

# Causal Relationships Between Gut Microbiota, Metabolites, and Diabetic Nephropathy: Insights from a Two-Sample Mendelian Randomization Analysis

Xixi Song <sup>1,2</sup>, Jingqiu Cui <sup>1</sup>, Shiwei Li<sup>1</sup>, Bo Huang<sup>1</sup>

<sup>1</sup>Department of Endocrinology and Metabolism, Tianjin Medical University General Hospital, Tianjin, People's Republic of China; <sup>2</sup>Department of Endocrinology and Metabolism, Baoding No.1 Central Hospital, Baoding, People's Republic of China

Correspondence: Jingqiu Cui, Department of Endocrinology and Metabolism, Tianjin Medical University General Hospital, No. 154 Anshan Dao, Heping District, Tianjin, 300052, People's Republic of China, Tel +8613920765604, Email [cuijingqiu@tmu.edu.cn](mailto:cuijingqiu@tmu.edu.cn)

**Background:** Previous studies have established a correlation between gut microbiota, metabolites, and diabetic nephropathy (DN). However, the inherent limitations of observational studies, including reverse causality and confounding factors, made this relationship uncertain.

**Methods:** In this study, we compiled summary statistics from a genome-wide association study (GWAS) conducted on gut microbiota, metabolites, and DN. We employed a two-sample Mendelian randomization (MR) approach, utilizing inverse variance weighted (IVW), MR-Egger, weighted median, and weighted mode methods.

**Results:** We detected the protective nature of genetically predicted representatives from the family Bacteroidaceae (OR: 0.716, 95% CI: 0.516–0.995,  $p = 0.046$ ), family Victivallaceae (OR: 0.871, 95% CI: 0.772–0.982,  $p = 0.026$ ), genus Bacteroides (OR: 0.716, 95% CI: 0.516–0.995,  $p = 0.046$ ), genus Coprococcus 2 (OR: 0.745, 95% CI: 0.576–0.963,  $p = 0.025$ ), and genus Lactococcus (OR: 0.851, 95% CI: 0.730–0.992,  $p = 0.039$ ) against the development of DN. Conversely, we identified a positive correlation between the incidence of DN and entities, such as Phylum Bacteroidetes (OR: 1.427, 95% CI: 1.085–1.875,  $p = 0.011$ ), class Bacteroidia (OR: 1.304, 95% CI: 1.036–1.641,  $p = 0.024$ ), order Bacteroidales (OR: 1.304, 95% CI: 1.035–1.641,  $p = 0.028$ ), genus Catenibacterium (OR: 1.312, 95% CI: 1.079–1.594,  $p = 0.006$ ), genus Lachnoclostridium (OR: 1.434, 95% CI: 1.129–1.821,  $p = 0.003$ ), and genus Parasutterella (OR: 1.270, 95% CI: 1.070–1.510,  $p = 0.006$ ). In our analysis, none of the gut metabolites demonstrated a causal relationship with DN.

**Conclusion:** Our results substantiated the potential causal association between specific gut microbiota and DN. Therefore, our study offers novel insight into the mechanisms underlying DN. This finding provides a theoretical foundation for the future development of targeted strategies for the prevention and treatment of DN.

**Keywords:** Gut microbiota, diabetic nephropathy, gut metabolites, Mendelian randomization

## Introduction

Diabetic nephropathy (DN) is the primary cause of chronic kidney disease (CKD), a prevalent microvascular complication caused by diabetes mellitus (DM), which is characterized by persistent proteinuria and decreased estimated glomerular filtration rate (eGFR).<sup>1</sup> Based on the International Diabetes Federation report, the global prevalence of diabetes in 2019 was estimated to be 9.3% (463 million people), with a projected increase to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045.<sup>2</sup> Approximately 20%–40% of people with DM develop DN.<sup>3</sup> DN significantly increases the risk of infection, end-stage kidney disease (ESRD), and cardiovascular diseases, such as coronary heart disease, heart failure, and hypertension. Based on 2002 data from the United States, nearly 44% to 45% of ESRD cases are attributed to DN. In Heidelberg, located in Southwest Germany, nearly 60% of patients who underwent kidney

