BMC Nephrology

RESEARCH

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Association between high-sensitivity C-reactive protein and diabetic nephropathy: a systematic review and meta-analysis

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Abstract

Background Diabetic nephropathy (DN) is a major complication of diabetes, driven by inflammation and progressive kidney damage. High-sensitivity C-reactive protein (hs-CRP), a marker of systemic inflammation, has been linked to DN progression, but study findings are inconsistent. This systematic review and meta-analysis aimed to evaluate the association between hs-CRP levels and DN risk.

Methods We searched PubMed, Scopus, Web of Science, Cochrane Central Register of Controlled Trials, and Embase from inception to July 22, 2024, for observational studies examining hs-CRP and DN. Although IL-6 and ESR were initially considered for analysis, they were excluded from the meta-analysis due to insufficient data for pooling. Fifteen studies involving 16,324 participants were included. A random-effects model pooled effect sizes, with heterogeneity assessed using the I^2 statistic and Cochran Q test. Subgroup analyses explored variations by study design and sample size.

Results From 8312 citations, 15 studies met the inclusion criteria, comprising 16,324 participants from diverse geographic locations. Meta-analysis of the 15 studies showed that elevated hs-CRP levels (above vs. below a clinical threshold of 2.5 mg/L) were associated with 65% increased odds of DN (OR = 1.65, 95% CI: 1.36–1.99, $P = 0.002$), with substantial heterogeneity ($I^2 = 79.4\%$, $P < 0.001$).

Conclusion Elevated hs-CRP levels are significantly associated with increased DN risk, supporting its clinical utility for risk stratification in diabetic patients and its relevance for guiding future research into anti-inflammatory therapies. However, high heterogeneity, likely due to differences in study design, population characteristics, and measurement methods, limits the generalizability of these findings. Future research should clarify causal mechanisms and validate hs-CRP's role in clinical decision-making for DN prevention.

Clinical trial number It is not applicable.

Keywords Diabetic nephropathy, High-sensitivity C-reactive protein, hs-CRP, Meta-analysis

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Introduction

Diabetic nephropathy (DN), a major microvascular complication of diabetes mellitus, has become a leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) worldwide [1]. As the prevalence of diabetes continues to rise globally, the burden of DN on healthcare systems is growing, demanding new strategies for early identification, prevention, and intervention [2]. Characterized by progressive albuminuria, decreased glomerular filtration rate (GFR), and ultimately, renal failure, DN profoundly impacts quality of life and life expectancy. Given the irreversible nature of ESRD, early identification of at-risk individuals is essential to mitigate disease progression and improve outcomes in diabetic populations [3–5].

C-reactive protein (CRP) and its derivatives are associated with a range of inflammatory conditions, including COVID-19, chronic liver inflammation, coronary artery disease, and thyroiditis [6–9]. Inflammation is increasingly recognized as a central mechanism in the pathogenesis of DN. In recent years, research has highlighted a potential role for inflammatory markers, especially high-sensitivity C-reactive protein (hs-CRP), in predicting both the development and progression of DN [10–12]. hs-CRP, an acute-phase protein produced by the liver in response to inflammatory cytokines, is commonly used as a biomarker in cardiovascular risk assessment due to its sensitivity in detecting low-grade inflammation. Its role in DN is of particular interest given that chronic inflammation is thought to contribute to the structural and functional kidney changes observed in diabetic patients. By exacerbating endothelial dysfunction, oxidative stress, and fibrosis, inflammation can accelerate renal damage in individuals with diabetes, thus underscoring the need for biomarkers that reflect these inflammatory processes [10, 11, 13–15].

Previous studies have investigated the association between hs-CRP and other inflammatory agents such as IL-6 and ESR levels and DN, with findings suggesting that higher inflammatory agent levels may correlate with increased risk and severity of nephropathy in diabetic patients [16–19]. However, these findings have been inconsistent, with some studies showing a strong association between elevated hs-CRP levels and DN progression, while others report weak or inconclusive results [20, 21]. Variability in study populations, methodologies, diabetes duration, and adjustments for confounding factors such as glycemic control and comorbidities may partly explain these discrepancies. Furthermore, hs-CRP, IL-6 and ESR levels can be influenced by a range of factors, including obesity, smoking, and lifestyle choices, which may complicate its interpretation as a specific biomarker for DN [18, 22, 23].

Given the inconsistencies in existing literature and the need for robust evidence, this systematic review and meta-analysis aims to quantify the association between hs-CRP levels and the risk of DN in diabetic patients. Although we initially sought to evaluate the pooled effect sizes of hs-CRP, IL-6, and ESR on DN, the meta-analysis focused on hs-CRP due to insufficient data for IL-6 and ESR in the included studies, which either lacked effect sizes or presented heterogeneous reporting unsuitable for pooling. Specifically, we seek to estimate the pooled effect size of hs-CRP on DN, assess the magnitude of this association, and identify sources of heterogeneity across studies. By synthesizing available evidence, we aim to determine whether hs-CRP can serve as a reliable, cost-effective biomarker for identifying diabetic patients at higher risk of DN, facilitating early intervention and personalized management. Additionally, this analysis will explore whether elevated hs-CRP levels are associated with DN progression indicators, such as the transition from microalbuminuria to macroalbuminuria and declining glomerular filtration rate. Insights from this review may elucidate inflammatory pathways driving DN, paving the way for future research into targeted anti-inflammatory therapies to mitigate renal damage in diabetic populations.

