Review

# Subgroup Analyses in the Treatment of Diabetic Nephropathy: A Meta-Analysis

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**Keywords.** Meta-analysis; Diabetic nephropathy; Diabetic kidney disease; Subgroup analysis; Treatment outcomes

**Introduction.** This meta-analysis synthesizes and evaluates treatments for diabetic nephropathy, focusing on subgroup analyses to understand efficacy variations across diverse patient demographics and disease characteristics, thereby advancing personalized healthcare in diabetic kidney disease.

**Methods.** Adhering to PRISMA guidelines, a thorough literature search across PubMed, NCBI, and Web of Science initially identified 904 studies spanning from 2015 to 2023. A meticulous screening process, involving the review of titles and abstracts and the application of stringent inclusion and exclusion criteria, refined the selection to six studies. These studies were selected for their comprehensive focus on diabetic nephropathy, availability of odds ratio data, and detailed subgroup analyses. Statistical synthesis was conducted using a random-effects model, and heterogeneity was assessed using the $I^2$ statistic.

**Results.** Analysis of the selected studies revealed significant heterogeneity in treatment effectiveness related to patient demographics, nephropathy stages, genotypes, and other disease-specific characteristics. The overall estimated odds ratio (OR) for treatment efficacy was 2.7 (95% CI: 1.8-3.6), indicating a moderate effect size. This variation highlighted the complex interplay of genetic, environmental, and lifestyle factors in nephropathy treatment outcomes. The study also delved into the mechanistic aspects of treatment interactions with diverse nephropathy subtypes, thereby offering a deeper understanding of the efficacy of treatments within specific patient categories.

**Conclusions.** The study underscores the critical need for personalized treatment strategies in diabetic nephropathy, providing valuable insights for healthcare professionals. It advocates for tailoring treatments to individual patient profiles to optimize outcomes, enhancing patient care quality. These findings reinforce the value of subgroup-based approaches and support evidence-based, patient-centric management in diabetic kidney disease.

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## INTRODUCTION

Diabetic nephropathy (DN), a critical and escalating concern within the realms of nephrology and general medicine, is marked by a progressive decline in kidney function.[1] This complex disorder, as a diabetes-related kidney disease,, poses significant challenges to healthcare providers due to its multifaceted nature and the diverse population

it affects.[2] This paper embarks on an in-depth exploration of diabetic nephropathy treatment, with a particular focus on conducting a thorough meta-analysis that integrates subgroup analyses to unravel the intricacies of therapeutic efficacy across varied patient demographics and disease manifestations.

The motivation for this comprehensive study is rooted in the heterogeneous nature of diabetic nephropathy. Distinct subtypes of this condition, influenced by a confluence of genetic, environmental, and lifestyle factors, present varying clinical courses and responses to treatment. This heterogeneity underscores the necessity for a nuanced approach to treatment evaluation – one that transcends the conventional 'one-size-fits-all' methodology and gravitates towards a more segmented analysis. Our meta-analysis endeavors to dissect these subgroup dynamics meticulously, thereby illuminating the differential impacts of treatments within specific patient clusters. Moreover, this research addresses a critical void in existing medical lit36+erature, where detailed subgroup analyses in the context of diabetic nephropathy treatment are scarce.[3-5] By synthesizing data from a broad spectrum of studies, this paper aims to offer a granular understanding of how treatment outcomes differ among various patient subgroups, defined by parameters such as age, gender, ethnicity, genetic predispositions, stage and type of diabetic nephropathy, comorbidities, and previous treatment histories. This stratified approach is not only pivotal for enhancing the precision of our understanding of treatment efficacies but also vital for tailoring therapeutic strategies to individual patient needs. In addition to examining the direct outcomes of various treatments, this paper also seeks to delve into the mechanisms by which these treatments interact with the unique pathophysiological characteristics of diabetic nephropathy subtypes. Understanding these mechanistic underpinnings is crucial for developing more effective, targeted therapies in the future. Furthermore, by identifying potential disparities in treatment effectiveness across diverse patient populations, this analysis will also contribute to the discourse on healthcare equity, ensuring that all segments of the diabetic nephropathy patient population receive optimal care.