replacement therapy in 1995 were diagnosed with diabetes.<sup>3</sup> DN increases all-cause mortality and imposes substantial economic burdens on patients with diabetes. Current management approaches for DN encompass meticulous control of blood glucose and blood pressure, modulation of lipid metabolism disorders, and mitigation of urinary protein excretion. RAAS blockers, SGLT-2 inhibitors, GLP-1 agonists, and mineralocorticoid receptor antagonists are the common medications used for treating DN.<sup>4</sup> In addition, aldose reductase inhibitors (ARIs) may help prevent the progression of DN.<sup>5</sup> Nonetheless, the persistent risk of DN underscores the existence of unidentified risk factors and mechanisms.

An increasing body of evidence highlights the involvement of gut dysbiosis in the pathogenesis of DN.<sup>6</sup> Numerous studies have demonstrated that DN alters gut microbial composition and affects microbial community richness and diversity.<sup>7,8</sup> Larsen et al found that the proportion of Firmicutes and Clostridium was significantly reduced in the intestinal flora of patients with diabetes, and class Betaproteobacteria was highly enriched and positively correlated with blood sugar.<sup>9</sup> A meta-analysis also found a decrease in the mean abundance of Firmicutes and an increase in the mean abundance of Actinomycetes in the gut microbiota of patients with DN. Furthermore, the meta-analysis reported a significant change in specific bacteria, such as Hungatella, Bilophila, and Escherichia, in patients with DM and DN compared to patients without DN.<sup>10</sup> The gut microbiota profoundly affects the homeostasis of the host's internal environment. It maintains the integrity of the intestinal barrier, regulates renal metabolism, induces anti-inflammatory responses, and fosters the homeostasis of the immune system.<sup>11</sup> Impaired renal function in patients with DN can lead to the accumulation of metabolic toxins, resulting in an imbalance in intestinal microbiota.<sup>12</sup> Abnormal intestinal flora also accelerates the progression of DN by triggering oxidative stress, promoting inflammation, aggravating insulin resistance, and activating the RAS system and other mechanisms.<sup>13</sup> Gut dysbiosis weakens the intestinal barrier, leading to the leakage of lipopolysaccharides (LPS) into the systemic circulation. LPS stimulates the release of various pro-inflammatory factors by binding to LBP, CD14, and TLRs, inducing systemic inflammation.<sup>14</sup> Chen et al investigated the effect of outer membrane vesicles (OMVs) released by intestinal gram-negative bacteria on renal tubules in DN rats and found that OMVs-derived LPS can induce inflammation and tubular damage by activating caspase-11.<sup>15</sup> Pedersen et al demonstrated that Prevotella copri can induce insulin resistance, worsen glucose intolerance, and affect host metabolism in mice.<sup>16</sup> Lu et al reported that excessive acetate produced due to gut dysbiosis can lead to kidney injury in rats with diabetic nephropathy by activating intrarenal RAS.<sup>17</sup> Specific microbial-derived-metabolites, such as lipopolysaccharide (LPS), short-chain fatty acids (SCFAs), bile acids (BAs), and trimethylamine-N-oxide (TMAO), are pivotal in shaping host-microbe interactions.<sup>18</sup> SCFAs exert protective effects on the kidneys of diabetic mice by activating GPR43 and GPR109A receptors. They downregulate inflammatory factors, chemokines, and pro-fibrotic proteins in the kidney.<sup>19</sup> On the other hand, TMAO exacerbates renal inflammation and fibrosis in rats with DN by activating pyrin domain-containing-3 (NLRP3) inflammatory vesicles.<sup>20</sup> Prebiotics, probiotics, fecal microbiota transplantation, and gut microbiota-modulating anti-diabetic medications enable the manipulation of intestinal microbial composition, thus ameliorating DN-associated kidney damage.<sup>13</sup> These findings highlight the importance of the gut-kidney axis as a therapeutic target to modulate the progression of DN.

