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SYSTEMATIC REVIEW

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Causal insights into major risk factors for diabetic kidney disease: a comprehensive meta-analysis and Mendelian randomization study

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ABSTRACT

Background: This study aims to identify major risk factors for diabetic kidney disease (DKD) and examine their causal relationships using meta-analysis and Mendelian randomization.

Materials and Methods: This study reviewed diabetic nephropathy literature up to September 2024, evaluating quality with NOS, AMSTAR 2, and JBI. It analyzed heterogeneity using the Baujat plot and leave-one-out method, and conducted meta-analysis with fixed- or random-effects models based on I^2. Publication bias was assessed with a funnel plot and Egger's test. Mendelian randomization using GWAS SNPs explored causal links through IVW, MR-Egger, weighted median, and weighted mode, while pleiotropy and heterogeneity were checked with the MR-Egger intercept and Cochran's Q.

Results: Meta-analysis identified several significant risk factors for DKD, including hypertension (relative risk [RR] = 6.33), comorbidities (RR = 4.96), poor glycemic control (RR = 3.27), non-adherence to treatment (RR = 3.30), an unhealthy diet (RR = 5.96), physical inactivity (RR = 5.60), and hyperuricemia (RR = 5.24). MR analysis further confirmed a causal relationship between high carbohydrate intake (odds ratio [OR] = 1.393, $p = 0.043$) and increased DKD risk, while vegetable consumption (OR = 0.816, $p = 0.011$) was identified as a protective factor. These findings reinforce the critical role of dietary and lifestyle interventions in DKD prevention.

Conclusions: By integrating meta-analysis with Mendelian randomization, this study provides robust evidence linking modifiable risk factors, particularly dietary habits and lifestyle behaviors, to DKD development. The findings highlight the need for early preventive strategies targeting glycemic control, hypertension, and dietary modifications to mitigate DKD progression.

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Diabetic kidney disease; risk factors; causal inference; meta-analysis; Mendelian randomization; lifestyle interventions

1. Introduction

Diabetic Nephropathy (DN) represents a prevalent complication associated with diabetes and is a principal contributor to End-Stage Renal Disease (ESRD) and renal failure. With the rising incidence of diabetes, the global burden of diabetic nephropathy is escalating, thereby constituting a significant public health concern that demands immediate attention [1]. The World Health Organization (WHO) identifies diabetes as the fourth leading cause of mortality worldwide, and diabetic nephropathy, as a major complication, significantly affects patients' quality of life and survival rates [2]. The global prevalence of diabetic nephropathy is increasing, with a pronounced impact in low- and middle-income countries. This trend is primarily attributable to the rising incidence of diabetes, which is driven by lifestyle changes and an aging population [3]. Current estimates from the International Diabetes Federation (IDF) indicate that approximately 420 million individuals worldwide are affected by diabetes, with projections suggesting this figure will escalate to 700 million within the next two decades [4].

Diabetic nephropathy is a prevalent and serious complication associated with diabetes mellitus. It is characterized by the presence of proteinuria, alterations in the tubulointerstitial region, and a progressive decline in renal function, which can eventually lead to end-stage renal disease (ESRD). Epidemiological research indicates that the prevalence of diabetic nephropathy among individuals with diabetes ranges from 20% to 40% [5]. Among these individuals, patients with type 2 diabetes are at an elevated risk of developing diabetic nephropathy, primarily due to extended exposure to hyperglycemia and the presence of insulin resistance [6].

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The prevalence of diabetic nephropathy is influenced not only by the degree of glycemic control but also by demographic factors including ethnicity, gender, and age. Empirical studies indicate that African American, Hispanic, and certain Asian populations exhibit a higher incidence of diabetic nephropathy. These demographic groups are frequently correlated with elevated risks of hypertension, metabolic syndrome, and deteriorating renal function [7–8].

Diabetic nephropathy significantly impairs patients' quality of life and reduces life expectancy. It manifests through clinical symptoms such as proteinuria, tubular damage, and elevated serum creatinine levels. Additionally, it can precipitate a range of complications, including cardiovascular disease, anemia, and electrolyte imbalances, thereby further elevating mortality risk [9]. Diabetic nephropathy constitutes a principal cause of end-stage renal disease, necessitating dialysis or kidney transplantation for numerous patients [10]. Empirical evidence indicates that the mortality rate among individuals with diabetic nephropathy is markedly elevated compared to the general population. Notably, approximately 60% to 80% of these patients succumb to cardiovascular disease rather than renal failure [11]. Furthermore, patients with diabetic nephropathy undergoing dialysis or kidney transplantation encounter elevated rates of infection and other complications, which substantially impair their quality of life. Despite therapeutic interventions, these patients continue to face an increased risk of mortality. The detrimental effect of diabetic nephropathy on quality of life is also considerable [12]. Dialysis therapy frequently necessitates significant alterations in patients' lifestyles, as it requires regular hospital visits for treatment. This requirement not only disrupts their daily routines but also imposes additional burdens on their families and society. Moreover, chronic kidney damage is associated with symptoms such as fatigue, depression, and anxiety, which further diminish patients' quality of life.

As the detrimental impact of diabetic nephropathy (DN) garners heightened attention, an increasing number of studies are dedicated to identifying its risk factors, with the objective of establishing a theoretical foundation for early prevention and intervention. In this context, meta-analysis and Mendelian randomization (MR) analysis have progressively emerged as predominant statistical methodologies. Meta-analysis, a systematic approach for evaluating and synthesizing the findings of multiple independent studies, holds substantial value in the identification of risk factors associated with diabetic nephropathy. Through the implementation of a meta-analysis, researchers are able to integrate data from studies encompassing diverse populations, regions, and methodological designs, thereby enhancing statistical power and bolstering the reliability of the conclusions drawn [13]. Recent meta-analyses on diabetic nephropathy have identified various risk factors contributing to its development, notably genetic polymorphisms and associated biomarkers [14–15]. Mendelian randomization (MR) analysis, which employs genetic instrumental variables, addresses the challenges of confounding and reverse causality that are typically associated with conventional observational studies [16]. This approach offers a robust framework for elucidating causal relationships in the context of diabetic nephropathy. The strength of Mendelian Randomization (MR) analysis resides in its capacity to utilize genetic variations as a natural experiment, thereby facilitating the investigation of causal relationships between exposure factors and diabetic nephropathy.

By integrating the strengths of meta-analysis and Mendelian randomization (MR) analysis, researchers can achieve a more comprehensive and precise understanding of the risk factors associated with diabetic nephropathy. Meta-analysis facilitates a holistic assessment of findings across multiple studies, enabling the identification of potential determinants that may influence the progression of diabetic nephropathy. Conversely, Mendelian Randomization (MR) analysis elucidates the genuine causal relationship between exposure factors and disease through causal inference. The integrated application of both methodologies can address the limitations inherent in each approach, thereby offering robust scientific evidence for early screening and intervention in diabetic nephropathy. Furthermore, these two methodologies facilitate the investigation of the pathogenesis of diabetic nephropathy from both macroscopic and microscopic perspectives, thereby providing a robust theoretical basis for early intervention and personalized treatment. This integrated approach enhances the comprehension of disease onset and enables the identification of modifiable risk factors, thereby informing more effective and targeted therapeutic strategies.

The objective of this study is to conduct a systematic investigation into the primary risk factors associated with diabetic nephropathy and to examine the causal relationships between these risk factors and the progression of diabetic nephropathy through the application of meta-analysis and Mendelian randomization (MR) analysis. Utilizing meta-analysis, this research aims to synthesize data from diverse regions and populations to identify overarching risk factors that are significantly correlated with the onset of diabetic nephropathy. Simultaneously, through the application of Mendelian randomization analysis and the use of genetic variations as instrumental variables, this study aims to elucidate the causal relationships between various exposure factors and diabetic nephropathy, thereby addressing the bias issues typically associated with traditional observational studies. The primary objective of this study is to furnish scientific evidence to facilitate early screening, prevention, and personalized treatment of diabetic nephropathy, while also contributing to the advancement of pertinent public health interventions.

2. Methodology and materials

2.1. The process of conducting research

As illustrated in Figure 1. This study undertook a comprehensive literature search on diabetic kidney disease utilizing the PubMed, Embase, and Cochrane Library databases, with the search concluding in September 2024. The search strategy

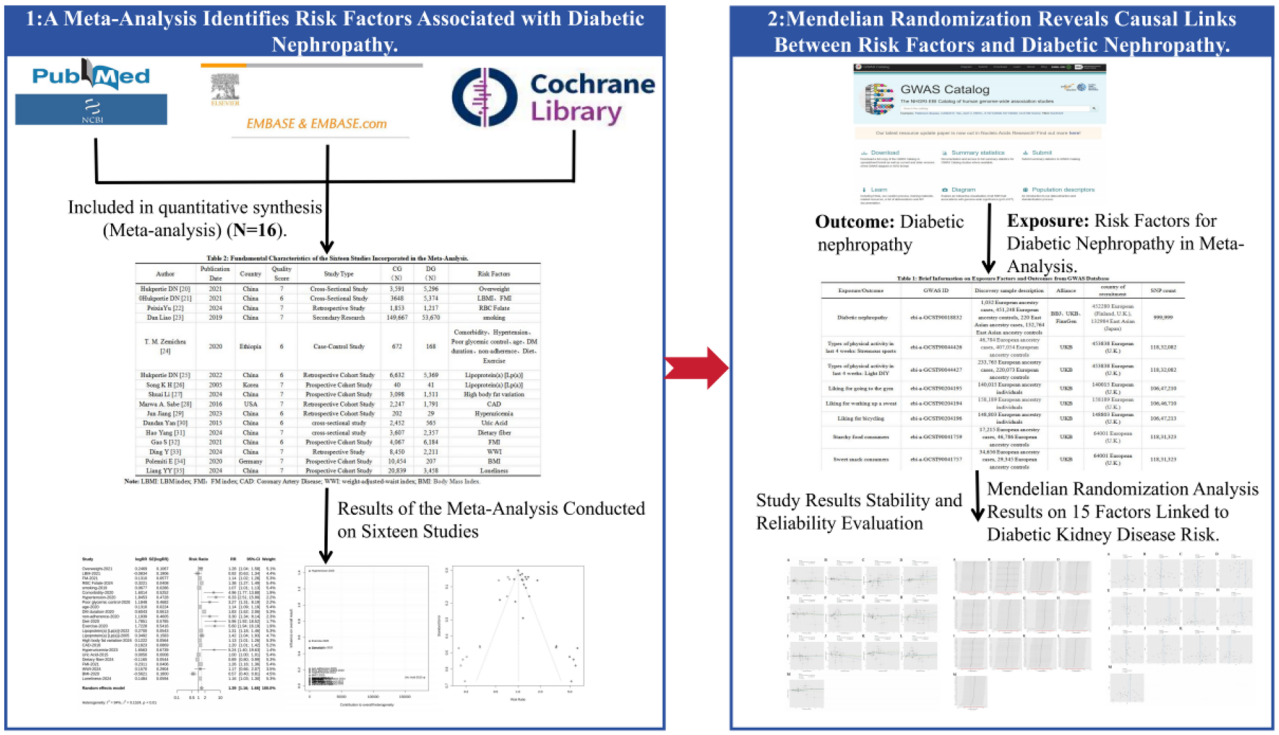

Figure 1. Research process Flowchart.