Method

The research adhered to the systematic review guidelines outlined in the Cochrane Handbook [24] and presented its findings in accordance with the PRISMA 2020 statement [25]. The research protocol has been officially recorded in the International prospective register of systematic reviews (PROSPERO: CRD42024542892).

Information sources and search strategy

We performed a systematic search in official databases (PubMed, Scopus, Web of Science, Cochrane Central Register of Controlled Trials, and Embase) and grey literature sources, including theses, posters, seminars, and Google Scholar. A comprehensive search was conducted from each database's earliest inclusive dates to July 22, 2024, with no restrictions on language or publication status. Due to the short timeframe between the search date and manuscript preparation, no additional search updates were performed; however, given the breadth of the initial search, the likelihood of missing relevant studies is considered low. Appropriate Boolean operators and database-specific filters were employed to refine the search process. The search strategies were evaluated by another author using the Peer Review of Electronic Search Strategies (PRESS) Checklist before implementation. The search included terms such as "C-Reactive Protein" OR "CRP" OR "High-Sensitivity CRP" OR "hs-CRP" OR "hypersensitive C-reactive protein" OR "Erythrocyte

sedimentation rate" OR "ESR" OR "IL-6" OR "IL6" OR "Interleukin 6" AND "Diabetic Nephropathy" OR "Diabetic Kidney Disease" OR "Diabetes Mellitus, Renal Complications" OR "Renal Disease in Diabetes" OR "Kidney Disease in Diabetes" OR "Diabetes-Related Nephropathy". The detailed search syntax for each database is provided in Supplementary File 1.

Eligibility criteria

We included observational studies (cohort, case-control, or cross-sectional) that reported effect sizes such as odds ratios (ORs) or risk ratios (RRs) for the association between hs-CRP, ESR, or IL-6 and diabetic nephropathy (DN), or provided sufficient data to calculate these effect sizes. To avoid duplication bias, we cross-checked studies for overlapping populations by examining author lists, study settings, recruitment periods, and participant characteristics; in cases of multiple publications from the same dataset, we selected the study with the most comprehensive data or the most recent publication.

Studies examining the association between hs-CRP, ESR, or IL-6 and kidney issues in non-diabetic populations (e.g., contrast-induced nephropathy or microalbuminuria unrelated to diabetes) were excluded. Additionally, studies where hs-CRP levels were influenced by other diabetes-related complications (e.g., cardiovascular disease, diabetic neuropathy, diabetic retinopathy) or comorbidities (e.g., infections such as diabetic foot ulcers) and these factors were not adequately adjusted for in the analysis were excluded. Studies lacking sufficient data on the status of comorbidities or other diabetes complications, or those without information to calculate effect sizes, were also excluded. These criteria were designed to ensure focus on the specific association between hs-CRP, ESR, or IL-6 and DN while minimizing the confounding effects of other diabetes-related complications or comorbidities.

Study selection and data extraction

Two independent reviewers (FB and MY) screened all titles and abstracts identified from the database search against the eligibility criteria to determine whether a full-text review was warranted. After title and abstract screening, the same reviewers independently evaluated full-text articles for inclusion. Disagreements at any stage were resolved through discussion or, if necessary, by consulting a third reviewer (MK). The inter-rater reliability was assessed using the kappa statistic ($\kappa = 0.92$, indicating excellent agreement).

For each included study, two independent investigators extracted the following data: first author, publication year, country, study design, sample size, mean age, sex distribution, type of diabetes, diagnostic criteria for diabetic nephropathy, adjusted confounders in multivariate models, and reported effect sizes (OR or RR with 95% CI) or data to calculate these effect sizes for the association between hs-CRP, ESR, or IL-6 and diabetic nephropathy. In cases of missing or unclear data (e.g., unreported effect sizes or participant characteristics), we attempted to contact study authors via email to obtain additional information; if no response was received within two weeks, only available data were used in the analysis. Data were entered into a standardized Microsoft Excel template by one reviewer and cross-checked by a second reviewer to ensure accuracy.

Risk of bias assessment

The quality of included studies was assessed using the Newcastle-Ottawa Scale (NOS), a validated and widely used tool specifically designed for evaluating the quality of cohort, case-control, and cross-sectional studies in systematic reviews and meta-analyses [26], which is designed for assessing the quality of non-randomized studies in meta-analyses. The NOS assesses three domains—selection, comparability, and outcome/exposure assessment—with a maximum score of 9. For cross-sectional studies, we applied an adapted NOS framework, ensuring criteria such as sample representativeness, exposure ascertainment, and outcome assessment were appropriately tailored to prevalence studies [27]. Studies with NOS scores ≥ 7 were classified as high quality. Two reviewers (FB, MA) independently conducted assessments, resolving discrepancies through consensus.