However, the aforementioned studies predominantly relied on animal models or cross-sectional observational analyses. The results of animal experiments cannot be fully translated into human clinical practice. In addition, observational studies cannot completely exclude the effect of confounding factors, such as pre-existing diseases, diet, and medications on the results, limiting their capacity to establish causal links. Mendelian randomization (MR), using the aggregated data of genome-wide association studies (GWAS), can mitigate confounding effects and facilitate the assessment of causal relationships between exposures and outcomes.<sup>21</sup> Thus, this study aimed to investigate the causal effect of specific gut microbiota and metabolites on DN. Our findings can help identify novel biomarkers and therapeutic targets to facilitate the early diagnosis and treatment of DN.

## Materials and Methods

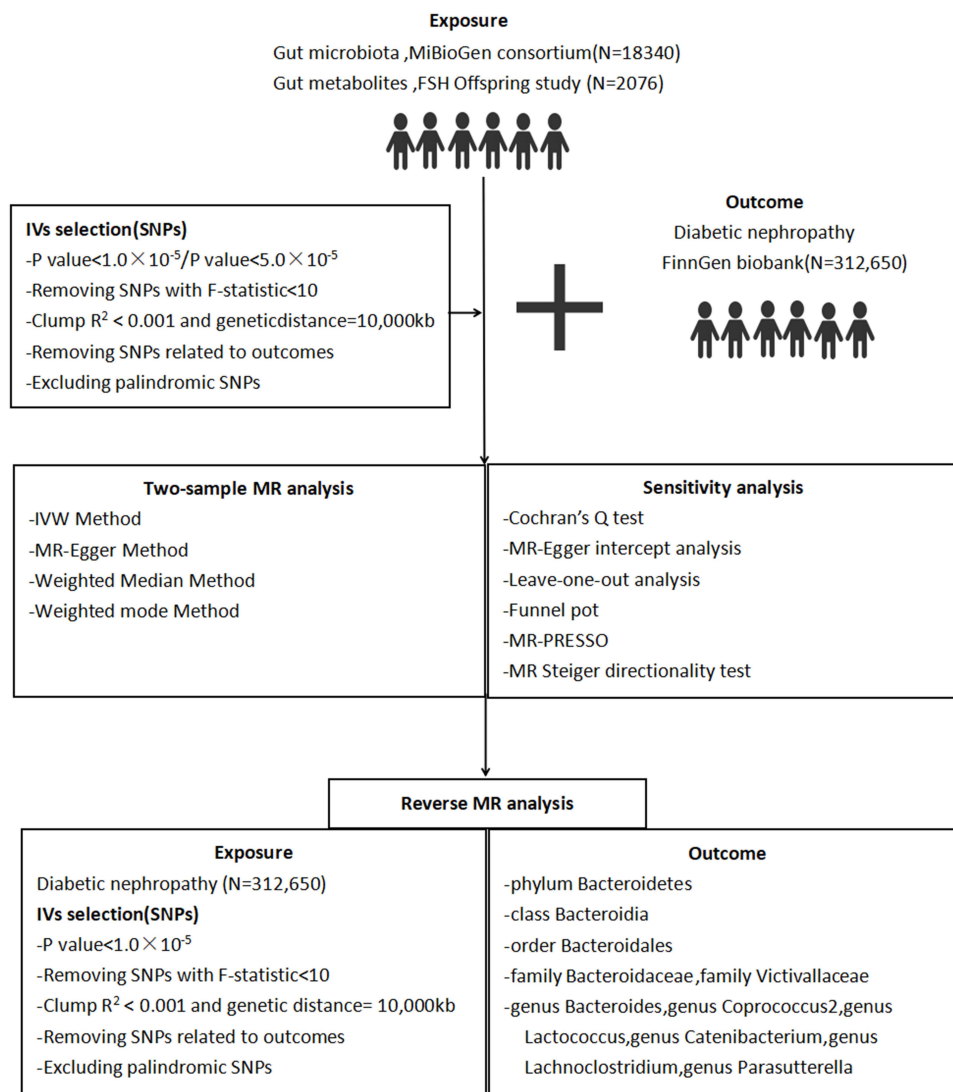
### Study Design

We conducted a two-sample MR study to explore whether there is a causal relationship between gut microbiota, metabolites, and DN. Additionally, we utilized a reverse MR approach to investigate whether there is a bidirectional

relationship between DN and gut microbiota and metabolites (Figure 1). This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology-Mendelian Randomization (STROBE-MR) guidelines (Supplementary Material).<sup>22</sup>