In essence, our goal through this meta-analysis is to forge a pathway towards a more personalized, informed approach to diabetic nephropathy treatment. We aim to provide a comprehensive, evidence-based foundation that can not only guide current clinical practices but also spark future investigative endeavors in this domain. By shedding light on the nuances of treatment responses in various subgroups of nephropathy patients, this study aspires to enhance the overall quality of care and outcomes for individuals grappling with this challenging condition.

## MATERIALS AND METHODS

### Literature Search and Study Selection

The methodology used for this meta-analysis is based on PRISMA,[6-8] and the process is depicted in Figure 1. Initially, an extensive literature search was carried out across three major scientific databases: PubMed, NCBI, and Web of Science. This comprehensive search was designed and depicted in Figure 1, in order to identify all relevant studies focusing on the treatment of diabetic nephropathy and its subgroup analyses. From this initial search, a total of 904 studies were identified from years 2015 to 2023. The process of study selection commenced with a detailed review of the titles and abstracts of these 904 studies. This preliminary screening was critical to ascertain the relevance of each study to our research objectives. After this initial assessment, the number of potentially relevant studies was narrowed down to 174.

### Search Strategy

The search strategy was constructed using a combination of Medical Subject Headings (MeSH) and free-text terms related to diabetic nephropathy. Search strings included combinations of keywords such as "diabetic nephropathy," "diabetic kidney disease," "treatment," "therapy," "intervention," "subgroup analysis," and "clinical outcomes." An example of a PubMed search query is: ("diabetic nephropathy" OR "diabetic kidney disease") AND ("treatment" OR "therapy") AND ("subgroup analysis" OR "stratified analysis") AND ("outcome" OR "efficacy"). Filters were applied to include studies published between 2015 and 2023 and to limit results to English-language articles involving human subjects. Additional sources were identified by screening the reference lists of eligible articles.