Data synthesis and analysis

We conducted a quantitative synthesis to assess the association between hs-CRP, ESR, or IL-6 levels and diabetic nephropathy. For studies that reported effect estimates such as Odds Ratios (ORs), Relative Risks (RRs), or Hazard Ratios (HRs) with 95% Confidence Intervals (CIs), we directly extracted these data. For studies reporting risk ratios (RR) or hazard ratios (HR), we converted these to OR using the formula $OR \approx RR / (1 - P_0 + (P_0 \times RR))$ for RR, where P_0 is the baseline risk in the control group, and approximated HR to OR assuming rare outcomes (i.e., incidence of DN < 10% in the control group, consistent with epidemiological data for DN in diabetic populations [28]. To address potential bias from non-rare outcomes, we conducted sensitivity analyses by excluding studies with DN prevalence $\geq 10\%$ in the control group, ensuring the robustness of the OR approximation. If studies provided raw data that allowed calculation of these effect sizes, they were also included in the meta-analysis. We used the DerSimonian and Laird random-effects model [29] to pool effect sizes, accounting for high heterogeneity across studies assessed in terms of population characteristics, study design, and hs-CRP or ESR or IL-6 measurement methods. This model accounts

for within-study and between-study variability, providing a more generalized estimate of the association. We assessed statistical heterogeneity using the I^2 statistic and Cochran's Q test. I^2 values of 25%, 50%, and 75% were interpreted as low, moderate, and high heterogeneity, respectively. When I^2 was more than 50% and Cochran Q test was statistically significant at $P < 0.05$, we adopted a random-effects approach, otherwise a fixed-effect model was used. To explore and mitigate heterogeneity among studies, we conducted subgroup analyses based on study design (cohort vs. non-cohort), sample size (< 1000 vs. ≥1000), mean participant age (< 54 years vs. ≥54 years), study quality (Newcastle-Ottawa Scale score < 7 vs. ≥7), hs-CRP levels (< 2.5 mg/L vs. ≥2.5 mg/L) and geographic region (Asia vs. non-Asia). Subgroup analysis by diabetes type (Type 1 vs. Type 2) was not feasible, as all included studies involved patients with type 2 diabetes only. The hs-CRP cutoff of 2.5 mg/L was chosen based on its clinical relevance in identifying moderate-to-high inflammatory states in diabetic populations, as levels ≥ 2 mg/L are associated with increased risk of microvascular complications, including diabetic nephropathy, in prior studies [28, 30]. This threshold aligns with clinical guidelines for assessing chronic inflammation in diabetes, such as those from the American Diabetes Association [31]. Publication bias was assessed using Egger's test and visualized through a funnel plot. For meta-analyses with significant asymmetry in the funnel plot, we applied Duval and Tweedie's trim-and-fill method to estimate and adjust for the impact of potential missing studies. We performed sensitivity analyses by excluding studies one at a time to evaluate the robustness of the pooled effect estimate. Additionally, we assessed the influence of studies with high risk of bias by conducting separate analyses for studies with NOS scores indicating low risk of bias. All statistical analyses were conducted using STATA Version 14 software. A p-value of < 0.05 was considered statistically significant for all analyses.

Results

Study characteristics

After removing duplicates from 8312 citations, 4693 unique citations were identified that was entered to the first phase of screening process. A summary of the primary studies selection process is summarized in Fig. 1. At the end of screening process, 15 studies comprised 16,324 participants were included in the final analysis [30–44]. A summary of the primary characteristics of the studies included in this article is summarized in Table 1. Evaluated studies were conducted on China [31, 33, 35], USA [37, 38], Taiwan [30], Turkey [32, 36], Ghana [34], Spain [41], Japan [39], India [42, 43], Iran [44], Egypt [45] and Thailand [40]. The examined sample size varied between 223 and 3924 people. This study included 15 studies comprising 16,324 participants, of which 11 were included in the meta-analysis. Four studies were limited