## Data Source

The genetic information pertaining to gut microbiota was obtained from an extensive GWAS study conducted by the MiBioGen consortium. This study included 18,340 individuals, predominantly of European descent, across 24 cohorts.<sup>23</sup> Utilizing 16S rRNA gene sequencing profiles, we aimed to elucidate the genetic underpinnings of gut microbiota composition. We removed 12 genera and 3 families that were categorized as “unknown” from the initial pool of 211 taxa to ensure data integrity. Consequently, 196 were retained for the analysis. Additionally, summary data pertaining to gut microbial metabolites were obtained from a distinct human GWAS study focused on the human metabolome with 2076 European participants.<sup>24</sup> Based on previous studies,<sup>25</sup> we selected 16 metabolites that play a key role in the progression of DM and DN. Summary statistics pertaining to DN were obtained from the FinnGen consortium R9 release



**Figure 1** Flowchart of the study.

**Abbreviations:** SNP, single-nucleotide poly-morphism; MR, Mendelian randomization; IVW, inverse variance weighted median; MR-PRESSO, MR-Pleiotropy Residual Sum and Outlier.

data,<sup>26</sup> which consisted of a cohort of 312,650 European individuals. The study encompassed three endpoints: DM kidney failure, DM dialysis, and DM kidney transplantation.

## Selection of Instrumental Variables

We organized the summary data from the gut microbiome GWAS into five different levels based on bacterial classes: phylum, class, order, family, and genus. We selected 16 key gut microbial metabolites for analysis. First, we ensured that the selected instrumental variables were strongly correlated with the exposure factors. Since the common gene loci associated with gut microbiota and metabolites exhibited limited genome-wide significance in GWAS, we opted to analyze SNPs at a significance level of  $p < 1.0 \times 10^{-5}$  for gut microbiota. This criterion allowed us to capture an adequate number of instrumental variables. We extracted gut metabolite SNPs at significance levels of  $P < 5.0 \times 10^{-5}$  and  $P < 1.0 \times 10^{-5}$ , respectively. The potency of the instrumental variables was assessed using the F-statistic. SNPs with F-statistic  $< 10$  were deemed weak instrumental variables and were removed from our analysis. Second, the selected instrumental variables had to exhibit independence. To this end, we evaluated the linkage disequilibrium using an  $R^2$  threshold of 0.001 and ensured genetic separation of at least 10,000 kb between selected markers. Third, we excluded variables with p-values (pertaining to outcomes) less than  $5.0 \times 10^{-5}$  to ensure that the instrumental variables were not associated with the outcome. Additionally, palindromic SNPs were also excluded to mitigate potential sources of bias.

## Mendelian Randomization Analysis

We conducted a two-sample MR analysis employing four main methodologies: inverse variance weighted (IVW), MR Egger, weighted median, and weighted mode. IVW is a canonical approach that combines Wald ratio estimates for each SNP through meta-analysis. MR Egger analysis can be utilized in the presence of horizontal pleiotropy. The weighted median approach computes the median of the inverse variance weighted ratio estimates, whereas the weighted mode approach determines the mode of the inverse variance weighted ratio estimates. These methods are resilient to potential instrumental variable violations and provide reliable results even when some instrumental variables fail to meet key assumptions. We also implemented the Bonferroni correction to reinforce the robustness of our findings. P-values more than the Bonferroni-corrected significance threshold, but less than 0.05, were regarded as nominally significant findings.