incorporated keywords such as 'diabetic kidney disease', 'diabetes', 'microvascular complications', and 'risk factors'. The quality of the selected studies was evaluated using the PEDro scale. Data analysis was conducted *via* meta-analysis, employing either fixed-effect or random-effect models based on the I^2 statistic. Sensitivity analyses and funnel plots were utilized to assess the robustness and validity of the findings. Furthermore, a Mendelian randomization analysis was performed utilizing single nucleotide polymorphisms (SNPs) sourced from the Genome-Wide Association Studies (GWAS) database to investigate the causal relationship between the principal risk factors identified in the meta-analysis and diabetic kidney disease. The inverse variance weighting (IVW) method was employed to evaluate these causal relationships, with validation conducted through MR-Egger regression, weighted median, and additional methodologies. Genetic pleiotropy and heterogeneity were assessed using the MR-Egger regression intercept and Cochran's Q statistic. An extensive analysis of the major risk factors and causal relationships associated with diabetic kidney disease will provide strong evidence for clinical practice.

2.2. Methodology and materials for meta-analysis

2.2.1. Study search and inclusion criteria

A comprehensive literature review will be performed utilizing the PubMed, Embase, and Cochrane Library databases, with the search period concluding in September 2024. The search strategy integrates both controlled vocabulary and free-text keywords, incorporating subject headings such as 'diabetic kidney disease' and 'diabetes', alongside free-text terms like 'microvascular complications' and 'risk factors'. The search queries employed include combinations such as 'diabetic kidney disease + risk factors' and 'diabetes + microvascular complications + risk factors'. Eligible studies are required to be pertinent original research articles that present comprehensive data on the numbers of both case and control groups. Furthermore, the inclusion criteria encompassed the comprehensiveness of data, the robustness of study design, and the outcome measures, including odds ratios (OR) and their corresponding 95% confidence intervals (CI). We excluded duplicate publications, basic research, studies with incomplete clinical data, conference abstracts, expert consensus documents, studies lacking indicators related to diabetic kidney disease, and studies without full-text availability (refer to Figure 2).

2.2.2. Review of literature and data extraction methodology

The study was executed by two researchers who rigorously adhered to predefined inclusion and exclusion criteria during the literature selection process. In instances of disagreement during the screening phase, a third researcher was engaged to make the final decision, thereby ensuring objectivity and consistency in the selection process. Data collection encompassed fundamental information from the studies, including the lead author, year of publication, sample sizes of the experimental and control groups, and the intervention strategies employed. Furthermore, the incidence of adverse events, specifically diabetic kidney disease, was meticulously documented in both the experimental and

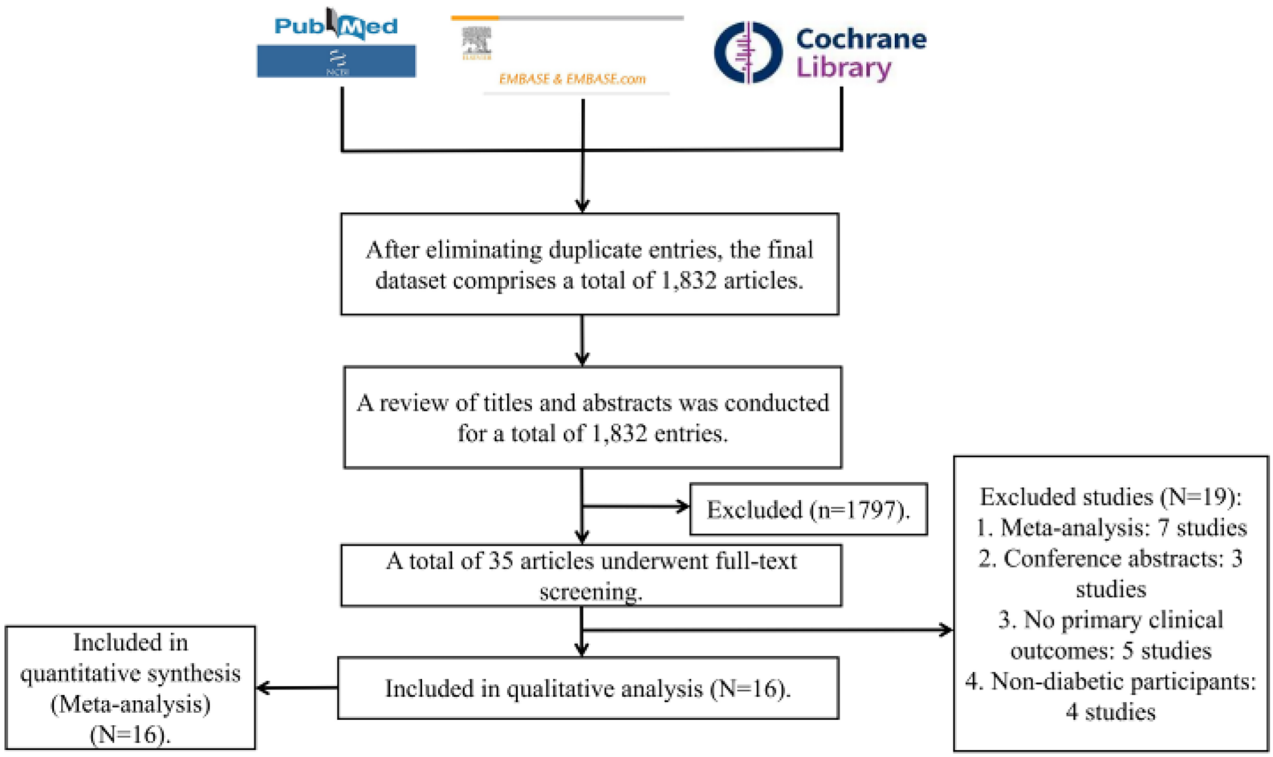

Figure 2. Flowchart depicting the selection process of literature for meta-analysis.

control groups. To uphold the quality of the studies, an evaluation was conducted on the randomization techniques, blinding procedures and types, as well as follow-up attrition rates. The systematic collection and analysis of this data were essential for ensuring the study's reliability and scientific validity.

2.2.3. Literature quality assessment and statistical analysis

This study used the Newcastle-Ottawa Scale (NOS) [17] to assess the methodological quality and bias risk in retrospective, case-control, retrospective cohort, and prospective cohort studies. The NOS evaluates non-randomized studies in systematic reviews and meta-analyses, focusing on Selection, Comparability, and Outcome. It scores studies from 0 to 9, categorizing them as high (7–9), moderate (4–6), or low quality (0–3) based on population representativeness, confounding control, follow-up duration, and outcome reliability. Systematic reviews were evaluated using AMSTAR 2, a tool with 16 items for assessing reviews involving RCTs or NRS. It examines: research question and design clarity, comprehensive literature search strategy, bias risk assessment, data extraction and analysis methods, result reliability, and conclusion validity. AMSTAR 2 [18] rates review quality as high, moderate, low, or very low. Cross-sectional studies were evaluated using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist [19] for Analytical Cross-Sectional Studies, which includes eight items. These focus on defining the study population clearly, ensuring reliable measurement of exposure and outcome, establishing that exposure precedes the outcome, and identifying and controlling potential confounding factors.These instruments facilitate the design and implementation of various study types, thereby minimizing bias and ensuring the generation of reliable and valid results.

A meta-analysis of the data will be performed utilizing the R package 'meta'. For categorical data, the statistical effect size will be represented by odds ratios (OR) along with their 95% confidence intervals (CI), whereas for continuous data, mean differences (MD) and their corresponding 95% confidence intervals (CI) will be employed. In cases where the I^2 statistic is less than or equal to 50%, indicating substantial homogeneity among studies, a fixed-effect model will be employed for the analysis. Conversely, if the I^2 statistic exceeds 50%, a random-effects model will be utilized. To evaluate the robustness of the results, a sensitivity analysis will be conducted by altering the effect model to examine the consistency of the findings. A funnel plot and Egger's regression test will be used to assess and verify publication bias if there are 10 or more studies. For any observed significant differences, a P-value of less than 0.05 will be regarded as statistically significant.