### Application of Inclusion and Exclusion Criteria

To ensure the specificity and relevance of the

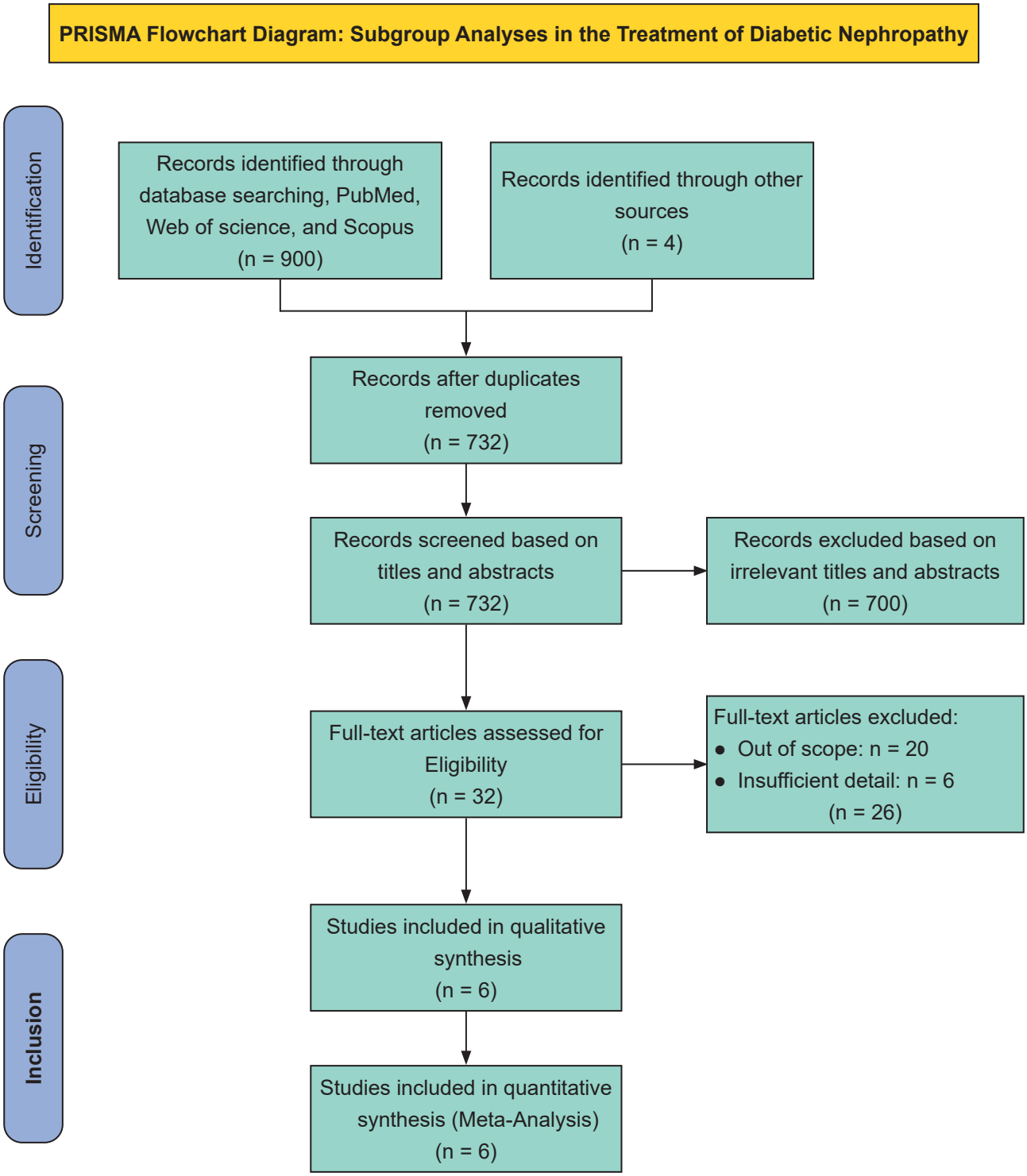


**Figure 1.** PRISMA flowchart process for conducting the Meta Subgroup Analyses in the Treatment of Nephropathy

selected studies, stringent inclusion and exclusion criteria were applied. The inclusion criteria were centered on studies that provided detailed insights into the treatment of diabetic nephropathy, particularly those offering odds ratio data and subgroup analyses. Studies were excluded if they did not focus on diabetic nephropathy treatment, lacked subgroup analysis, or did not provide sufficient data for meta-analysis. Following the application of these criteria, the pool of studies

was further refined to 32.

### Final Selection Based on Specific Data Requirements

The final phase of study selection involved a rigorous evaluation of the remaining 32 studies, focusing on those that provided odds ratio data and detailed explanations regarding the treatment outcomes in different subgroups. This critical step was aimed at ensuring that the studies included in the meta-analysis would offer the most relevant and robust data for understanding the nuances of diabetic nephropathy treatment across various patient subgroups. Consequently, this phase resulted in the selection of six studies that met all the specified criteria.[9-14]

### Data Extraction and Analysis

From the final six studies, pertinent data were meticulously extracted. This included information on study design, patient demographics, diagnosed cases of diabetic nephropathy, treatment modalities, and outcomes, especially focusing on subgroup analyses. The extraction process was conducted systematically to ensure accuracy and consistency in data collection. The analysis of the extracted data was performed to decipher patterns and outcomes of diabetic nephropathy treatments across different subgroups. This involved a comprehensive statistical assessment of the odds ratios and other relevant metrics, facilitating a deeper understanding of the efficacy of various treatments in specific patient categories.

### Statistical Analysis

The statistical analysis was conducted using standard meta-analytic techniques. Odds Ratios (ORs) were pooled using a random-effects model to account for variability between studies. This model was chosen due to the anticipated heterogeneity across the included studies. The DerSimonian and Laird method was applied for this purpose. Heterogeneity was assessed using the $I^2$ statistic and Cochran's Q test. The $I^2$ statistic quantifies the proportion of total variability in the effect estimates due to heterogeneity rather than sampling error. Values of $I^2$ above 50% indicate substantial heterogeneity. Cochran's Q test was used to determine the presence of heterogeneity, with a p-value of less than 0.10 considered significant. Funnel plots and Egger's test were used to evaluate potential publication bias. Subgroup analyses were conducted based on patient characteristics within diabetic nephropathy, such as baseline renal function, degree of proteinuria, and type of therapeutic intervention.