## Sensitivity Analysis

We utilized numerous sensitivity analyses to detect potential gene pleiotropy and heterogeneity and assess the stability of our findings. These analyses included Cochran's Q statistic, MR-Egger intercept tests, leave-one-out (LOO) analyses, and funnel plots. These methods were collectively used to detect potential gene pleiotropy and heterogeneity within the MR analysis and evaluate the robustness of our results. Additionally, we conducted an MR-pleiotropy residual sum and outlier (MR-PRESSO) test. The MR-PRESSO Global test was employed to assess overall horizontal pleiotropy across instrumental variables, whereas the outlier test was used to evaluate the significance of pleiotropy for each SNP. Through an iterative process, we progressively removed outlier SNPs until the p-value of the global test was more than 0.05. The MR Steiger directionality test was employed to assess the robustness of the causal direction. All statistical analyses were conducted using R (version 4.2.3) and the associated MR software packages (TwoSampleMR, MendelianRandomization, Radial MR, MR-PRESSO).

## Confounding Analysis

In addition to several methods of sensitivity analysis, we used the PhenoScanner database (<http://www.phenoscanter.medchsl.cam.ac.uk/>) to exclude SNPs associated with potential confounding factors, particularly hypertension, obesity, dyslipidemia, hyperuricemia, and smoking. Previous studies have identified significant associations between triglycerides and systolic blood pressure and the development of macroalbuminuria. Obesity has been linked to an increased risk of DN. Smoking was shown to be associated with an increased risk of albuminuria and declined eGFR in patients with T1D and T2D. Additionally, hyperuricemia, as a predictor of DN, may play a pathogenetic role in interstitial inflammation and

the progression of renal diseases.<sup>27,28</sup> Recognizing their potential effects on our analysis, we excluded SNPs associated with these factors. Next, we conducted a replication of the IVW method to corroborate the robustness of our results.

## Reverse MR Analysis

For gut microbiota and metabolites causally associated with DN as screened by forward MR analysis, we conducted a reverse MR analysis to explore the possibility of reverse causality between DN and gut microbiota and metabolites. The method employed in this analysis mirrored the aforementioned protocol utilized for two-sample MR. The detailed steps are shown in the flowchart (Figure 1).