2.3. Methods and materials for conducting Mendelian Randomization analysis

2.3.1. Research methodology

This research employs single nucleotide polymorphisms (SNPs) from the Genome-Wide Association Studies (GWAS) database (https://www.ebi.ac.uk/gwas/) as instrumental variables to evaluate the influence of exposure factors on the susceptibility to diabetic kidney disease. The selection of exposure factors is informed by the primary risk factors

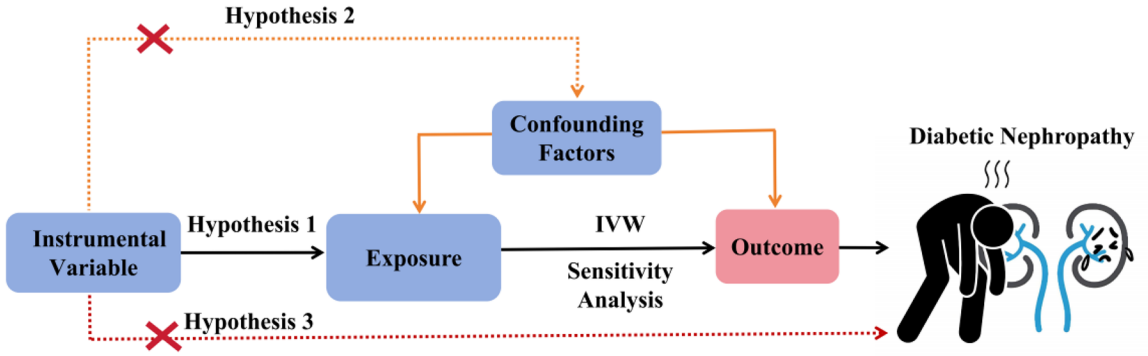

Figure 3. Schematic representation of mendelian Randomization analysis illustrating the relationship between exposure variables and outcome.

identified in a meta-analysis, with diabetic kidney disease serving as the outcome variable. The study is predicated on three fundamental assumptions: (1) A significant association exists between single nucleotide polymorphisms (SNPs) and the exposure factors, specifically the risk factors identified in the meta-analysis; (2) SNPs are not correlated with confounding variables, thereby ensuring the validity of the instrumental variables; and (3) SNPs exert an influence on the risk of diabetic kidney disease solely through the exposure factors, as identified in the meta-analysis, thereby excluding genetic pleiotropy, meaning the effect of SNPs on the outcome is restricted to their impact *via* the exposure factors. These assumptions are critical to maintaining the validity of the Mendelian randomization analysis and ensuring the reliability of its conclusions (refer to Figure 3).

2.3.2. Selection of SNP data

The Genome-Wide Association Study (GWAS) data pertaining to outcomes and exposure factors in this study are presented in Table 1. In accordance with the prerequisites for Mendelian Randomization (MR) analysis, the selected single nucleotide polymorphisms (SNPs) must exhibit a robust association with diabetic kidney disease. To ensure that the chosen SNPs possess a sufficiently strong association with diabetic kidney disease and to mitigate bias arising from weak instrumental variables, this study employed an F-statistic threshold greater than 10 to exclude weak instrumentss [20]. Specifically, the F-statistic is calculated using the following formula: $F = N\text{-}K\text{-}1/K \times R^2/1\text{-}R^2$. In this context, N represents the total sample size, K denotes the number of exposure variables, and R^2 signifies the squared correlation between the single nucleotide polymorphism (SNP) and the exposure factor. An F-statistic exceeding 10 is established as the criterion for mitigating weak instrument bias, thereby enhancing the robustness and reliability of the Mendelian randomization (MR) analysis outcomes. To ascertain whether the GWAS dataset satisfies the minimum sample size requirement, the formula $N=(Z_{1-\alpha/2}+Z_{1-\beta})^{2\cdot\sigma 2}/\beta 2$ is utilized. This computation integrates the exposure effect estimate (β), variance (σ2), significance level (α), and statistical power (1 − β). Employing this methodology allows for the determination of the requisite minimum sample size, which can then be compared to the available GWAS dataset to evaluate its adequacy.

2.3.3. MR statistical analysis

In this study, R version 4.1.0 was employed to conduct Mendelian randomization (MR) analysis utilizing the Two Sample MR and MRPRESSO packages. The primary analytical approach was inverse variance weighting (IVW), with the robustness of the MR results being further corroborated through four supplementary methods: MR-Egger regression, weighted median (WME), weighted mode, and simple mode. Consistency in causal inference across all five MR analytical methods was regarded as indicative of highly reliable findings [21].

Genetic pleiotropy was identified through the intercept term in the MR-Egger regression analysis. An intercept P-value of less than 0.05 indicates the presence of horizontal pleiotropy, suggesting that the single nucleotide polymorphism (SNP) may affect the outcome *via* multiple pathways. Heterogeneity was evaluated using Cochran's Q statistic, with a P-value of less than 0.05 denoting significant heterogeneity in the findings. Furthermore, a sensitivity analysis was conducted employing the 'leave-one-out' technique, wherein each single nucleotide polymorphism (SNP) was sequentially excluded, and the aggregate effect of the remaining SNPs was recalculated. This approach facilitates the assessment of whether any particular SNP exerts a substantial influence on the causal relationship between the exposure and the outcome. This method is instrumental in testing the robustness of the results and in evaluating the potential impact of individual instrumental variables.

3. Results

3.1. Meta-analytical findings on the risk factors contributing to the incidence of diabetic kidney disease

3.1.1. Details of studies incorporated in the quantitative meta-analysis

Utilizing the established inclusion and exclusion criteria, a total of 1,832 potentially pertinent articles concerning the risk of diabetic kidney disease were retrieved from various databases: 754 from PubMed, 321 from Embase, and 757 from the Cochrane Library. Subsequent to the removal of duplicates and the exclusion of evidently unrelated studies, the abstracts of 35 articles were subjected to review. A comprehensive full-text analysis of these 35 articles resulted in

Table 1. Brief information on exposure factors and outcomes from GWAS database.

Exposure/Outcome	GWAS ID	Discovery sample description	Alliance	Country of recruitment	SNP count
Diabetic nephropathy	ebi-a-GCST90018832	1,032 European ancestry cases, 451,248 European ancestry controls, 220 East Asian ancestry cases, 132,764 East Asian ancestry controls	BBJ、UKB、FinnGen	452280 European (Finland, U.K.), 132984 East Asian (Japan)	999,999
Types of physical activity in last 4 weeks: Strenuous sports	ebi-a-GCST90044426	46,784 European ancestry cases, 407,054 European ancestry controls	UKB	453838 European (U.K.)	118,32,082
Types of physical activity in last 4 weeks: Light DIY	ebi-a-GCST90044427	233,765 European ancestry cases, 220,073 European ancestry controls	UKB	453838 European (U.K.)	118,32,082
Liking for going to the gym	ebi-a-GCST90204195	140,015 European ancestry individuals	UKB	140015 European (U.K.)	106,47,210
Liking for working up a sweat	ebi-a-GCST90204194	158,189 European ancestry individuals	UKB	158189 European (U.K.)	106,46,710
Liking for bicycling	ebi-a-GCST90204196	148,803 European ancestry individuals	UKB	148803 European (U.K.)	106,47,213
Starchy food consumers	ebi-a-GCST90041759	17,215 European ancestry cases, 46,786 European ancestry controls	UKB	64001 European (U.K.)	118,31,323
Sweet snack consumers	ebi-a-GCST90041757	34,656 European ancestry cases, 29,345 European ancestry controls	UKB	64001 European (U.K.)	118,31,323
Dessert consumers	ebi-a-GCST90041756	20,622 European ancestry cases, 43,379 European ancestry controls	UKB	64001 European (U.K.)	118,31,323
Savory snack consumers	ebi-a-GCST90041758	22,768 European ancestry cases, 41,233 European ancestry controls	UKB	64001 European (U.K.)	118,31,323
Vegetable consumers	ebi-a-GCST90041767	52,696 European ancestry cases, 11,305 European ancestry controls	UKB	64001 European (U.K.)	118,31,323
Fruit consumers	ebi-a-GCST90041768	52,183 European ancestry cases, 11,818 European ancestry controls	UKB	64001 European (U.K.)	118,31,323
Tea consumed	ebi-a-GCST90041729	50,994 European ancestry cases, 13,007 European ancestry controls	UKB	64001 European (U.K.)	118,31,323
Decaffeinated coffee	ebi-a-GCST90041728	7,241 European ancestry cases, 56,760 European ancestry controls	UKB	64001 European (U.K.)	118,31,323
Meat consumers	ebi-a-GCST90041762	44,190 European ancestry cases, 19,811 European ancestry controls	UKB	64001 European (U.K.)	118,31,323
Essential hypertension	ebi-a-GCST90043949	1,105 European ancestry cases, 455,243 European ancestry controls	UKB	456348 European (U.K.)	118,31,323

the exclusion of 19 articles for diverse reasons (refer to Figure 2). Consequently, 16 studies were incorporated into the meta-analysis (refer to Table 2).

The meta-analysis comprised 16 studies: 4 cross-sectional [22,23,32,33], 2 retrospective [24,35], 1 secondary research [25], 1 case-control [26], 3 retrospective cohort [27,30,31], and 5 prospective cohort studies [28,29,34,36,37]. Published between 2005 and 2024, these studies involved 310,967 participants from China ($n=12$), Ethiopia ($n=1$), South Korea ($n=1$), Germany ($n=1$), and the United States ($n=1$). Among these studies, those conducted by Peixia Yu [24], Hao Yang [33], and Ding Y [35] utilized the NHANES database, whereas Liang YY's research [37] employed the UK Biobank database. Consequently, the participants in these studies were not exclusively of Chinese origin. The quality scores for all 16 studies ranged from 6 to 7, reflecting a high level of research quality. Collectively, these studies identified 23 risk factors associated with diabetic kidney disease, thereby contributing significant evidence to the understanding of risk factors for this condition.

The quality assessment of the included studies indicated that all 11 studies [24,26–31,34–37], evaluated using the Newcastle-Ottawa Scale (NOS), were of medium to high quality, with no studies identified as low quality (refer to Figure 4A). Additionally, the Joanna Briggs Institute (JBI) assessment results for four studies [22,23,32,33] demonstrated a low risk of bias (refer to Figure 4B). In contrast, the study by Dan Liao [25], evaluated using the AMSTAR 2 tool, was rated as moderate quality. Overall, the analysis confirmed that the included studies were of reliable quality with a low risk of bias.