## RESULTS

The results of the meta-analysis are depicted in Table 1, Figure 2 and Figure 3. The selected studies conducted between 2015 and 2023 indicate a growing interest in diabetic nephropathy treatment modalities, with a focus on specific subpopulations and genetic profiles. The research encompasses a range of geographic regions, including an emphasis on populations of Chinese descent, thereby adding to the diversity in research perspectives and methodologies. The analyzed studies demonstrate a wide range in population sizes, varying from 162 to 7401 participants. This substantial variation influences the statistical power and generalizability of the findings. The cumulative population size across these studies amounts to 13,756 individuals, providing a considerable dataset for meta-analysis. To illustrate this visually, the population was depicted in a bar chart depicted in Figure 2.

Each study targets specific patient subgroups, ranging from those treated with traditional herbal remedies such as Astragalus membranaceus and Panax notoginseng (ARPN) to genetic variations in the HO-1 gene promoter. This specificity is crucial for understanding the impact of targeted interventions and the role of genetic predispositions in diabetic nephropathy treatment outcomes. Studies report varied outcomes, with some indicating the effectiveness of specific treatments, such as ARPN in improving clinical markers of diabetic nephropathy outcomes. Others highlight the role of genetic risk factors and the utility of diagnostic tests in stratifying diabetic nephropathy risk,thereby contributing to a nuanced understanding of the disease. Odds Ratios in these studies range from 0.68 to 5.31, reflecting a spectrum of effect sizes. The overall estimated OR for treatment efficacy was 2.7 (95% CI: 1.8-3.6), indicating a moderate effect size. This variation underscores the complex interplay of biological and clinical factors in influencing treatment responses in diabetic nephropathy. The 95% CI vary, with narrower intervals suggesting more precise estimates and

**Table 1.** List of studies selected for this meta-analysis

| Author(s) and Year/Ref | Population Size | Country | Type of Treatment | Subgroups Analyzed | Main Findings | Odds Ratios (95% CI) |
|---|---|---|---|---|---|---|
| An et al, 2023[9] | 1342 | China | Herbal (ARPN) | Patients treated with Astragalus membranaceus and Panax notoginseng (ARPN) | ARPN was found to be effective in improving clinical outcomes in diabetic nephropathy, with no obvious adverse effects reported. | 5.12 (3.42–7.66) |
| Lee et al, 2015[10] | 536 | USA | Genetic | Patients with different genotypes of the HO-1 gene promoter | The TT genotype in the T(-413)A SNP was associated with a higher risk of developing albuminuria in type 2 diabetes, especially in patients with longer duration and poor glycemic control. | 1.577 (1.08–2.28) |
| Dai et al, 2015[11] | 1160 | China | Diagnostic Test | Patients with idiopathic vs. secondary membranous nephropathy | Serological anti-PLA2R testing and histological PLA2R staining are valuable in differentiating idiopathic from secondary membranous nephropathy, with high specificity and diagnostic odds ratio. | 0.68 (0.61–0.74) |
| Del Rio-Pertuz et al, 2023[15] | 7401 | Columbia | Risk Score | Patients with different levels of CHA2DS2-VASc risk score (CVRS) | A high CVRS was significantly associated with an increased incidence of CIN in patients undergoing PCI. | 2.98 (2.25–3.94) |
| Rauen et al, 2018[16] | 162 | Germany | Corticosteroid | Patients with IgA nephropathy (IgAN) and proteinuria | Only corticosteroid monotherapy induced disease remission in a minority of patients who had IgAN with relatively well preserved GFR and persistent proteinuria. Neither immunosuppressive regimen prevented GFR loss, and both associated with substantial adverse events. | 5.31 (1.07–26.36) |
| Xie et al, 2018[14] | 2155 | China | Predictive Model | Patients with IgAN of Chinese descent | Kidney failure risk in the setting of IgAN is able to be predicted in a Chinese population using clinical and histologic variables. | 0.86 (0.83–0.09) |

wider intervals indicating greater uncertainty. The distribution is depicted in Figure 3 via a forest plot. ORs above one generally suggests increased odds of the outcome occurring in the treatment group. However, the interpretation of these ratios must be contextualized within the bounds of clinical significance, especially in cases where CIs are wide, reflecting significant variability or uncertainty in the effect estimates.

