Wang et al. 2016	-1.1361	0.4539	0.32	[0.13 – 0.78]	1.3	3.1
Yahya et al. 2024	-0.5212	0.3717	0.59	[0.29 – 1.23]	1.9	3.7
Common effects model	–	–	0.59	[0.51 – 0.67]	51.8%	–
Random effects model	–	–	0.59	[0.47 – 0.75]	–	55.9%
AER (Heterogeneity: $I^2 = 58.3\%$, $t^2 = 0.0730$, $p = 0.0102$)						
Arfa et al. 2008	-0.1823	0.5589	0.83	[0.28 – 2.49]	0.9	2.4
Fathi et al. 2015	-0.3879	0.2177	0.68	[0.44 – 1.04]	5.6	5.3
Hadjadji et al. 2003	-0.0952	0.1137	0.91	[0.73 – 1.14]	20.6	6.3
Hsieh et al. 2000	-0.4048	0.2198	0.67	[0.43 – 1.03]	5.5	5.3
Kuramoto et al. 1999	0.9318	0.5517	2.54	[0.86 – 7.49]	0.9	2.4
Nikzamir et al. 2009	-0.6526	0.2695	0.52	[0.31 – 0.88]	3.7	4.7
Ohno et al. 1996	-1.2130	0.3710	0.30	[0.14 – 0.62]	1.9	3.7
Okuno et al. 2003	-2.6092	1.0942	0.07	[0.01 – 0.63]	0.2	0.8
Parchwani et al. 2013	-0.0189	0.2868	0.98	[0.56 – 1.72]	3.2	4.6
Young et al. 1998	-0.2869	0.3847	0.75	[0.35 – 1.60]	1.8	3.6
Common effects model	–	–	0.77	[0.66 – 0.90]	44.3%	–
Random effects model	–	–	0.71	[0.55 – 0.92]	–	39.2%
RFTs (Heterogeneity: Not Computed)						
Shaihk et al. 2014	0.8803	0.2591	2.41	[1.45 – 4.01]	4.0	4.9
Common effects model	–	–	0.70	[0.63 – 0.77]	100%	–
Random effects model	–	–	0.68	[0.55 – 0.84]	–	100%

This table presents a subgroup meta-analysis stratified by the biomarker used to define diabetic nephropathy: Albumin-Creatinine Ratio (ACR), Albumin Excretion Rate (AER), and Renal Function Tests (RFT). For each study within the subgroups, the log odds ratio (logOR), standard error of the logOR, odds ratio (OR), 95% confidence interval (CI), and study weights under both common and random effects models are reported. Heterogeneity within each subgroup is indicated using I^2 , τ^2 , and corresponding p-values. In the ACR subgroup ($I^2 = 60.3\%$, $p = 0.0019$), a random effect pooled OR of 0.59 (95% CI: 0.47–0.75) suggests a protective association. The AER subgroup ($I^2 = 58.3\%$, $p = 0.0102$) showed a similar trend with a random effect OR of 0.71 (95% CI: 0.55–0.92). The RFT subgroup includes a single study (Shaikh et al., 2014), reporting a significant association (OR = 2.41, 95% CI: 1.45–4.01), though heterogeneity could not be computed.

Abbreviations: AER, albumin excretion rate; ACR, albumin-creatinine ratio; RFT, renal function tests; OR, odds ratio; CI, confidence interval; SE, standard error; I^2 , percentage of variation across studies due to heterogeneity; τ^2 , between-study variance.

Table 5. Sensitivity analysis of individual studies included in the meta-analysis of ACE I/D genotypes and diabetic nephropathy.