3.1.2. Results of the meta-analysis conducted on sixteen studies

In the quantitative meta-analysis of 16 studies, the heterogeneity test results demonstrated significant heterogeneity (I^2 = 94%, $p<0.01$). Analysis using the Baujat plot revealed that the hypertension factor in T.M. Zemichea's study contributed substantially to the overall heterogeneity (refer to Figure 5A). Subsequent sensitivity analysis employing the Leave-One-Out method indicated that the pooled risk ratio (RR) was 1.39, with a 95% confidence interval of 1.16 to 1.66 and a P-value of 0.0003, suggesting robustness and minimal influence from any single study. Despite the high heterogeneity observed (refer to Figure 5B), the results remained statistically significant. Consequently, a random-effects model was utilized for this meta-analysis.

The findings of the meta-analysis, conducted utilizing the random-effects model, identified the following factors as significant risk determinants for the development of diabetic kidney disease: Comorbidities (RR = 4.96, 95% CI = 1.77–13.88); Hypertension (RR = 6.33, 95% CI = 2.51–15.99); Inadequate Glycemic Control (RR = 3.27, 95% CI = 1.31–8.19); Non-adherence to Treatment (RR = 3.30, 95% CI = 1.34–8.14); Dietary Factors (RR = 5.96, 95% CI = 1.92–18.52); Physical Activity (RR = 5.60, 95% CI = 1.94–16.19); Hyperuricemia (RR = 5.24, 95% CI = 1.40–19.63); BMI (RR = 0.57, 95% CI = 0.40–0.81). These factors were identified as having a substantial influence on the risk of developing diabetic kidney disease, as illustrated in Figure 5C.

In the funnel plot analysis of publication bias for the 16 studies, the relative risk (RR) was plotted on the horizontal axis

Table 2. Fundamental characteristics of the sixteen studies incorporated in the meta-analysis.

Author	Publication date	Country	Study type	CG (N)	DG (N)	Risk factors
Hukportie DN [22]	2021	China	Cross-Sectional Study	3,591	5,296	Overweight
0Hukportie DN [23]	2021	China	Cross-Sectional Study	3648	5,374	LBMI、FMI
PeixiaYu [24]	2024	China	Retrospective Study	1,853	1,217	RBC Folate
Dan Liao [25]	2019	China	Secondary Research	149,667	53,670	smoking
T. M. Zemichea [26]	2020	Ethiopia	Case-Control Study	672	168	Comorbidity、Hypertension、Poor glycemic control、age、DM duration、non-adherence、Diet、Exercise
Hukportie DN [27]	2022	China	Retrospective Cohort Study	6,632	5,369	Lipoprotein(a) [Lp(a)]
Song K H [28]	2005	Korea	Prospective Cohort Study	40	41	Lipoprotein(a) [Lp(a)]
Shuai Li [29]	2024	China	Prospective Cohort Study	3,098	1,511	High body fat variation
Marwa A. Sabe [30]	2016	USA	Retrospective Cohort Study	2,247	1,791	CAD
Jun Jiang [31]	2023	China	Retrospective Cohort Study	202	29	Hyperuricemia
Dandan Yan [32]	2015	China	cross-sectional study	2,452	565	Uric Acid
Hao Yang [33]	2024	China	cross-sectional study	3,607	2,357	Dietary fiber
Gao S [34]	2021	China	Prospective Cohort Study	4,067	6,184	FMI
Ding Y [35]	2024	China	Retrospective Study	8,450	2,211	WWI
Polemiti E [36]	2020	Germany	Prospective Cohort Study	10,454	207	BMI
Liang YY [35]	2024	China	Prospective Cohort Study	20,839	3,458	Loneliness

Note: LBMI: LBM index; FMI: FM index; CAD: Coronary Artery Disease; WWI: weight-adjusted-waist index; BMI: Body Mass Index.

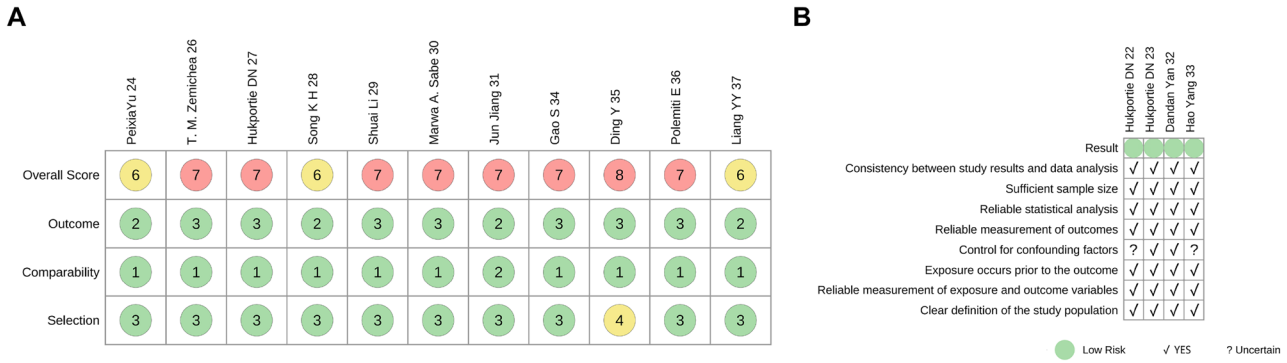

Figure 4. Results of the quality assessment conducted on 16 studies.
Note: A. Evaluation results of the eleven studies were assessed using the Newcastle-Ottawa Scale (NOS) (It scores studies from 0 to 9, categorizing them as high (7–9), moderate (4–6), or low quality (0–3) based on population representativeness, confounding control, follow-up duration, and outcome reliability). **B.** Evaluation results of the four studies were assessed utilizing the Joanna Briggs Institute (JBI) criteria.

and the log of the standard error (SE) of RR on the vertical axis. Significant differences ($T=7.64$, df = 59, $p<0.001$) indicated notable publication bias (refer to Figure 5D). After applying the trim-and-fill model, the corrected funnel plot became more symmetrical, with studies more centrally distributed and the pooled effect size converging toward the center, suggesting reduced bias (refer to Figure 5E). Egger's regression test showed an intercept of 0.08357 (P-value = 0.405), indicating no significant publication bias. The residual standard error was 0.38, suggesting a good model fit without extreme residuals or outlier influence. The model was significant (F-test P-value = 1.162×10^{-7}), confirming its applicability (refer to Figure 5F). Initially, the funnel plot suggested potential bias, but corrections reduced it, and Egger's test confirmed no significant bias. The model is stable and applicable.

3.2. Results of Mendelian Randomization analysis on 15 exposure factors associated with the risk of diabetic kidney disease

3.2.1. SNPs selection results

Drawing from the findings of the meta-analysis, this study identified comorbidities, hypertension, inadequate glycemic control, non-adherence to treatment regimens, dietary habits, Exercise, and hyperuricemia as significant risk factors contributing to the development of diabetic kidney disease. Therefore, we selected 5 physical activity-related factors (Strenuous sports, Light DIY, Liking for going to the gym, Liking for working up a sweat, Liking for bicycling) and 9 dietary-related factors (Starchy food consumers, Sweet snack consumers, Dessert consumers, Savory snack consumers, Vegetable consumers, Fruit consumers, Tea consumption, Decaffeinated coffee, Meat consumers) from the GWAS database, along with hypertension as an exposure factor, with diabetic kidney disease as the outcome, to conduct a multi-sample Mendelian randomization (MR) analysis. In the process of selecting instrumental variables, after adjusting for confounding factors related to the 15 exposure variables and diabetic kidney disease, single nucleotide polymorphisms (SNPs) with potential alternative effect relationships were excluded. The final count of SNPs included is presented in Table 3, all exhibiting F-values exceeding 10. This criterion confirms the absence of weak instrumental variables in the Mendelian randomization (MR) analysis concerning these exposure factors and diabetic kidney disease, thereby enhancing the reliability of the analytical outcomes.