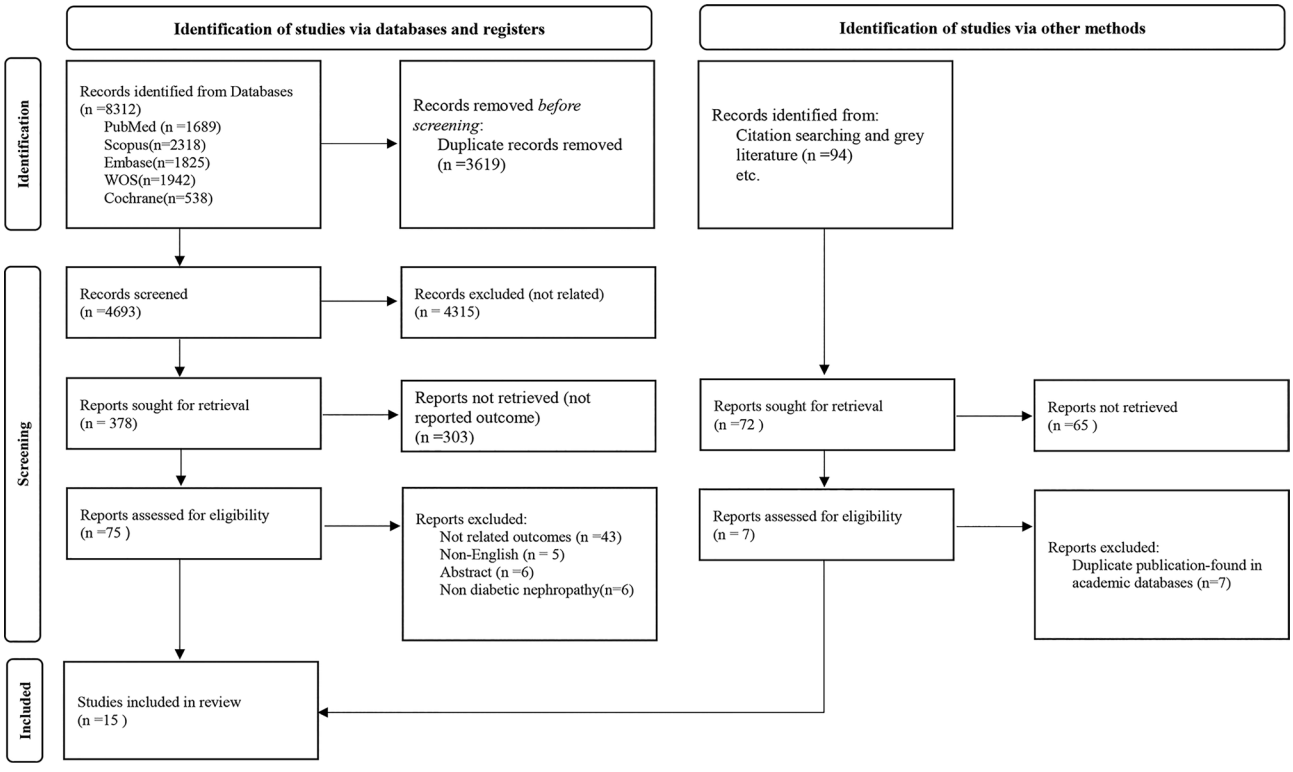

Fig. 1 Preferred reporting items for systematic reviews and meta-analyses flow diagram (2020) of search process

Table 1 Baseline characteristics of included studies

Author	Country	Sample size	design	Measurement Method of hs-CRP	Diagnosis of Diabetic nephropathy	T2DM duration	Age	hs.CRP level(mg/dl)	Total quality score
Lin et al. 2023	Taiwan	2332	Cohort	Immunoassay	ACR ≥ 300 mg/g cr or an eGFR < 60mL/min per 1.73 m2	Not reported	58.43 ± 7.69	1.21 ± 0.75	7
Vutukuru Kalyan Kumar Reddy 2023	India	80	cross-sectional	Commercial kit with nephelometric	WHO criteria	Not reported	53.7 ± 6.19	-	7
Tang et al.2022	China	927	cross-sectional	ELISA study	Clinical examination	6.8 ± 1.8	54.0 ± 15.56	1.9 ± 1.7	6
Sanchez-Alamo et al.2022	Spain	70	cohort	ELISA study	WHO criteria	Not reported	53.2 ± 9.10	NR	7
Bilgin et al.2021	Turkey	223	Case-control	Commercial kit with nephelometric	Clinical examination	Not reported	59.0 ± 33.3	5.4 ± 2.8	5
Liu et al. 2020	China	3924	cohort	Immunoturbidimetry method	WHO criteria	Not reported	54.9 ± 10	6 ± 5.6	8
Hayfron-Benjamin et al.2020	Ghana	583	cross-sectional	Particle enhanced immunoturbidimetric assay	WHO criteria	Not reported	52.65 ± 9.73	1.5 ± 4.4	9
Guo et al. 2020	China	1210	cross-sectional	iCHROMA reader	KDOQI clinical practice guidelines	9.80 ± 2.5	65.24 ± 11.85	3.6 ± 4.7	6
Çoner et al.2019	Turkey	170	Case-control	Commercial kit	WHO criteria	Not reported	43.3 ± 6.9	1.03 ± 1.24	5
Aryan et al.2018	Iran	1301	cross-sectional	ELISA	Clinical examination	5.9 ± 6.4	55.1 ± 0.3	-	8
Sinha et al.2016	United States	2500	cohort	Commerical ELISA kits	Clinical examination	Not reported	54.6 ± 7.5	2.87 ± 1.19	7
Ahluwalia et al. 2009	United States	495	Case-control	ELISA	WHO criteria	16.3 ± 3.3	60.12 ± 6.2	2.62 ± 1.2	5
Hayashino et al.2014	Japan	2518	cohort	Ultrasensitive competitive immunoassay	Clinical examination	Not reported	66.1 ± 10.9	2.44 ± 2.57	8
Chuengsamarn et al.2014	Thailand	608	cross-sectional	Nephelometry study with available kit	Clinical examination	Not reported	57.79 ± 12.35	2.37 ± 1.74	6
Choudhary et al.2008	India	60	cross-sectional	Commerical ELISA kits	WHO criteria	10.15 ± 3.52	54.08 ± 7.94	2.38 ± 3.14	6

ACR, Urine albumin to creatinine ratio; cr, creatinine; KDOQI, The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative; WHO, World Health Organization

to descriptive reporting in the systematic review due to high methodological heterogeneity (e.g., differences in study design, hs-CRP measurement methods, or diabetic nephropathy definitions) or because their reported effect sizes could not be converted to odds ratios for pooling with the other studies, as per our eligibility criteria.