Study	OR	95% CI lower	95% CI upper
Araz et al. 2001	-0.3966089	-0.6166201	-0.1765978
Arfa et al. 2008	-0.3945578	-0.6110598	-0.1780557
Doi et al. 1996	-0.3771501	-0.5979375	-0.1563626
Ezzidi et al. 2009	-0.3353554	-0.5341380	-0.1365728
Fathi et al. 2015	-0.3901966	-0.6134694	-0.1669238
Felehgari et al. 2011	-0.3749063	-0.5898228	-0.1599899
Gupta et al. 2023	-0.3906916	-0.6114558	-0.1699273
Ha et al. 2003	-0.3891762	-0.6107695	-0.1675828
Hadjadj et al. 2003	-0.4090621	-0.6311435	-0.1869808
Hsieh et al. 2000	-0.3892575	-0.6124589	-0.1660562
Kuramoto et al. 1999	-0.4196006	-0.6267025	-0.2124986
Lee YJ and Tsai JC. 2002	-0.3890242	-0.6136330	-0.1644155
Mansouri et al. 2017	-0.4072607	-0.6214458	-0.1930757
Nikzamir et al. 2009	-0.3765290	-0.5966524	-0.1564056
Ohno et al. 1996	-0.3558761	-0.5648249	-0.1469272
Okuno et al. 2003	-0.3697799	-0.5791523	-0.1604074
Oue et al. 1999	-0.3871209	-0.6034409	-0.1708009
Parchwani et al. 2013	-0.4071222	-0.6259972	-0.1882471
Rahimi et al. 2012	-0.3881874	-0.6076244	-0.1687504
Shaihk et al. 2014	-0.4473571	-0.6255171	-0.2691971
Tseng et al. 2010	-0.4139499	-0.6325336	-0.1953663
Viswanathan et al. 2001	-0.3675264	-0.5801649	-0.1548878
Wang et al. 2016	-0.3649410	-0.5771711	-0.1527110
Yahya et al. 2024	-0.3845316	-0.6039635	-0.1650997
Young et al. 1998	-0.3936058	-0.6130589	-0.1741526

This table summarizes the results of sensitivity analyses for individual studies included in the meta-analysis. For each study, the log-transformed odds ratio (OR) and its corresponding 95% confidence interval (CI) bounds are presented. The sensitivity analysis evaluates the stability and influence of each study on the overall pooled estimate by recalculating the log OR after removing one study at a time. **Abbreviations:** ACE – Angiotensin-Converting Enzyme; I/D – Insertion/Deletion; DN – Diabetic Nephropathy; OR – Odds Ratio; CI – Confidence Interval.

Publication bias

The funnel plot shown in [Figure 7](#) and Egger's regression test were used to assess the publication bias. The plot shows a relatively symmetrical distribution around the pooled effect size, with no substantial asymmetry. Egger's test ($t = -0.61$, $df = 23$, $p = 0.55$; bias = -0.50, SE = 0.82) indicated no significant small study effects. The residual heterogeneity variance was $\tau^2 = 3.62$, using standard error as the predictor and inverse-variance weights. Given the lack of asymmetry, a trim-and-fill analysis was not performed. These results suggest that the pooled estimates are unlikely to be affected by publication bias.

Reporting bias assessment

Assessment of reporting bias was informed by the "Selection of Reported Result" domain in ROBINS-E and several reporting items in STREGA. In ROBINS-E, most studies were rated as having a moderate risk for selective reporting, indicating that not all measured outcomes may have been reported. In the STREGA assessment, most studies did not report sample size justification or apply multiple testing correction, and Hardy-Weinberg Equilibrium (HWE) was tested in only a few. These findings suggest a moderate risk of bias due to missing or selectively reported results across the included studies.