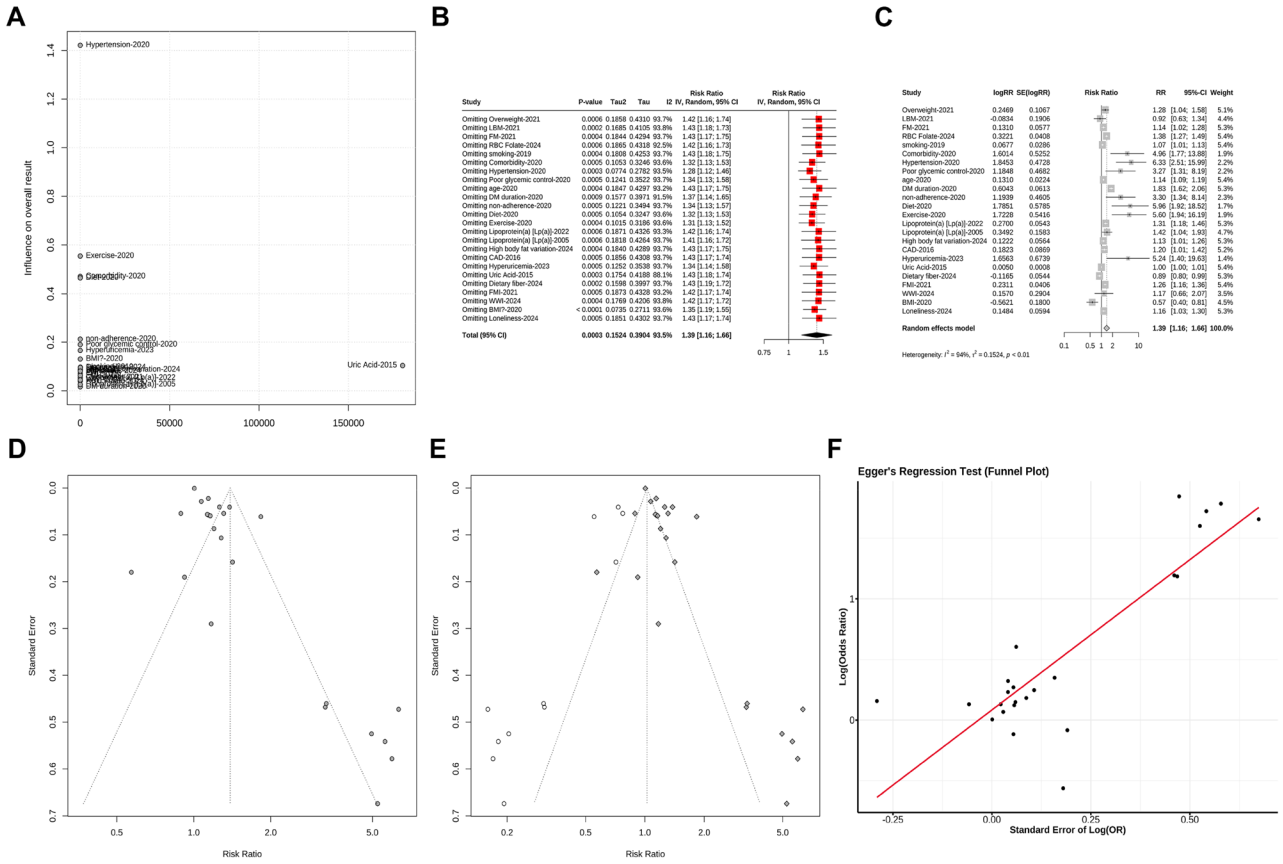

Figure 5. Results of the meta-analysis and their validation.
Note: A. Baujat plot is utilized to illustrate the contribution of individual studies to overall heterogeneity (I^2) on the x-axis, while the y-axis depicts the effect size of each study on the aggregate estimate. Analysis of the Baujat plot reveals that the hypertension factor identified in the study by T.M. Zemichea exerts a substantial influence on the overall effect estimate. **B.** The sensitivity analysis conducted using the leave-one-out approach demonstrated robust results, as no individual study exhibited significant heterogeneity. **C.** Forest Plot of Meta-Analysis: This plot, encompassing 16 studies, depicts the Risk Ratio (RR) along with the 95% confidence intervals for various risk factors across the included studies. **D.** Pre-correction Funnel Plot: This plot illustrates the association between the standard error (SE) and the relative risk (RR) values for each study. Studies characterized by a larger SE, indicative of a smaller sample size, are situated higher on the plot. Conversely, studies with a smaller SE, reflecting a larger sample size, are positioned closer to the bottom. **E.** Post-Correction Funnel Plot: This plot illustrates the association between the standard error and relative risk (RR) values for each study following calibration. Data points with larger standard errors remain positioned higher on the plot, whereas those with smaller standard errors are situated lower. This distribution reflects the impact of adjustments made to account for publication bias. **F.** The results of Egger's regression test demonstrated that the intercept did not reveal any significant evidence of publication bias.

Furthermore, an assessment of the sample size within the GWAS dataset reveals that it satisfactorily fulfills the necessary criteria for this analysis.

3.2.2. Results of Mendelian Randomization analysis

Utilizing Mendelian randomization analysis to examine 15 exposure factors in relation to diabetic kidney disease, and employing the random-effects inverse-variance weighted (IVW) analysis method, the findings revealed a statistically significant positive association between starchy food consumption and diabetic kidney disease ($p = 0.043$; OR = 1.393, 95% CI = 1.011–1.919). This suggests that elevated consumption of starchy foods may increase the risk of developing diabetic kidney disease (refer to Table 3). In the interim, vegetable consumers were identified as having a protective effect against diabetic kidney disease ($p = 0.011$; OR = 0.816, 95% CI = 0.697–0.955), with vegetable consumption demonstrating a significant negative correlation with the incidence of diabetic kidney disease (refer to Table 3). Additional analyses, which included scatter plots and various Mendelian Randomization (MR) methods—namely MR-Egger, Weighted Median Estimator (WME), Weighted Mode, and Simple Mode—yielded results consistent with those obtained from the Inverse Variance Weighted (IVW) analysis, thereby corroborating the reliability of these findings (refer to Figures 6A, B).

However, the remaining 13 exposure factors (Strenuous sports, Light DIY, Liking for going to the gym, Liking for working up a sweat, Liking for bicycling, Sweet snack consumers, Dessert consumers, Savory snack consumers, Fruit consumers, Tea consumption, Decaffeinated coffee, Meat consumers, Hypertension) did not establish a significant causal relationship with diabetic kidney disease (all IVW $p > 0.05$, refer to Table 3). These analysis results were further validated through scatter plots and other MR methods, confirming their consistency and reliability (refer to **S** Figures 1A-M).

3.2.3. Study results stability and reliability evaluation

In the heterogeneity analysis examining the causal relationship between the consumption of starchy foods and

vegetables and the incidence of diabetic kidney disease (refer to Table 4), the Inverse Variance Weighted (IVW) method revealed no significant heterogeneity for starchy food consumers ($p = 0.475$) or vegetable consumers ($p = 0.639$). Similarly, the MR-Egger analysis demonstrated no significant heterogeneity in the causal relationship for starchy food consumers ($p = 0.422$) or vegetable consumers ($p = 0.602$) with diabetic kidney disease. These findings suggest that the causal effects are consistent across different sample populations. In the pleiotropy assessment, the MR-Egger intercept values for consumers of starchy foods and vegetable consumers were 0.99 and 0.591, respectively, both of which did not demonstrate a statistically significant deviation from zero. This finding further substantiates the conclusion of an absence of pleiotropic bias. Furthermore, the application of the leave-one-out method, which involved the sequential removal of each single nucleotide polymorphism (SNP), yielded stable results, with no individual SNP exerting a significant influence on the overall findings (refer to Figure 7A and B). This consistency reinforces the reliability of the results and confirms the absence of weak instrument bias. The funnel plot demonstrated symmetry, suggesting that the causal relationship in this analysis was minimally influenced by bias when employing individual SNPs as instrumental variables (refer to Figure 8A and B). This observation further corroborates the validity of the selected instruments and the robustness of the analytical outcomes.

In the heterogeneity analysis examining the causal relationship between sweet snack consumption and tea consumption with diabetic kidney disease, the Inverse Variance Weighted (IVW) method revealed significant heterogeneity for sweet snack consumers ($p = 0.011$) and tea consumption ($p = 0.040$). Similarly, the MR-Egger analysis demonstrated significant heterogeneity in the causal relationship for sweet snack consumers ($p = 0.011$) and tea consumption ($p = 0.042$) with diabetic kidney disease. These findings suggest that the causal effects of these exposure factors on diabetic kidney disease may be influenced by variations across different samples or single nucleotide polymorphisms (SNPs) (refer to Table 4). In the pleiotropy test, the MR-Egger intercept values for sweet snack consumers and tea consumers were 0.43 and 0.344, respectively. These values did not differ significantly from zero, suggesting the absence of pleiotropic bias and supporting the conclusion that pleiotropy is not an issue. Furthermore, the application of the leave-one-out method, which involves the sequential removal of each SNP, demonstrated that the analysis results remained consistent, with no single SNP exerting a substantial influence on the findings (refer to S Figure 2F and J). This further corroborates the reliability of the results and indicates the absence of weak instrument bias. Despite the significant heterogeneity observed in the causal relationship between sweet snack consumers and tea consumers with diabetic kidney disease, further analyses, including pleiotropy testing, leave-one-out analysis, and funnel plot analysis (refer to S Figures 3F and J), demonstrated that this heterogeneity had a minimal impact on the final results. No evidence of pleiotropic bias was detected, and the instrumental variables proved effective, thereby supporting the potential existence of a true causal relationship between these exposure factors and diabetic kidney disease.

In the heterogeneity analysis of the causal relationship between the remaining 11 exposure factors (Strenuous sports, Light DIY, Liking for going to the gym, Liking for working up a sweat, Liking for bicycling, Dessert consumers, Savory snack consumers, Fruit consumers, Decaffeinated coffee, Meat consumers, Hypertension) and diabetic kidney disease, the results showed that neither the heterogeneity tests nor the pleiotropy tests for all exposure factors reached statistical significance ($p > 0.05$), indicating no significant heterogeneity or horizontal pleiotropy (refer to Table 4). This suggests that the causal relationships between these exposure factors and diabetic kidney disease are stable across different samples and are not affected by pleiotropy issues. Upon employing the leave-one-out approach by systematically excluding each single nucleotide polymorphism (SNP) in turn, the analytical outcomes demonstrated consistency and stability, with no individual SNP exerting a significant influence on the results. This observation further corroborates the robustness of the findings (refer to S Figure 2). Additionally, the funnel plots exhibited near symmetry (refer to S Figure 3), suggesting that the causal relationship, when utilizing individual SNPs as instrumental variables, was minimally influenced by bias. This provides robust evidence supporting the causal inference in this analysis.

4. Discussion

This study conducted a systematic evaluation of various exposure factors linked to the risk of Diabetic Kidney Disease (DKD) utilizing meta-analysis and Mendelian randomization (MR) analysis, yielding several findings of substantial public health and clinical significance. Through a comprehensive analysis of 16 high-quality observational studies and the integration of data from Genome-Wide Association Studies (GWAS) concerning 15 exposure factors, our research corroborated established risk factors for diabetic kidney disease (DKD) and identified novel potential targets for intervention. These findings hold significant theoretical and practical implications for informing the prevention and management of DKD, particularly in the development of personalized intervention strategies tailored to diverse population groups.

4.1. The primary risk factors associated with diabetic kidney disease

The findings of the meta-analysis demonstrate that the incidence risk of diabetic kidney disease (DKD) is significantly affected by a variety of factors. In particular, complications, hypertension, hyperuricemia, inadequate blood glucose management, non-adherence to treatment, dietary habits, and physical activity are strongly correlated with the onset of DKD, exhibiting elevated relative risks (RR) for these variables.

Table 3. Presents the results of the Mendelian Randomization analysis for 15 exposure factors in relation to diabetic kidney disease.