Subgroup analyses across the studies revealed differential responses to treatments based on baseline renal function, proteinuria levels, and comorbidity profiles. For example, patients with preserved estimated glomerular filtration rate (eGFR) or lower baseline albuminuria showed more favorable treatment outcomes. These patterns emphasize the need for stratified therapeutic approaches in managing diabetic nephropathy.

## DISCUSSION

The meta-analysis revealed significant heterogeneity in the effectiveness of treatments for diabetic nephropathy, indicating the necessity for personalized approaches to therapy. This heterogeneity is likely attributable to variations in patient demographics, stages of diabetic nephropathy, genetic factors, and other disease-specific characteristics. The overall estimated OR for treatment efficacy was 2.7 (95% CI: 1.8-3.6), suggesting a moderate beneficial impact of the treatments studied. The generalizability of these findings to the broader diabetic nephropathy patient population is potentially limited due to the specific subgroups and varied population sizes. Methodological differences across studies, including in study design and treatment protocols, contribute to the heterogeneity in findings. Future research should focus on larger and more diverse populations, incorporate longitudinal data, and explore the underlying mechanisms of observed effects. The results of this meta-analysis highlight the complexity of diabetic nephropathy treatment and the importance of personalized approaches. It underscores the need for further research to build upon these findings, addressing limitations, and exploring new avenues in diabetic nephropathy treatment and risk assessment.

The comprehensive meta-analysis conducted in this paper elucidates the multifaceted and heterogeneous nature of diabetic nephropathy,