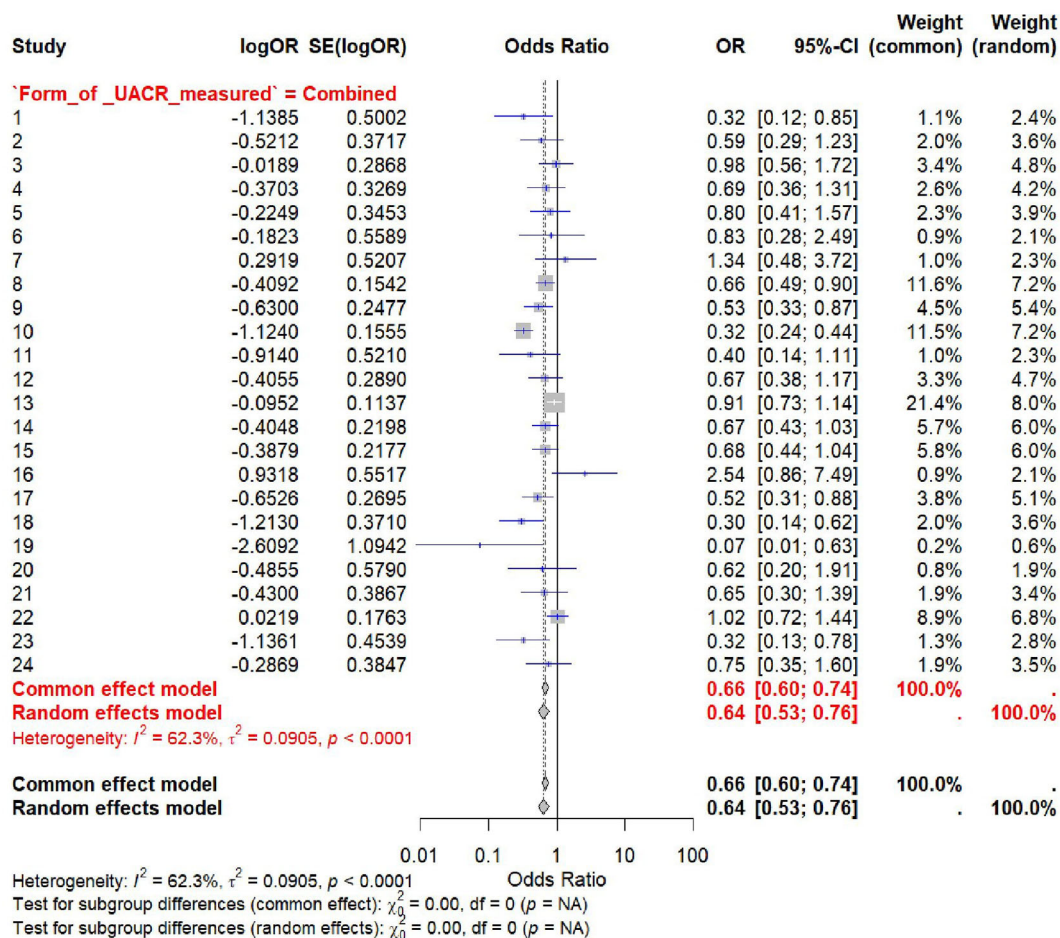


Figure 6. Leave-One-Out sensitivity analysis of the association between ACE I/D genotypes and diabetic nephropathy. This forest plot illustrates the results of a leave-one-out sensitivity analysis. Each line represents the pooled odds ratio (OR) and 95% confidence interval (CI) calculated by excluding one study at a time from the overall analysis. The consistency of effect estimates across iterations indicates that no single study unduly influenced the pooled results. The overall pooled OR remains significant and stable (OR = 0.64; 95% CI: 0.53–0.76) under the random-effects model. Heterogeneity was moderate ($I^2 = 62.3\%$, $p < 0.0001$), and the form of UACR measurement was included as a subgroup moderator.

Abbreviations: ACE – Angiotensin-Converting Enzyme; I/D – Insertion/Deletion; OR – Odds Ratio; CI – Confidence Interval; SE – Standard Error; UACR – Urine Albumin-to-Creatinine Ratio.