Exposure	SNP count	Method	SE	*P*	OR (95%CI)
Strenuous sports	30	MR Egger	0.569	0.501	0.679 (0.223–2.069)
		Weighted median	0.431	0.924	0.960 (0.413–2.232)
		IVW	0.287	0.770	0.920 (0.524–1.613)
		Simple mode	0.694	0.675	0.746 (0.192–2.904)
		Weighted mode	0.533	0.807	0.877 (0.309–2.492)
Light DIY	33	MR Egger	0.998	0.509	0.513 (0.073–3.630)
		Weighted median	0.593	0.152	0.427 (0.134–1.367)
		IVW	0.413	0.221	0.603 (0.269–1.354)
		Simple mode	0.999	0.339	0.379 (0.053–2.687)
		Weighted mode	0.8064	0.273	0.407 (0.083–1.976)
Liking for going to the gym	30	MR Egger	0.450	0.438	1.425 (0.59–3.442)
		Weighted median	0.316	0.312	1.376 (0.741–2.554)
		IVW	0.223	0.274	1.276 (0.824–1.976)
		Simple mode	0.547	0.244	1.917 (0.656–5.602)
		Weighted mode	0.515	0.216	1.917 (0.699–5.261)
Liking for working up a sweat	27	MR Egger	2.196	0.915	8.987 (1.496–53.998)
		Weighted median	0.20	0.474	1.221 (0.482–3.092)
		IVW	0.32	0.421	1.297 (0.691–2.421)
		Simple mode	0.835	0.948	0.944 (0.184–4.85)
		Weighted mode	0.779	0.948	1.053 (0.229–4.841)
Liking for bicycling	31	MR Egger	0.650	0.529	0.661 (0.185–2.365)
		Weighted median	0.336	0.456	0.778 (0.403–1.504)
		IVW	0.236	0.413	0.824 (0.519–1.309)
		Simple mode	0.564	0.791	0.860 (0.285–2.598)
		Weighted mode	0.500	0.499	0.710 (0.266–1.893)
Starchy food consumers	30	MR Egger	0.371	0.373	1.400 (0.676–2.896)
		Weighted median	0.245	0.441	1.208 (0.747–1.954)
		IVW	0.164	0.043	1.393 (1.011–1.919)
		Simple mode	0.453	0.474	1.389 (0.572–3.377)
		Weighted mode	0.419	0.769	1.132 (0.498–2.573)
Sweet snack consumers	29	MR Egger	0.233	0.800	0.942 (0.597–1.488)
		Weighted median	0.201	0.498	1.146 (0.773–1.699)
		IVW	0.153	0.599	1.084 (0.803–1.464)
		Simple mode	0.3860	0.125	0.543 (0.2545–1.158)
		Weighted mode	0.162	0.453	1.132 (0.823–1.555)
Dessert consumers	28	MR Egger	0.308	0.397	1.304 (0.713–2.386)
		Weighted median	0.265	0.891	1.037 (0.617–1.744)
		IVW	0.179	0.635	0.918 (0.646–1.305)
		Simple mode	0.368	0.819	1.089 (0.529–2.241)
		Weighted mode	0.243	0.840	1.051 (0.653–1.691)
Savory snack consumers	26	MR Egger	0.376	0.106	1.882 (0.901–3.935)
		Weighted median	0.258	0.925	0.976 (0.589–1.618)
		IVW	0.195	0.564	1.119 (0.764–1.638)
		Simple mode	0.519	0.244	1.858 (0.672–5.143)
		Weighted mode	0.392	0.700	0.858 (0.398–1.849)
Vegetable consumers	28	MR Egger	0.098	0.09	0.841 (0.694–1.02)
		Weighted median	0.193	0.317	0.825 (0.565–1.203)
		IVW	0.08	0.011	0.816 (0.697–0.955)
		Simple mode	0.280	0.734	0.908 (0.525–1.573)
		Weighted mode	0.111	0.103	0.829 (0.667–1.03)
Fruit consumers	32	MR Egger	0.254	0.721	0.912 (0.554–1.501)
		Weighted median	0.1789	0.723	1.065 (0.750–1.513)
		IVW	0.129	0.762	1.04 (0.807–1.340)
		Simple mode	0.279	0.825	1.064 (.616–1.838)
		Weighted mode	0.248	0.704	1.100 (0.677–1.788)
Tea consumed	30	MR Egger	0.284	0.865	0.952 (0.546–2.025)
		Weighted median	0.222	0.224	1.310 (0.848–2.025)
		IVW	0.17	0.32	1.185 (0.848–1.654)
		Simple mode	0.367	0.137	1.752 (0.853–3.596)
		Weighted mode	0.265	0.689	1.113 (0.662–1.87)
Decaffeinated coffee	25	MR Egger	0.304	0.223	0.738 (0.476–1.142)
		Weighted median	0.395	0.174	0.910 (0.646–1.280)
		IVW	0.121	0.397	0.903 (0.713–1.144)
		Simple mode	0.268	0.714	0.905 (0.536–1.53)
		Weighted mode	0.245	0.542	0.859 (0.531–1.39)
Meat consumers	28	MR Egger	0.283	0.219	1.428 (0.821–2.486)
		Weighted median	0.262	0.311	1.304 (0.780–2.179)
		IVW	0.169	0.537	1.110 (0.797–1.546)
		Simple mode	0.491	0.354	0.629 (0.240–1.647)
		Weighted mode	0.275	0.226	1.406 (0.812–2.412)
Essential hypertension	28	MR Egger	0.068	0.877	1.011 (0.8845–1.154)
		Weighted median	0.061	0.430	1.050 (0.9301–1.183)
		IVW	0.041	0.09	1.073 (0.989–1.164)
		Simple mode	0.101	0.638	0.953 (0.781–1.162)
		Weighted mode	0.057	0.925	1.005 (0.90–1.123)

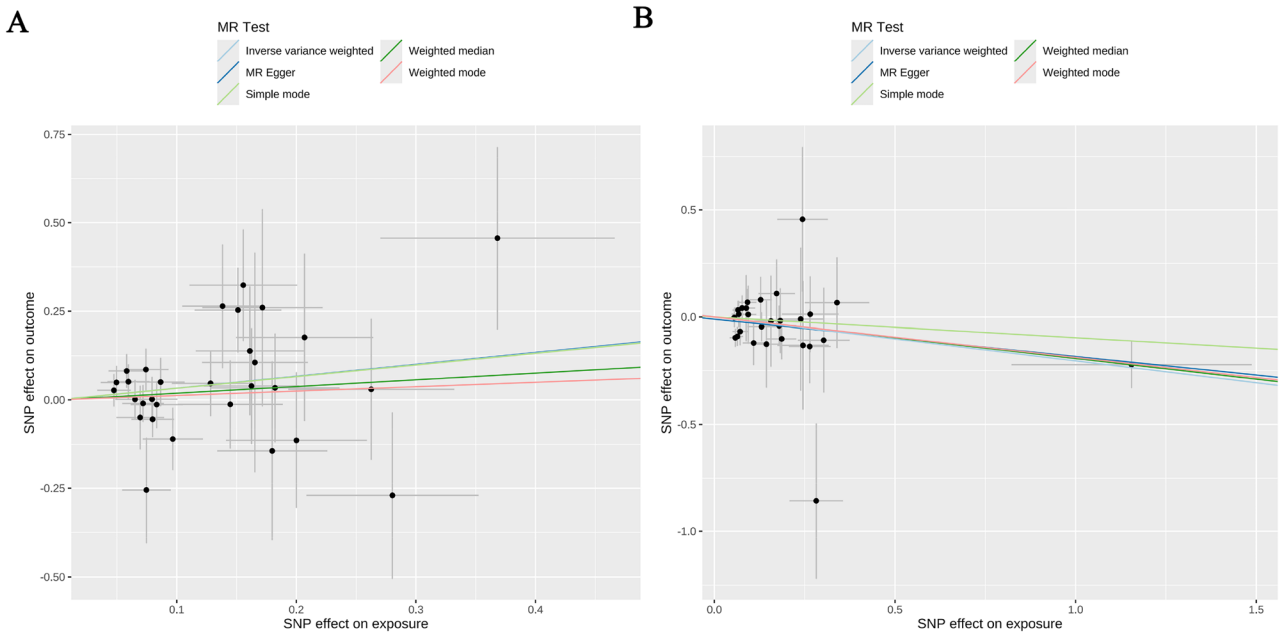

Figure 6. Scatter plots from Mendelian Randomization analysis comparing starchy food and vegetable consumption among individuals with diabetic kidney disease.
Note: A. The x-axis illustrates the impact of each individual single nucleotide polymorphism (SNP) on individuals who consume starchy foods, whereas the y-axis depicts the influence of each SNP on diabetic kidney disease. The colored diagonal line denotes the estimated causal effect of starchy food consumption on diabetic kidney disease. The analysis indicates that an increase in the consumption of starchy foods is associated with an elevated risk of developing diabetic kidney disease. **B.**The x-axis illustrates the impact of each individual single nucleotide polymorphism (SNP) on vegetable consumption, whereas the y-axis depicts the influence of each SNP on diabetic kidney disease. The colored diagonal line indicates the estimated causal effect of vegetable consumption on diabetic kidney disease. The analysis suggests that an increase in vegetable consumption is associated with a decreased risk of developing diabetic kidney disease.

Table 4. Reliability assessment of fifteen exposure variables in relation to diabetic kidney disease.

	Heterogeneity analysis				Pleiotropy test
	IVW		MR-Egger		MR-Egger
Exposure	Cochran's Q	*P*	Cochran's Q	*P*	*P*
Strenuous sports	21.208	0.851	20.825	0.833	0.541
Light DIY	30.000	0.568	29.968	0.519	0.86
Liking for going to the gym	21.204	0.852	21.124	0.820	0.78
Liking for working up a sweat	26.184	0.453	21.077	0.688	0.033
Liking for bicycling	27.580	0.593	27.448	0.548	0.718
Starchy food consumers	28.813	0.475	28.813	0.422	0.99
Sweet snack consumers	47.773	0.011	46.663	0.011	0.43
Dessert consumers	38.264	0.074	35.626	0.099	0.177
Savory snack consumers	31.742	0.166	28.684	0.232	0.123
Vegetable consumers	23.835	0.639	23.540	0.602	0.591
Fruit consumers	25.824	0.730	25.467	0.702	0.554
Tea consumed	43.588	0.040	42.192	0.042	0.344
Decaffeinated coffee	23.687	0.480	22.529	0.489	0.293
Meat consumers	21.443	0.765	20.207	0.782	0.276
Essential hypertension	29.571	0.571	28.241	0.241	0.279

This finding aligns with the existing body of literature, which identifies hypertension, inadequate glycemic control, and unhealthy lifestyle habits as significant predictors of diabetic kidney disease (DKD). Numerous studies have corroborated the strong association between hypertension and the progression of DKD. Specifically, hypertension has been shown to exacerbate tubulointerstitial and glomerular damage in individuals with diabetes, thereby accelerating the decline in renal function [38–39]. In this study, the relative risk (RR) for hypertension was determined to be 6.33 (95% confidence interval: 2.51–15.99), corroborating the significant association of hypertension with the onset of diabetic kidney disease (DKD). However, MR analysis did not substantiate a causal relationship between hypertension and DKD at the genetic level. This outcome may be attributed to the current limited availability of single nucleotide polymorphisms (SNPs). As more comprehensive genetic data become accessible, future research may be able to validate the causal genetic relationship between hypertension and DKD.