## Results

### Selection of Instrumental Variables

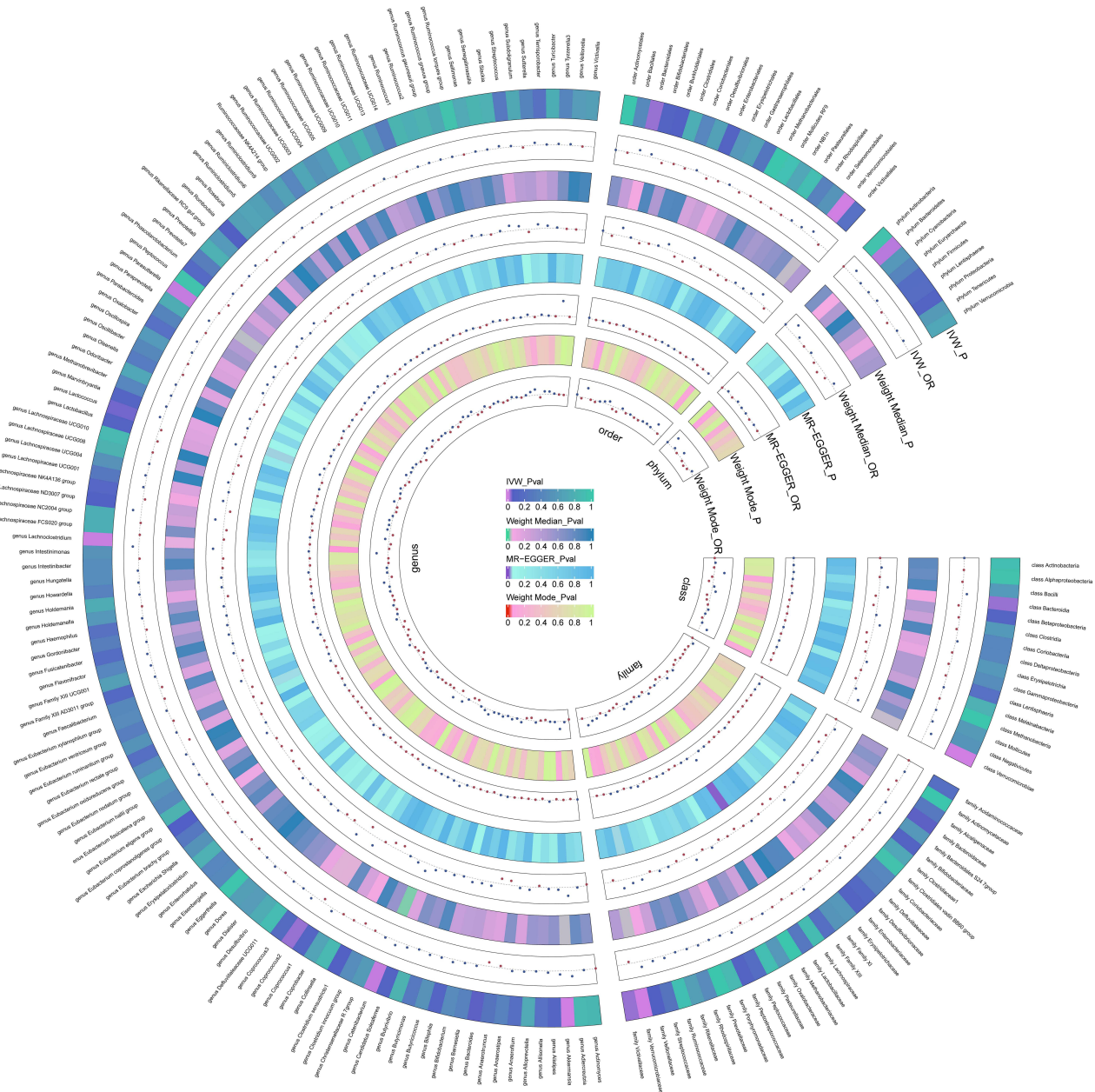
A refined set of instrumental variables was obtained after removing palindromic SNPs, excluding SNPs associated with the outcome, and conducting clustering and harmonization. Specifically, 2,036 SNPs originating from 196 different microorganisms ( $p < 1 \times 10^{-5}$ ), 124 SNPs representing gut microbial metabolites ( $p < 1 \times 10^{-5}$ ), and 524 SNPs representing gut microbial metabolites ( $p < 5 \times 10^{-5}$ ) were selected for further analysis. The taxonomic delineation of the gut microbiome comprised five biological classification units, encompassing: phylum (103 SNPs), class (179 SNPs), order (217 SNPs), family (341 SNPs), and genus (1,196 SNPs). Simultaneously, 16 gut microbial metabolites were screened, comprising adipic acid (7/38 SNPs), alpha hydroxybutyric acid (5/25 SNPs), amino adipic acid (6/28 SNPs), beta aminoisobutyric acid (15/46 SNPs), beta-hydroxybutyric (5/23 SNPs), gamma aminoisobutyric acid (10/36 SNPs), gentisic acid (6/33 SNPs), indole 3 propionate (13/33 SNPs), indoxyl sulfate (7/38 SNPs), kynurenine (12/43 SNPs), propionic acid (3/22 SNPs), trimethylamine N oxide (5/43 SNPs), tryptophan (3/25 SNPs), ureidopropionic acid (10/31 SNPs), phenylalanine (7/32 SNPs), and uric acid (10/28 SNPs). The F-statistics for all instrumental variables was more than 10, suggesting the absence of susceptibility to weak instrument bias (Supplementary Tables 1–3).