Certainty of evidence

The certainty of the evidence in this review was appraised qualitatively, as the GRADE approach was not applied due to the observational nature of the included genetic association studies. Instead, confidence in the findings was supported by several methodological safeguards: risk of bias was assessed using the ROBINS-E tool, guiding the inclusion of only low-risk studies in the meta-analysis; reporting quality was evaluated using the STREGA checklist to ensure transparency and reproducibility; and consistency, direction, and precision of effect estimates were examined across studies. Out of 46 studies, 25 were rated as having low risk of bias, 15 as moderate or some concerns, and 6 as high according to ROBINS-E. STREGA compliance ratings showed that 19 studies were rated as very good, 13 as fair, 9 as good, and 5 as excellent. Based on this distribution, the overall confidence in the evidence is moderate, reflecting generally sound methodology and reporting, though limitations in transparency and bias remain in a subset of studies.

Heterogeneity was assessed using I^2 and τ^2 statistics and explored further through subgroup and meta-regression analyses. Publication bias was evaluated through funnel plots and Egger's regression test. Together, these assessments provide a moderate to high level of confidence in the observed association between ACE I/D genotypes and diabetic nephropathy, particularly the protective effect of the II genotype. However, the certainty of evidence for secondary outcomes, such as mortality and comorbidities, remains low due to limited data.

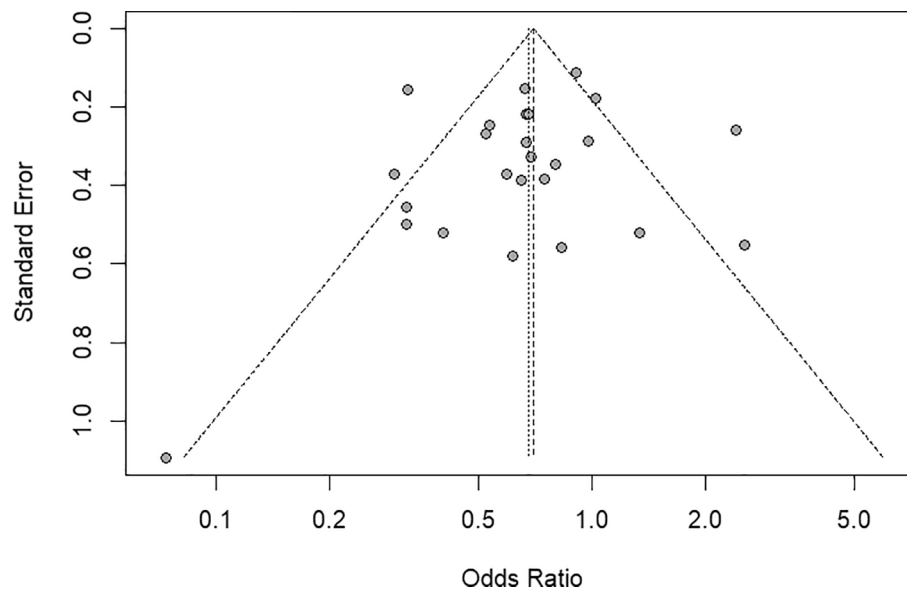


Figure 7. Funnel plot for assessing publication bias in studies on ACE I/D genotypes and diabetic nephropathy. This funnel plot visualizes the distribution of studies included in the meta-analysis. The plot displays the standard error (y-axis) against the odds ratio (x-axis) for each study. Symmetry of the scatter around the pooled effect estimate suggests the absence of significant publication bias. The majority of studies fall within the pseudo 95% confidence limits (dashed lines).

Abbreviations: ACE – Angiotensin-Converting Enzyme; I/D – Insertion/Deletion; OR – Odds Ratio; SE – Standard Error.

Discussion

We evaluated the association between ACE insertion/deletion (I/D) polymorphisms and DN in T2DM patients, with a focus on differences in UACR assessments, study populations, and clinical outcomes such as hypertension, cardiovascular disease, stroke and mortality from DN. Narrative synthesis demonstrated a generally consistent association between ACE I/D variants and DN risk, although the effect sizes varied across studies. The extent to which ACE I/D genotypes influence DN outcomes likely varies depending on several intersecting factors. Population characteristics, such as geographical location, age, sex, and prevalence of hypertension or other metabolic comorbidities, which modify the genetic effect of the ACE I/D polymorphism. For example, the distribution of I/D alleles and their association with DN may differ among Asian, African, and European populations due to underlying genetic diversity and environmental exposure.