This study identifies dietary factors as a critical area for further investigation concerning their influence on diabetic kidney disease (DKD). Both meta-analysis and MR analysis

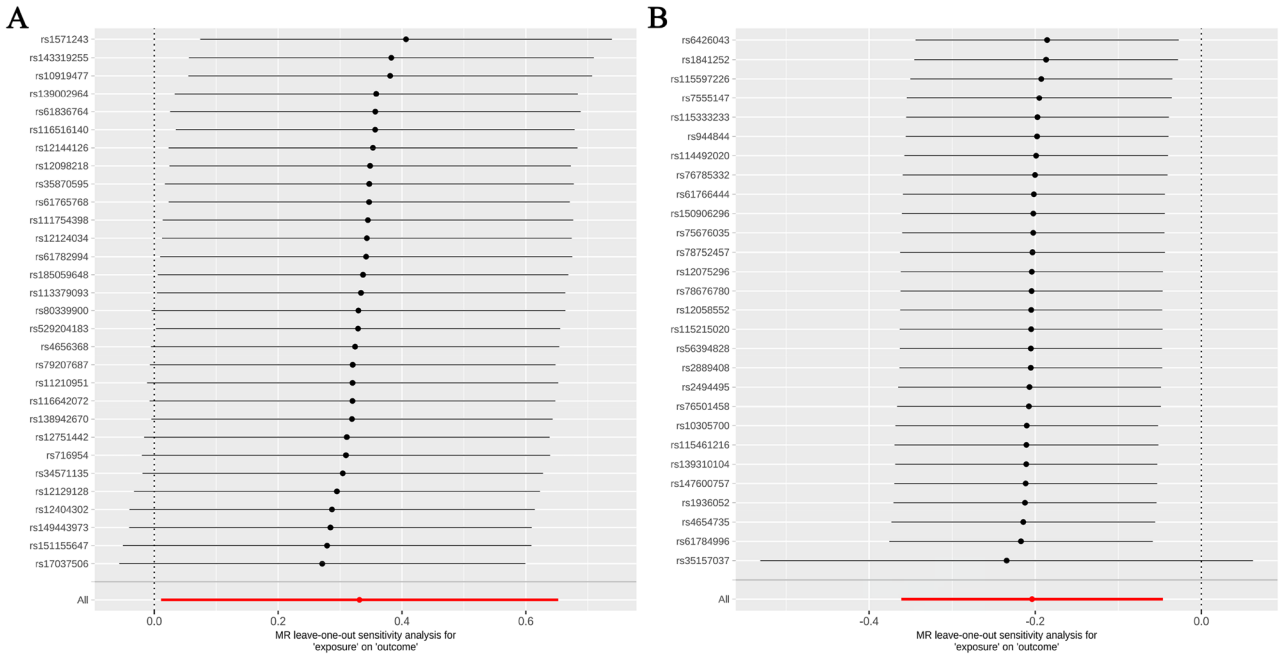

Figure 7. Leave-one-out sensitivity analysis for consumers of starchy foods and vegetables with diabetic kidney disease.
Note: The black dots denote the causal effect estimates for consumers of starchy foods and vegetables on diabetic kidney disease, following the exclusion of each individual single nucleotide polymorphism (SNP). The solid black line illustrates the corresponding 95% confidence interval (CI). The red dots represent the overall causal effect estimates of starchy food and vegetable consumption on diabetic kidney disease, as determined using the selected single nucleotide polymorphisms (SNPs). The red line denotes the combined estimate, accompanied by the corresponding 95% confidence interval (CI).

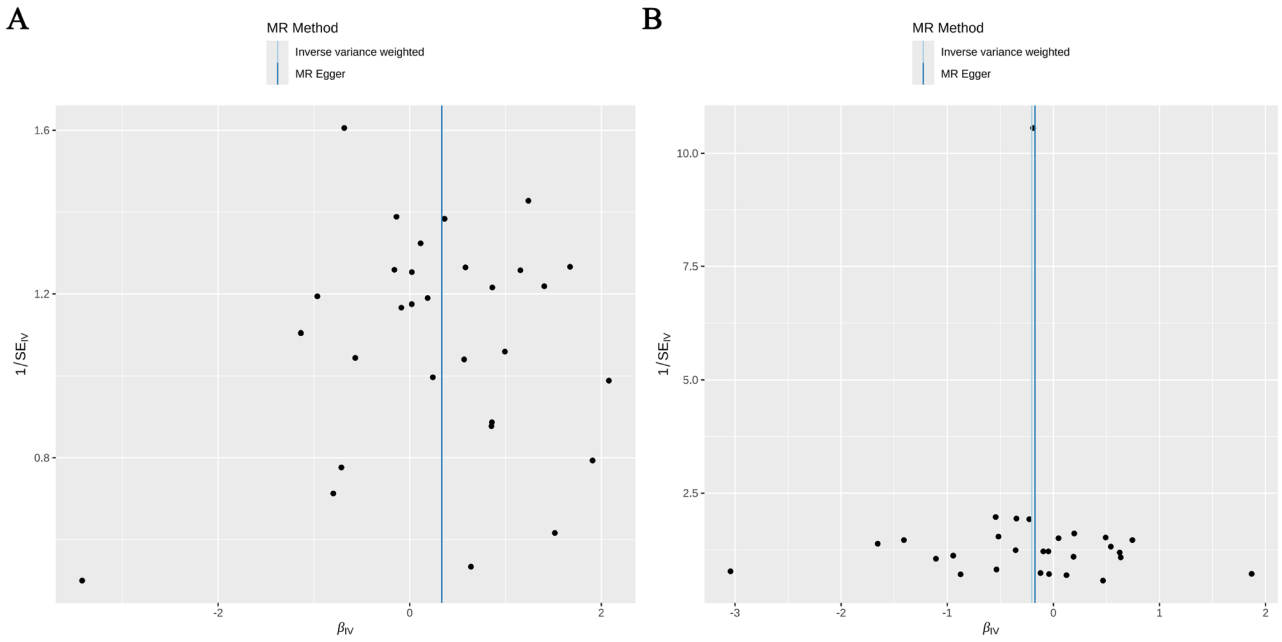

Figure 8. Funnel plot of MR analysis for causal association between starchy food consumers, vegetable consumers, and diabetic kidney disease.
Note: The horizontal axis denotes the effect size (β) of the instrumental variables. The vertical axis denotes the inverse of the standard error (1/S). This funnel plot is employed to visually evaluate symmetry and assess potential publication bias within the context of instrumental variable analysis.

reveal a significant positive correlation between high carbohydrate intake and an increased risk of DKD, whereas vegetable consumption is recognized as a protective factor against the development of DKD. These findings highlight the potential of dietary modifications as an effective strategy for mitigating the risk of DKD. Furthermore, existing research indicates that diets rich in fiber and low in sugar can enhance renal health among individuals with diabetes [40–41], thereby underscoring the significant role of dietary interventions in the management of DKD.

4.2. The influence of elevated carbohydrate consumption and vegetable intake on the management of diabetic kidney disease

Prolonged excessive consumption of carbohydrates, particularly refined carbohydrates like sugar and white bread, has been demonstrated to be closely linked with the onset and progression of diabetes. In individuals with diabetes, the hyperglycemic condition results in an increased renal workload, thereby expediting damage to the renal tubules and glomeruli, which may ultimately culminate in DKD. Research has demonstrated a substantial correlation between the intake of high glycemic index (GI) foods and the onset of diabetic kidney disease (DKD). High GI foods induce more pronounced fluctuations in blood glucose levels, and sustained fluctuations contribute to increased oxidative stress in the kidneys, thereby facilitating the development of DKD. Conversely, low-carbohydrate diets have been shown to enhance blood glucose regulation in diabetic patients and positively influence risk factors associated with diabetic kidney disease [42]. For example, empirical evidence indicates that a low-carbohydrate diet not only substantially lowers blood glucose levels but also reduces urinary protein excretion, thereby potentially delaying the progression of diabetic kidney disease [43]. Consequently, restricting carbohydrate consumption, especially refined sugars, may offer significant benefits in the prevention and management of diabetic kidney disease.

Vegetables are abundant sources of dietary fiber, antioxidants, and minerals, which have been shown to enhance the metabolic conditions in individuals with diabetes. Their anti-inflammatory and antioxidant properties are essential for maintaining kidney health. Empirical studies indicate an inverse relationship between the consumption of high-fiber vegetables and the prevalence of diabetic kidney disease. Antioxidants present in vegetables, including vitamin C, vitamin E, and carotenoids, have been demonstrated to effectively mitigate oxidative stress and chronic inflammation associated with diabetes, thereby contributing to the deceleration of kidney damage progression [44]. In diabetic patients, renal impairment is frequently associated with a persistent low-grade inflammatory condition. The anti-inflammatory properties of vegetables contribute to mitigating this inflammation, thereby decelerating the progression of diabetic nephropathy [45]. An enhanced intake of vegetables offers a substantial source of antioxidants and dietary fiber, and also enhances renal perfusion and function, thereby exerting a beneficial effect on the prevention and management of diabetic kidney disease.