### MR Analysis of Gut Microbiota and DN

The number of SNP considered for each gut microbial phenotype assessment ranged from 3 to 18. Utilizing the IVW method, we identified 15 bacterial taxa (including 1 phylum, 2 orders, 3 families, 2 orders, and 7 genera) exhibiting causal relationships with DN (Supplementary Tables 4). In alternative MR analyses, we noted a discrepancy between the MR Egger method and the IVW method regarding four bacterial taxa: class Verrucomicrobiae, order Verrucomicrobiales, family Verrucomicrobiaceae, and genus Akkermansia. Out of the 15 taxa, 11 demonstrated relevance to DN. Among them, five bacterial taxa displayed a negative correlation with the risk of DN, specifically family Bacteroidaceae (OR: 0.716, 95% CI: 0.516–0.995,  $p = 0.046$ ), family Victivallaceae (OR: 0.871, 95% CI: 0.772–0.982,  $p = 0.026$ ), genus Bacteroides (OR: 0.716, 95% CI: 0.516–0.995,  $p = 0.046$ ), genus Coprococcus 2 (OR: 0.745, 95% CI: 0.576–0.963,  $p = 0.025$ ), and genus Lactococcus (OR: 0.851, 95% CI: 0.730–0.992,  $p = 0.039$ ). Conversely, six bacterial taxa were positively correlated with the risk of DN, including phylum Bacteroidetes (OR: 1.427, 95% CI: 1.085–1.875,  $p = 0.011$ ), class Bacteroidia (OR: 1.304, 95% CI: 1.036–1.641,  $p = 0.024$ ), order Bacteroidales (OR: 1.304, 95% CI: 1.035–1.641,  $p = 0.028$ ), genus Catenibacterium (OR: 1.312, 95% CI: 1.079–1.594,  $p = 0.006$ ), genus Lachnoclostridium (OR: 1.434, 95% CI: 1.129–1.821,  $p = 0.003$ ), and genus Parasutterella (OR: 1.270, 95% CI: 1.070–1.510,  $p = 0.006$ ) (Figures 2 and 3).

### MR Analysis of Gut Microbiota Metabolites and DN

When the level of significance for the instrumental variables was set at  $P < 1 \times 10^{-5}$ , based on the results of the IVW analysis, each 1 unit increase in ureidopropionic acid corresponded to a 7.0% decrease in the relative risk of DN (OR: 0.926, 95% CI: 0.859–0.998,  $P = 0.046$ ). This association was verified across the three alternative methods of MR analysis. Importantly, our analyses did not reveal any causal relationship between the remaining gut microbial metabolites and DN (Figure 4, Supplementary Table 5).



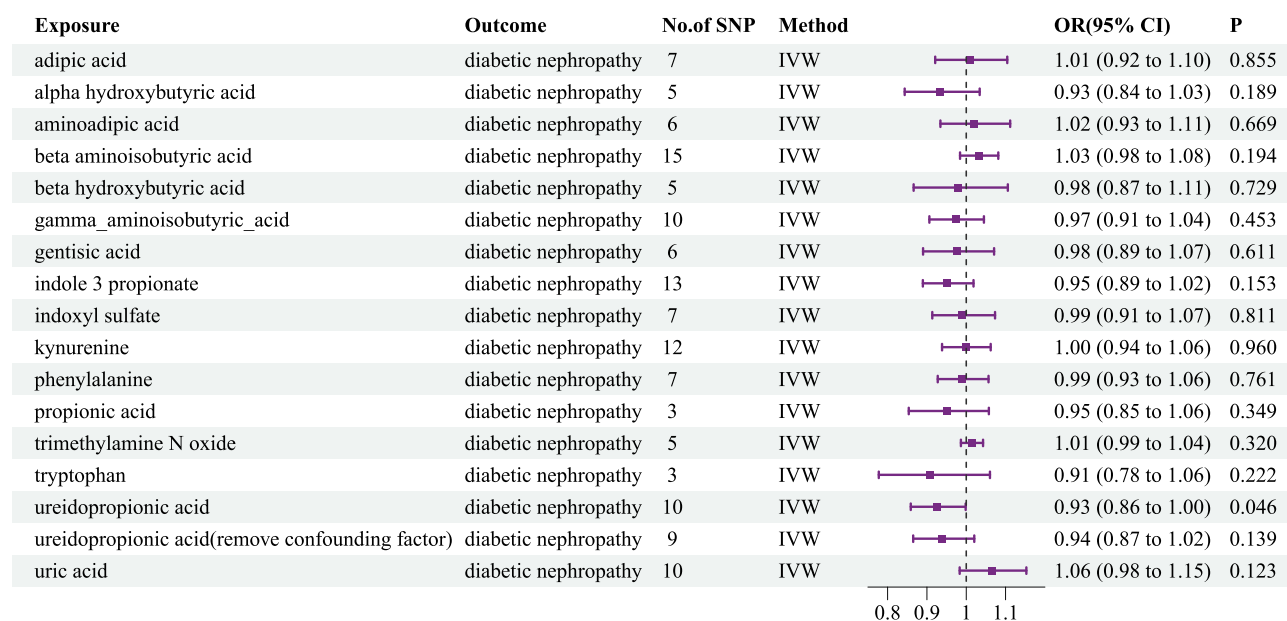
**Figure 2** Preliminary Mendelian randomization results between all the gut microbiota and diabetic nephropathy.