The meta-analysis revealed that individuals with the ACE II genotype had significantly lower odds of developing diabetic nephropathy compared to those with ID or DD genotypes, highlighting a protective genetic association as the primary outcome of this systematic review. Previous studies that encompassed ethnicity on this topic found that there was a reduced risk of diabetic nephropathy associated with genotype II among Europeans (Caucasians) with type 2 diabetes, although this observation was more applicable to Asians (Chinese, Japanese, Koreans).^{22,95} Moreover, the meta-analysis confirmed a statistically significant protective association of the II genotype compared to both ID and DD genotypes, consistent with prior research implicating the renin–angiotensin–aldosterone system (RAAS) in DN pathogenesis.^{22,56,95} These findings reinforce the hypothesis that genetic variation at the ACE locus contributes to an individual's susceptibility to DN. However, the modest magnitude of the effect suggests that this polymorphism is likely one of multiple genetic contributors within a polygenic framework, as noted from the heterogeneity in the method used to assess diabetic nephropathy in primary studies.

We observed that the identification of DN cases varied considerably across studies. Most studies assessed DN using either ACR or AER, while only one study relied on traditional renal function tests, such as serum creatinine, estimated glomerular filtration rate (eGFR), or urea levels. This inconsistency in diagnostic criteria significantly affects the comparability and generalizability of reported genotype-phenotype associations. Moreover, in our meta-regression analysis, the UACR measurement method emerged as a critical moderator of heterogeneity, underscoring the methodological influence on the pooled effect sizes. Although these biochemical markers are practical for large-scale research and clinical use, they are surrogates rather than definitive diagnostic tools. Notably, kidney histology remains the gold

standard for diagnosing DN, offering detailed insight into glomerular and tubular changes.⁹⁶ However, renal biopsy is rarely performed due to its invasive nature, associated risks, and ethical limitations in asymptomatic populations.⁹⁷

Subgroup analyses revealed stronger genotype-phenotype associations in studies using urinary albumin-to-creatinine ratio (UACR) compared to albumin excretion rate (AER) or serum-based renal function tests. These findings align with prior recommendations advocating standardized albuminuria assessment in DN research to improve reproducibility and comparability across studies.^{98,99} Methodological inconsistency in DN diagnosis remains a major source of heterogeneity in the genetic literature.¹⁰⁰ These methodological differences may obscure or exaggerate the true effects of ACE I/D polymorphism.^{101,102}

Sensitivity analyses confirmed the robustness of the pooled estimates, with no individual study unduly influencing the overall results. While studies by Shaikh et al.,⁹² Kuramoto et al.,⁸¹ and Tseng et al.⁶⁶ showed relatively greater influence when excluded, the overall direction and significance of the associations remained unchanged. This stability across leave-one-out analyses supports the internal validity of the meta-analysis. Assessment of publication bias using funnel plot symmetry and Egger's regression test indicated no evidence of small-study effects.¹⁰³ The non-significant test and symmetrical funnel distribution suggest that selective reporting did not materially influence the meta-analysis findings.

Despite the breadth of studies evaluating the genetic associations with DN, a major gap exists in the reporting of clinical outcomes. From the narrative synthesis of the included studies in this review, only one study addressed DN-related mortality,⁸³ and five reported comorbidities such as metabolic disease,¹⁰⁴ neuropathy⁵⁶ and retinopathy.^{52,57,70} Most studies have been conducted in broader T2DM populations without disaggregating the outcomes for DN-specific cohorts. Consequently, the translational relevance of ACE I/D polymorphisms to clinical endpoints in DN remains poorly defined. Future studies should prioritize DN-specific outcomes and adopt standardized reporting frameworks to improve clinical interpretability.