According to current evidence, the implementation of dietary interventions that limit carbohydrate intake while increasing vegetable consumption has proven effective in preventing diabetic kidney disease. Specifically, reducing the consumption of refined carbohydrates enhances blood glucose regulation, alleviates renal burden, and may consequently diminish the risk of developing diabetic kidney disease. Conversely, an increase in vegetable consumption contributes essential antioxidants, anti-inflammatory compounds, and dietary fiber, which can mitigate the progression of diabetic kidney disease. Modifying dietary patterns not only assists in the regulation of blood glucose levels but may also enhance the overall health of individuals with diabetes by alleviating oxidative stress and inflammation.

4.3. This study's value is significantly enhanced by the application of Mendelian randomization and meta-analysis methodologies

In this study, the meta-analysis yielded robust evidence substantiating the association between dietary factors and diabetic kidney disease (DKD). By synthesizing findings from various cohort and cross-sectional studies, the research identified a significant positive correlation between dietary patterns and the risk of developing DKD. This methodology effectively mitigated biases associated with sample size and regional constraints inherent in individual studies, while simultaneously elucidating the extensive influence of dietary factors on diabetic kidney disease (DKD). These findings indicate that modifying dietary composition may constitute a crucial strategy for mitigating the risk of DKD. Nevertheless, although meta-analysis, through the aggregation of extensive datasets, has identified correlations, the associations observed in observational studies remain insufficient to establish causality [45]. This limitation is particularly pronounced in epidemiological research, where reverse causality or confounding variables may hinder the accurate determination of the true causal relationship between exposure factors (such as diet) and disease outcomes. Mendelian randomization, employing genetic instruments, offers robust evidence for causal inference [46].

While both Mendelian Randomization (MR) and meta-analysis possess distinct advantages, their integration in this study enhances the robustness of causal inference and the reliability of evidence. Meta-analysis synthesizes evidence from multiple studies, facilitating the identification of potential associations between dietary factors and diabetic kidney disease (DKD). In contrast, MR serves to verify the causal nature of these associations. Through the integration of both methodologies, this study not only identified a significant correlation between high carbohydrate intake and diabetic kidney disease (DKD) but also furnished causal evidence at the genetic level. This offers a robust theoretical foundation for the development of clinical interventions and public health policies. Moreover, the strength of this integrated methodology resides in its ability to account for the heterogeneity present across various study designs, while simultaneously employing genetic instruments to mitigate the confounding factors typically associated with conventional observational research. Consequently, this study enhances our confidence in the effects of dietary modifications—specifically, the reduction of refined carbohydrate intake and the increase in vegetable consumption—on the incidence and progression of diabetic kidney disease (DKD). This approach facilitates the development of more targeted interventions for individuals with diabetes.

4.4. Constraints and prospective research avenues

Although this study provides a comprehensive examination of genetic and environmental factors, several limitations must be acknowledged and addressed.

Data Source and Insufficient Ethnic Diversity: The Mendelian Randomization (MR) analysis conducted in this study predominantly utilizes data from the UK Biobank, which results in a limited representation of genetic diversity within the study population. Relying on a single genetic database may not sufficiently capture global genetic variation, thereby constraining the generalizability of the findings. Additionally, in the observational studies incorporated into the meta-analysis, the research conducted by Peixia Yu [24], Hao Yang [33], and Ding Y [35] utilized populations from the NHANES database, while Liang YY [37] employed data from the UK Biobank. Nevertheless, the extent of ethnic and geographical diversity remains constrained, which may compromise the precision of correlations between disease risk factors and causal inferences across various ethnic groups and healthcare settings. To improve the robustness of genetic associations and causal inferences, future research should incorporate data from multiple biobanks, encompassing populations from diverse ethnic and geographical backgrounds. For example, integrating data from international databases such as Finngen and BioBank Japan could enhance the representativeness and generalizability of the findings.

Insufficient analysis of the interactions among risk factors: This study conducted an independent analysis of the impact of each risk factor on the disease, yet it did not consider the interactions among these risk factors. Complex interrelationships, such as those between diet and exercise or obesity and metabolic disorders, may substantially influence disease risk. Future research should employ network meta-analysis techniques to examine the interactions among risk factors. Developing comprehensive models to explore these intricate relationships will offer a more robust scientific foundation for disease prevention and intervention strategies.

Inadequate consideration of temporal effects in the data: This study encompasses data spanning from 2005 to 2024; however, it does not sufficiently evaluate the impact of temporal changes in diagnostic criteria, treatment methodologies, and healthcare systems on the findings. The evolution of medical practices may modify the influence of risk factors, potentially affecting the accuracy of the analysis. Future research should perform subgroup analyses across different time periods, stratifying data to assess how alterations in medical practices and diagnostic criteria affect risk factors. This approach would facilitate a comprehensive interpretation of the dynamic changes in risk factors and establish a foundation for long-term trend analysis.

Limitations in Drawing Causal Inferences: The observed non-significant causal relationship between hypertension and diabetic kidney disease in this study may be attributed to limitations in genetic data and the presence of confounding factors. Firstly, the low variance explained by instrumental variables, such as single nucleotide polymorphisms (SNPs), may lead to insufficient statistical power, thereby weakening the ability to detect causal relationships. Furthermore, the analysis predominantly utilizes data from European populations, such as the UK Biobank, which restricts the generalizability of the findings to non-European populations. Additionally, horizontal pleiotropy may influence diabetic kidney disease through alternative pathways, such as obesity or metabolic syndrome, thereby confounding the independent causal effect of hypertension. Environmental factors, including dietary habits, lifestyle, and access to healthcare, may also interact with genetic factors through gene-environment interactions (GxE), further complicating the causal pathway. Despite these limitations, the findings do not refute the association between hypertension and diabetic kidney disease but rather underscore the constraints of current genetic data in elucidating complex, multifactorial diseases.

To advance the understanding of hypertension mechanisms, future research should incorporate genetic data from diverse populations, such as Finngen and BioBank Japan, and prioritize the selection of robust single nucleotide polymorphisms (SNPs). It is essential to systematically assess potential confounding variables and develop multi-layered causal models utilizing multivariable Mendelian Randomization (MR) or mediation MR analyses. Furthermore, investigating gene-environment interactions and assessing the moderating effects of environmental factors on causal relationships will yield more comprehensive scientific insights.

In conclusion, future research should prioritize enhancing sample diversity, examining the complex interactions of risk factors, investigating the influence of temporal dimensions, and conducting more thorough validation of causal relationships. These advancements are essential to augment the scientific rigor and extend the broader applicability of the findings, thereby offering more robust support for precision prevention and personalized treatment of the disease.

4.5. An evaluation of the clinical applicability of research findings

This study demonstrates that high carbohydrate intake increases the risk of diabetic kidney disease (DKD), while vegetable consumption provides a protective effect, highlighting the importance of targeted dietary adjustments in diabetes management and DKD prevention to improve long-term health outcomes.

To enhance the early risk assessment of diabetic kidney disease (DKD) in patients with diabetes, clinical practice may incorporate the Food Frequency Questionnaire (FFQ) to systematically evaluate the frequency and quantity of food and beverage consumption over the preceding six months. This approach can be further augmented by employing 24-h dietary recall and dietary record methods to achieve a comprehensive analysis of dietary habits. Through the application of multivariable regression analysis or machine learning algorithms, critical dietary risk factors—such as high carbohydrate intake, as identified in this study—can be discerned. By integrating these dietary insights with data on glycemic control, comorbid conditions (including hypertension and

hyperuricemia), and physical activity levels, a nomogram-based risk prediction model can be developed to facilitate precise assessment of DKD risk.

Moreover, the identified high-risk dietary factors can provide a basis for dietitians and endocrinologists to develop low-carbohydrate, balanced dietary plans. Additionally, these factors can aid digital health platforms in offering personalized dietary recommendations. This strategy can facilitate patients' comprehension of the relationship between diet and diabetic kidney disease (DKD), improve adherence to dietary guidelines, and optimize treatment outcomes.

5. Conclusion

This study employs both meta-analysis and Mendelian randomization (MR) analysis to identify significant risk factors associated with diabetic kidney disease (DKD) and offers compelling evidence supporting dietary interventions as viable preventive strategies. Notably, the findings indicate a causal relationship between the consumption of high-starch foods and low vegetable intake, suggesting that enhancing dietary composition by increasing vegetable consumption may effectively mitigate the risk of developing DKD. Furthermore, the novel application of Mendelian Randomization (MR) analysis in this study effectively mitigated biases commonly associated with traditional observational studies, thereby establishing a more robust evidential foundation for research into risk factors for diabetic kidney disease (DKD). Future investigations should aim to delve deeper into the potential interactions between genetic and environmental factors and explore the translation of these findings into clinical practice interventions. These results provide critical insights for the formulation of public health policies concerning DKD and furnish scientific support for personalized dietary and lifestyle interventions for individuals with diabetes.

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Ethics statement

All 16 studies incorporated in this research asserted their adherence to the ethical standards and guidelines delineated in the Declaration of Helsinki. Likewise, the GWAS data employed for Mendelian randomization analysis was accompanied by pertinent ethical compliance statements furnished by the researchers.

Informed consent

All studies included in this analysis confirmed that participants signed written informed consent forms after being fully informed about the nature, purpose, and procedures of the research. Participants were informed of their right to withdraw from the study at any stage without any obligations. Additionally, participants in each cohort also provided written informed consent.

Author contributions

All authors substantially contributed to the conception and design of this study. Yucong Zhou were involved in data analysis, data interpretation, manuscript drafting, and critical revisions. Yahong Liu, Liang Wu, Yucai Zhan, Huixin Wen, Jiangwei Hu, Zhenxia Huo, Shuyuan Ju, Ruizheng Sheng contributed to the study design and provided critical revisions of the manuscript. Yucong Zhou granted final approval of the version to be published.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

All studies incorporated into this analysis rigorously safeguarded participants' privacy throughout the research process. Personal identifying information was anonymized and securely stored to uphold confidentiality. The data collected was utilized solely for research purposes and was not disclosed to any unauthorized individuals.

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