The duration of diabetes of the patients was not reported in most of the studies, however, in some studies it was reported between 6 and 16 years. Among the included studies, five study conducted in the cohort design, seven in cross-sectional design and four in case-control design. The quality of the 15 included studies was assessed using the NOS. Table 2 summarizes the NOS scores, ranging from 5 to 8 (median: 7), indicating moderate to high quality. Most studies scored well in selection (e.g., representativeness of cases) and outcome ascertainment (e.g., reliable DN diagnosis), but limitations were noted in comparability, with five studies scoring only one point due to inadequate adjustment for key confounders such as body mass index or smoking (Table 2).

This study aimed to evaluate the prediction models of hs-CRP, IL-6 and IL-6 among the patients with DKD and some studies were included in the meta-analysis and some of them due the high methodological heterogeneity only included in the systematic review.

Table 2 Quality assessment of included studies *using the Newcastle-Ottawa scale*

First Author (year)	Selection	Comparability	Features of outcome	Quality Score
Lin et al. 2023	3	2	2	7
Vutukuru Kalyan Kumar Reddy 2023	3	2	2	7
Tang et al.2022	4	0	2	6
Sanchez-Alamo et al.2022	3	2	2	7
Bilgin et al.2021	1	2	2	5
Liu et al. 2020	3	2	3	8
Hayfron-Benjamin et al.2020	4	2	3	9
Guo et al. 2020	2	2	2	6
Çoner et al.2019	2	1	2	5
Aryan et al.2018	3	2	3	8
Sinha et al.2016	3	2	2	7
Ahluwalia et al. 2009	2	1	2	5
Hayashino et al.2014	3	2	3	8
Chuengsamarn et al.2014	2	2	2	6
Shelbaya et al.2012	2	2	1	5
Choudhary et al.2008	3	1	2	6

Association between inflammatory agents with diabetic nephropathy in included studies

Sanchez-Alamo et al. in a prospective study among the patients with T2DM evaluated the association of IL-6 levels with diabetic nephropathy and after 36 months of follow up, they found that participants with higher levels of IL-6 (>4.84 pg/ml) had 4.10 times higher risk of diabetic nephropathy [41]. Choudhary et al. in another study among 60 diabetic patients observed a significant positive correlation between urinary albumin excretion and levels of hs-CRP ($r=0.781$, $P<0.001$) and IL-6 ($r=0.708$, $P<0.001$) [42]. In line with the results of this study, in a cross-sectional study on a sample of the Egyptian population, researchers found a considerable linear correlation between serum levels of hs-CRP and IL-6 with urinary albumin excretion ($r=0.927$ for hs-CRP and $r=0.838$ for IL-6; $P<0.001$) [45]. Kumar Reddy et al. in a case-control study in India determined a higher concentration of IL-6 in diabetic patients with nephropathy than patients without nephropathy (15.48 ± 4.27 mg/dl vs. 7.02 ± 2.46 mg/dl; $P<0.001$) [43]. Finally, in a population-based study by Aryan et al., 1301 participants with T2DM were followed for more than 7 years (mean follow-up of 7.5 years). Risk assessment for vascular events was done at baseline, and serum hs-CRP was measured. End points of this study include CHD events, diabetic retinopathy, neuropathy, and diabetic kidney disease. Median serum hs-CRP was 2.00 ranging from 0.1 to 17 mg/L. Hazards ratio of each SD increment in baseline hs-CRP was 1.028 (1.024–1.032) for CHD, 1.025 (1.021–1.029) for diabetic neuropathy, 1.037 (1.030–1.043) for diabetic retinopathy, and 1.035 (1.027–1.043) for diabetic kidney disease. The results of this study revealed that higher concentration of hs-CRP could act as a predictive agent of diabetic nephropathy [44].

Meta analysis results

Association between hs-CRP and odds of diabetic nephropathy

Figure 2 showed the association between hs-CRP concentration and odds of DN. The results of pooled analysis revealed that higher levels of hs-CRP significantly increase the risk of DN (OR = 1.65 [95% CI: 1.36, 1.99], $P=0.002$), with a significant heterogeneity among the evaluated studies ($I^2=79.4\%$, $P<0.001$). In the subgroup analysis, we found a strong effect size in cohort studies (OR = 2.15 [95% CI: 1.48, 2.64], $P=0.001$) and studies with sample size less than 100 (OR = 2.04 [95% CI: 1.34, 3.11], $P=0.001$) (Table 3).

The sensitivity analysis assessment indicated that no single article markedly affected the association between hs-CRP and odds of DN. Based on the visual inspection of funnel plot, we found an asymmetry (Fig. 3); however, when we did the Begg ($P=0.74$) and Egger's regression tests ($P=0.31$), no significant publication bias was seen.