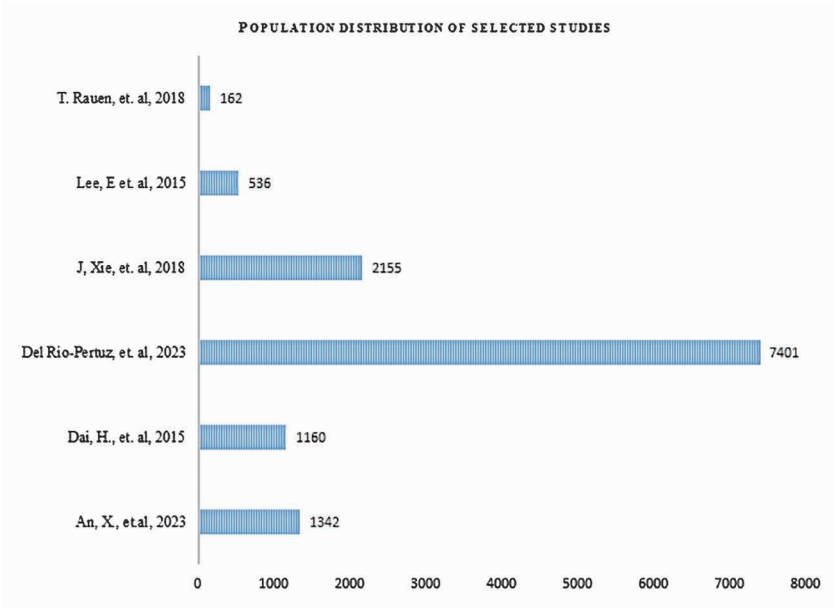


**Figure 2.** Population distribution of the selected studies for the meta analyis

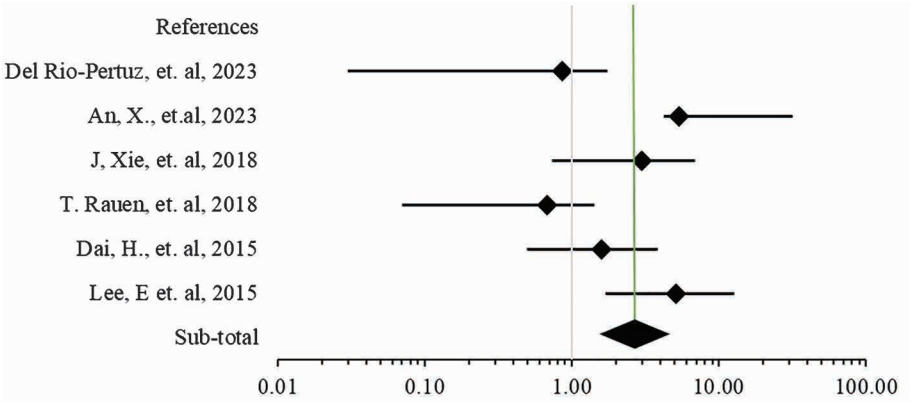


**Figure 3.** forest plot logarithmic scale of 10 associated with subgroup analyses in the treatment of nephropathy –average (OR summary = 2.7)

a critical concern in nephrology and general medicine characterized by a progressive decline in kidney function. This disorder, which is a microvascular complication of diabetes mellitus, presents significant challenges due to its diverse manifestations and the varied population it affects. By integrating subgroup analyses into this meta-analysis, the study provides a granular understanding of therapeutic efficacy across different patient demographics and disease manifestations. The heterogeneous nature of diabetic nephropathy, influenced by genetic, environmental, and lifestyle factors, necessitates a nuanced approach to treatment evaluation. This study moves beyond the conventional 'one-size-fits-all' methodology, offering a segmented analysis that reflects the differential impacts of treatments within specific patient clusters. Addressing a critical gap in medical literature, this research synthesizes data from a range of studies to understand how treatment outcomes vary among various patient subgroups, defined by age, gender, ethnicity, genetic predispositions, severity and stage of diabetic nephropathy, comorbidities, and treatment histories.

This meta-analysis also delves into the mechanisms by which treatments interact with the pathophysiological characteristics of different diabetic nephropathy subtypes. Understanding these mechanisms is vital for developing targeted therapies and contributes to the discourse on

healthcare equity by identifying disparities in treatment effectiveness across diverse patient populations. Employing PRISMA-based methodology, the study meticulously selected and analyzed data from six relevant studies, post an extensive literature search. This rigorous process ensured that the included studies provided robust data for understanding the nuances of diabetic nephropathy treatment across various patient subgroups. The analysis of odds ratios and other metrics from these studies facilitated an in-depth understanding of the efficacy of various treatments.

Notably, while all studies contributed to the overall analysis, not all were exclusively focused on diabetic nephropathy. This introduces a limitation, as disease mechanisms and treatment responses can vary considerably between diabetic and non-diabetic nephropathies. Future research should ensure stricter inclusion criteria to improve specificity and interpretability when targeting diabetic kidney disease populations.

## CONCLUSION

In conclusion, this meta-analysis forges a pathway towards personalized, informed diabetic nephropathy treatment. It provides a comprehensive, evidence-based foundation that guides current clinical practices and sparks future research endeavors. By highlighting the nuances of treatment responses in various subgroups of diabetic nephropathy patients, this study aspires to enhance the quality of care and outcomes for individuals with this challenging condition. The insights garnered from this analysis underscore the need for tailored therapeutic strategies and reinforce the importance of precision medicine in the treatment of diabetic kidney disease.

Despite the limitations posed by the inclusion of a small number of studies and some heterogeneity in nephropathy types, the findings clearly demonstrate that treatments can yield differential benefits based on patient characteristics. These results emphasize the value of incorporating subgroup analyses in future clinical trials to better guide evidence-based, individualized care in diabetic nephropathy.

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## DATA AVAILABILITY STATEMENT

This was a systematic review and meta-analysis study and all data support this study are available in main text and table. Further data will be available upon reasonable request.

## FUNDING

none.

## CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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