One limitation in this study is the presence of moderate between-study heterogeneity. This heterogeneity persisted even after subgroup and meta-regression analyses were conducted. A likely explanation for this is residual confounding. This may be due to variations in ethnicity, environmental exposure, and gene-environment interactions. Unfortunately, these variables were not captured in the data-extraction process. For instance, although the review predominantly included studies defining diabetic nephropathy based on urinary albuminuria markers (ACR or AER), one study using serum creatinine and eGFR was retained to incorporate relevant genetic data. This slight deviation was carefully considered and does not substantially compromise the consistency or validity of the overall findings, as the included outcome remains clinically relevant to nephropathy assessment. In addition, the primary diagnostic marker for DN in our systematic review was urinary albumin-to-creatinine ratio (UACR), as reported in the original studies. However, we acknowledge that there are differences between the quantitative and semi-quantitative methods for measuring urinary albumin levels. To address this, we used the ROBINS-E tool to assess the risk of bias related to outcome measurements. Studies that lacked clarity or likely used semi-quantitative methods were rated as moderate-to-high risk, and only those with low overall risk (25 studies) were included in the meta-analysis. This helped ensure a more accurate DN classification in our pooled estimates. Moreover, in our subgroup/meta-regression analyses, the form of urinary albumin measurement; ACR vs. AER was statistically significant, reinforcing the impact of methodology on DN diagnosis. This review did not include unpublished studies or abstracts, and no author contact was made for missing data, which may have limited access to additional insights; however, efforts were made to ensure comprehensive coverage through rigorous database and reference list searches.

Therefore, we suggest that future studies prioritize standardized methods for assessing microalbuminuria, particularly the use of ACR over AER, to reduce heterogeneity in outcome reporting. There is also a clear need for well-designed, large-scale genetic association studies that specifically examine ACE I/D polymorphisms in relation to DN-related mortality and comorbidities, such as hypertension and cardiovascular disease, which are underrepresented in the current literature. Additionally, future research should explore gene-environment and gene-gene interactions, as well as the utility of ACE genotyping in clinical risk prediction models for DN progression within diverse populations, especially in regions such as sub-Saharan Africa, where such data are scarce.

Conclusion

This systematic review and meta-analysis provides evidence for a protective association between ACE insertion/deletion (I/D) polymorphism and diabetic nephropathy (DN), with genotype II consistently linked to reduced DN risk. Subgroup and meta-regression analyses identified the method of urinary albumin measurement; in particular, the albumin-to-creatinine ratio (ACR), which, according to our study, was a significant moderator of effect size variability, highlighting the need for methodological standardization in DN research and clinical practice. These findings were robust to

sensitivity testing and showed no evidence of publication bias. However, the limited reporting of DN-specific clinical outcomes, including mortality and comorbidities, highlights persistent gaps in the literature. Moderate heterogeneity across studies suggests additional contributing factors; therefore, future research should prioritize harmonized diagnostic criteria, expand the evaluation of clinical outcomes, and incorporate polygenic and environmental risk models. Such efforts are essential for advancing precision medicine approaches for the prevention and management of DN in individuals with type 2 diabetes.

Ethics approval and consent to participate

This study is part of a doctoral research project approved by the Mbarara University of Science and Technology Research Ethics Committee (MUST-REC), reference number MUST-2024-1725. The review was conducted using publicly available data and therefore did not require additional ethical clearance.

Author abbreviations

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Data availability

Underlying data

No data associated with this article.

Extended data

The materials used in this review are available in Zenodo. The project title is “ACE I/D gene mutations in diabetic nephropathy” <https://doi.org/10.5281/zenodo.15765008>¹⁰⁵

The project contains the following extended data;

- Completed Table 2
- 2020 PRISMA checklist
- MOOSE checklist
- SWiM checklist
- ROBINS-E assessment
- STREGA assessment
- Compiled meta-analysis dataset
- Compiled systematic review dataset

Data are available under the terms of the [Creative Commons Attribution 4.0 International license](#) (CC-BY 4.0).

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