Discussion

Our systematic review and meta-analysis demonstrated a statistically significant association between elevated hs-CRP levels and an increased risk of diabetic nephropathy (DN). The pooled analysis indicated that diabetic patients with higher hs-CRP concentrations had a 65% greater likelihood of developing DN, a finding that remained robust across various subgroup analyses. This result underscores the pivotal role of chronic, low-grade inflammation in the pathogenesis of DN and strengthens the case for hs-CRP as a valuable predictive biomarker.

Our findings are consistent with previous research that identifies inflammation as a central mechanism in DN progression [46]. Studies, such as those by Tang et al. [47]

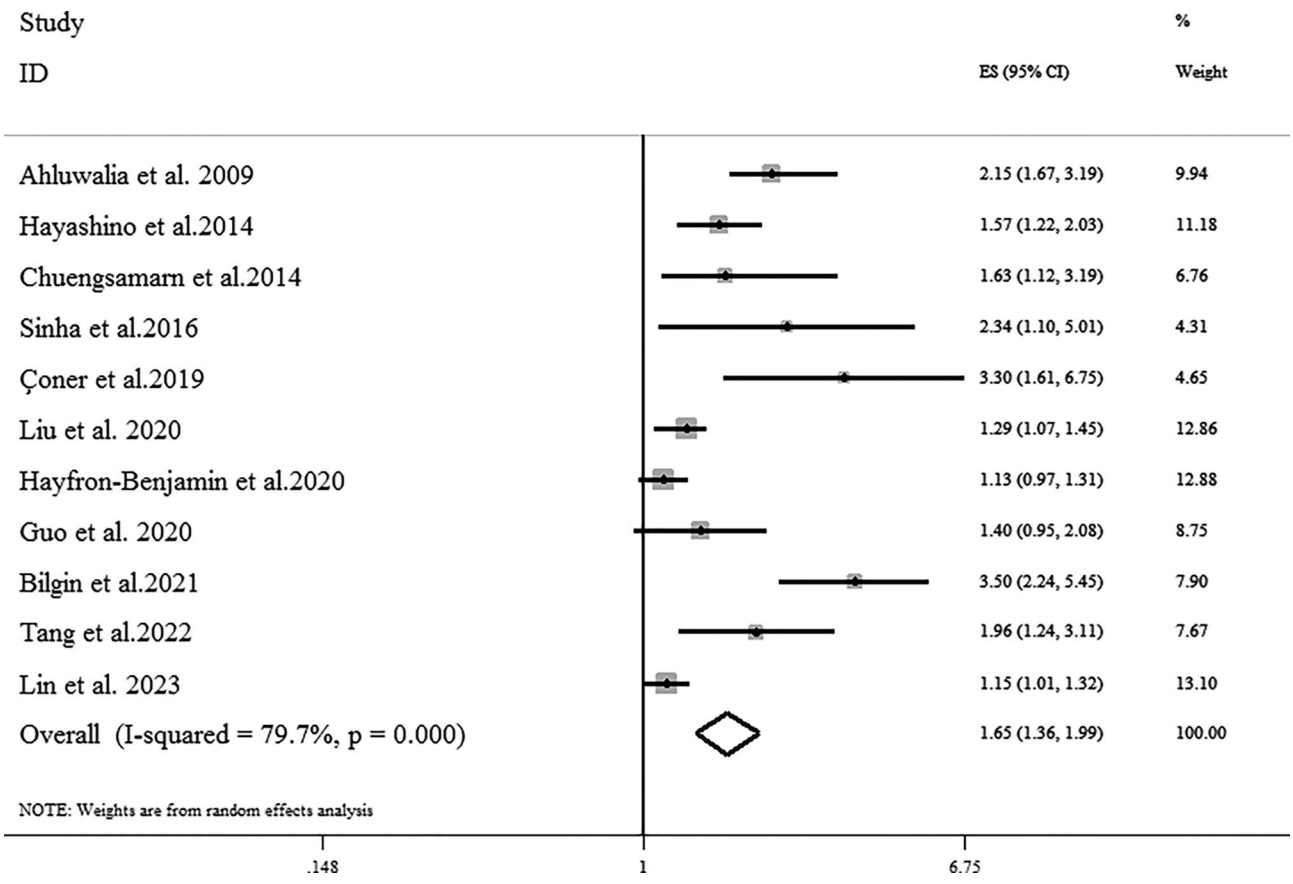

Fig. 2 Forest plot detailing odds of ratio and 95% confidence intervals for the association between hs-CRP and odds of diabetic nephropathy

Table 3 Subgroup analyses of the association between hs-CRP and odds of diabetic nephropathy

Sub-groups	Number of effect sizes	OR (95%CI), P_{value}	I^2 (%), $P_{heterogeneity}$	$P_{between}$
Design				**< 0.001**
Cohort	4	2.15 (1.48, 2.64), 0.001	48.9, 0.063	
non-cohort	7	1.12 (0.93, 1.35), 0.175	84.3, < 0.001	
Sample size				**< 0.001**
Less than 1000	6	2.04 (1.34, 3.11), 0.001	86.9, < 0.001	
1000 and more	5	1.33 (1.15, 1.54), < 0.001	47, 0.109	
hs-CRP				**0.001**
< 2.5 mg/dl	5	1.42 (1.12, 1.80), 0.004	72.1, 0.006	
>=2.5 mg/dl	6	1.82 (1.37, 2.43), 0.000	79, < 0.001	
Age				**0.001**
< 54	5	1.54 (1.18, 2.01), 0.001	73.5, 0.005	
>=54	6	1.73 (1.26, 2.36), 0.001	84.6, 0.000	
Study quality				**< 0.001**
< 7	6	2.13 (1.60, 2.83), < 0.001	57.3, 0.039	
>=7	5	1.26 (1.11, 1.44), < 0.001	54.8, 0.010	
Geographic region				**0.001**
Asia	8	1.45(1.14,2.13), < 0.001	61.25, 0.004	
non-Asia	3	1.86(1.35,2.26), < 0.001	74.35, 0.001	

[1]Calculated by Random-effects model

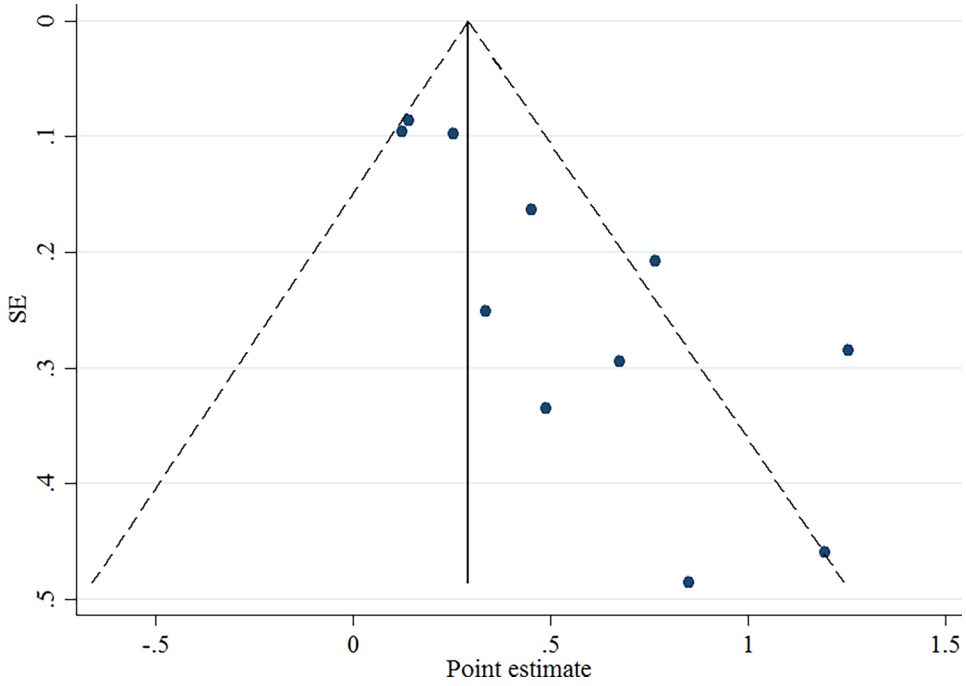

Fig. 3 Funnel plots detailing publication bias in the studies evaluated the association between hs-CRP and odds of diabetic nephropathy

and Hayashino et al. [39], have similarly reported strong correlations between increased hs-CRP levels and DN, reinforcing the hypothesis that chronic low-grade inflammation exacerbates renal damage in diabetic patients. Our meta-analysis, which found that elevated hs-CRP levels (above vs. below 2.5 mg/L) were associated with a 65% increased odds of DN (OR = 1.65, 95% CI: 1.36–1.99, $P = 0.002$), supports the role of hs-CRP as a marker of inflammatory processes driving DN. Hs-CRP, an acute-phase protein produced in response to cytokine activity, particularly IL-6 and tumor necrosis factor-alpha (TNF-α), reflects systemic inflammatory states that contribute to DN pathogenesis. Specifically, the elevated hs-CRP levels associated with increased DN risk in our study likely exacerbate endothelial dysfunction, a hallmark of DN driven by hyperglycemia-induced inflammation [48, 49]. This dysfunction, characterized by impaired nitric oxide bioavailability and increased endothelial permeability, facilitates albuminuria, aligning with our findings of a significant association between hs-CRP and DN risk. Furthermore, hs-CRP may amplify oxidative stress by enhancing macrophage activity and pro-inflammatory cytokine production, creating a feedback loop that accelerates renal injury, as evidenced by the consistent association across our included studies [50, 51]. This interplay between hs-CRP, endothelial dysfunction, and oxidative stress underscores the biological plausibility of our meta-analysis results, suggesting that the observed 65% increased odds of DN reflects these inflammatory and oxidative pathways contributing to glomerular and tubular damage [47].

In the other hand, oxidative stress plays a critical role in the pathogenesis of DN, and hs-CRP may be both a marker and a mediator of this process. Hyperglycemia and insulin resistance in diabetes increase the generation of reactive oxygen species (ROS) within kidney cells [52]. Elevated ROS levels damage cellular components, leading to mitochondrial dysfunction, lipid peroxidation, and DNA damage, which can further activate inflammatory pathways [53, 54]. hs-CRP may amplify oxidative stress by enhancing macrophage activity and stimulating the production of additional pro-inflammatory cytokines like IL-6 and TNF-α. As inflammation and oxidative stress are mutually reinforcing processes, the presence of high hs-CRP levels may create a feedback loop that accelerates renal injury, particularly in the glomeruli and renal tubules, where oxidative damage is most pronounced [5, 55–59].

While our study demonstrated a significant association between elevated hs-CRP levels and increased risk of diabetic nephropathy (DN), it is important to recognize that hs-CRP is a non-specific marker of inflammation and may also be associated with other diabetes-related complications, such as cardiovascular disease, diabetic retinopathy, and diabetic neuropathy [60]. For instance, some studies found that cardiovascular health, linked to hs-CRP levels, predicts the risk of diabetic complications, including kidney disease, as well as all-cause mortality in individuals with type 2 diabetes [54, 61, 62]. These

findings suggest that systemic inflammation, as reflected by hs-CRP, may play a broader role in the pathogenesis of both microvascular and macrovascular complications of diabetes [54, 58, 63, 64]. To mitigate the potential confounding effects of these complications, our study prioritized the inclusion of studies that either adjusted for these factors in their analyses or provided sufficient data to assess the impact of comorbidities. However, variability in the reporting of diabetes complications across included studies remains a potential limitation. Future research should specifically investigate the interplay between concurrent diabetes complications and comorbidities to determine whether hs-CRP serves as a specific predictive marker for DN or reflects a more generalized inflammatory state in diabetes.

The findings of this meta-analysis have significant clinical implications. Given its association with 65% increased odds of DN (OR = 1.65, 95% CI: 1.36–1.99, $P = 0.002$), hs-CRP may have potential as a biomarker for identifying diabetic patients at higher risk of DN in clinical practice, particularly when used alongside traditional markers like albuminuria and eGFR. However, this potential is tempered by limitations such as high heterogeneity (I^2 = 79.4%) and the observational nature of the included studies, which preclude causal inferences and limit generalizability. In clinical contexts, hs-CRP could support risk stratification to guide intensive glycemic or blood pressure control, but its utility requires validation through prospective studies with standardized thresholds. In research contexts, hs-CRP's association with DN highlights its value in exploring inflammatory pathways and identifying candidates for anti-inflammatory therapies, though further studies are needed to establish its specificity and predictive accuracy. Clinicians and researchers should interpret hs-CRP's role cautiously, considering the variability in study designs, populations, and measurement methods observed in our analysis.

This study has several strengths, including its comprehensive search strategy, adherence to PRISMA guidelines, and rigorous quality assessment of included studies. The use of a random-effects models also allowed for a generalized estimate across diverse populations. However, limitations must be acknowledged. First, significant heterogeneity was observed, likely due to variations in study design, populations, and DN diagnostic criteria. While explored through subgroup analysis (e.g., study design, sample size, geographic region), this variability could impact the pooled estimates. Notably, subgroup analysis by diabetes type (Type 1 vs. Type 2) was not feasible, as all included studies involved patients with type 2 diabetes only, limiting our ability to assess differences in hs-CRP's association with DN across diabetes types. Future studies should stratify analyses by Type 1 and Type 2 diabetes to explore potential differences in inflammatory profiles and DN risk. Second, the observational nature of the included studies establishes a strong association but cannot prove causation. Finally, residual confounding from factors like BMI, smoking, or diabetes duration, despite adjustments in many studies, may influence the results. For instance, BMI and smoking, which are associated with elevated hs-CRP levels, could lead to overestimation of the association between hs-CRP and DN if not adequately controlled, as these factors may independently contribute to inflammation and renal damage. Conversely, underadjustment for these confounders in some studies could underestimate the true effect if hs-CRP's association with DN is partially masked by their influence. Future research should quantify the impact of these confounders to refine effect estimates.

Conclusion

This meta-analysis of 15 studies, involving 16,324 participants, demonstrates a significant association between elevated hs-CRP levels and diabetic nephropathy. However, high heterogeneity and the observational nature of the included studies limit the strength of this evidence, necessitating caution in interpreting hs-CRP as a potential biomarker for DN risk stratification. While these findings underscore the role of inflammation in DN progression, the lack of standardized hs-CRP thresholds, variability in DN definitions, and potential for residual confounding highlight the need for prospective studies and randomized trials to establish causality and clinical utility. Future research should focus on validating hs-CRP's predictive value, establishing standardized cutoffs, and evaluating inflammation-targeted interventions to prevent or mitigate DN.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-025-04358-y.

Supplementary Material 1

Author contributions

FB, MY and AF designed the research. FB, MS, MA, and MK conducted the research. MY and AF wrote the article. FB and MS revised the article. MY had primary responsibility for the final content. All authors read and approved the final manuscript.

Funding

This study received no financial support.

Data availability

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author/s.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication
The authors provided final approval for the publication.

Competing interests
The authors declare no competing interests.

Received: 16 March 2025 / Accepted: 22 July 2025
Published online: 26 July 2025

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