### Bonferroni Correction and Sensitivity Analysis

Our analysis indicated that none of the bacterial taxa reached the Bonferroni-corrected p-value threshold. Moreover, consistent with the MR-Egger and MR-PRESSO analyses (Table 1, Supplementary Tables 6 and 7), we could not identify any evidence of horizontal pleiotropy, evidenced by p-values > 0.05 across all tests. Notably, the Cochran’s Q test revealed no discernible heterogeneity in study effects (Table 1 and Supplementary Table 8). All of the MR Steiger directionality tests consistently indicated a robust causal direction from the gut microbiota and metabolites to DN for all outcome measures. Subsequently, LOO analyses were conducted, demonstrating the robustness of our estimates against the effect of individual instrumental variables (Supplementary Figure 1A-K). The majority of funnel diagrams exhibited a symmetrical pattern, supporting the coherence of our findings (Supplementary Figure 2A-K).



**Figure 3** Forest plot summarizing the Mendelian randomization results of gut microbiota with a causal relationship to diabetic nephropathy. **Abbreviations:** OR, odds ratio; CI, confidence interval; IVW, inverse variance weighted; MR, Mendelian randomization.



**Figure 4** Forest plot summarizing the IVW method results of gut microbial metabolites to diabetic nephropathy (Instrumental variables with  $p < 1.0 \times 10^{-5}$ ).

## Analysis of Confounding Factors

Several factors, including hypertension, obesity, dyslipidemia, hyperuricemia, and smoking, could potentially affect the observed correlation between gut bacteria and the risk of DN. To determine the potential effects of such confounders, we searched the Phenoscan database and identified instrumental variables that were associated with the aforementioned factors. Notably, a specific SNP (rs62273907) from the genus *Parasutterella* exhibited linkage with hypertension-related phenotypes. Remarkably, the causality remained robust even after the removal of this SNP (IVW OR= 1.360, 95% CI =1.090–1.700,  $p=0.007$ ). We also found that an SNP (rs4738679) within the genus *Lachnoclostridium* and an SNP (rs6101934) associated with ureidopropionic-acid that were potentially associated with dyslipidemia-related phenotypes. After excluding these two SNPs, statistical significance persisted for genus *Lachnoclostridium* (IVW OR= 1.399, 95% CI =1.091–1.793,  $p=0.008$ ), whereas ureidopropionic acid no longer showed statistical significance (IVW OR= 0.940, 95% CI =0.865–1.020,  $p=0.139$ ). None of the other SNPs were correlated with any of the confounders ([Supplementary Table 9](#)).

## Reverse Analysis

For results with nominal significance, we conducted a reverse MR analysis to identify potential reverse causality between DN and the flora species. This analysis identified no evidence of the presence of reverse causality between DN and the 11 gut flora species ([Figure 5](#), [Supplementary Table 10](#)).

## Discussion

This study represents the first MR study to investigate the causal implications of gut microbiota and metabolites in the context of DN. Using the MR framework, we identified the associations between gut bacterial taxa and the risk of DN. Specifically, we found that five bacterial taxa were associated with a reduced risk of DN, while six bacterial taxa were linked to an increased risk of DN. This finding is not exactly consistent with the conclusions of a previous MR study. This inconsistency may be related to our stricter criteria for selecting instrumental variables and the analysis of confounding factors.<sup>29</sup> These findings offer insights into potential avenues for DN prevention and treatment by targeting specific gut microbiota.

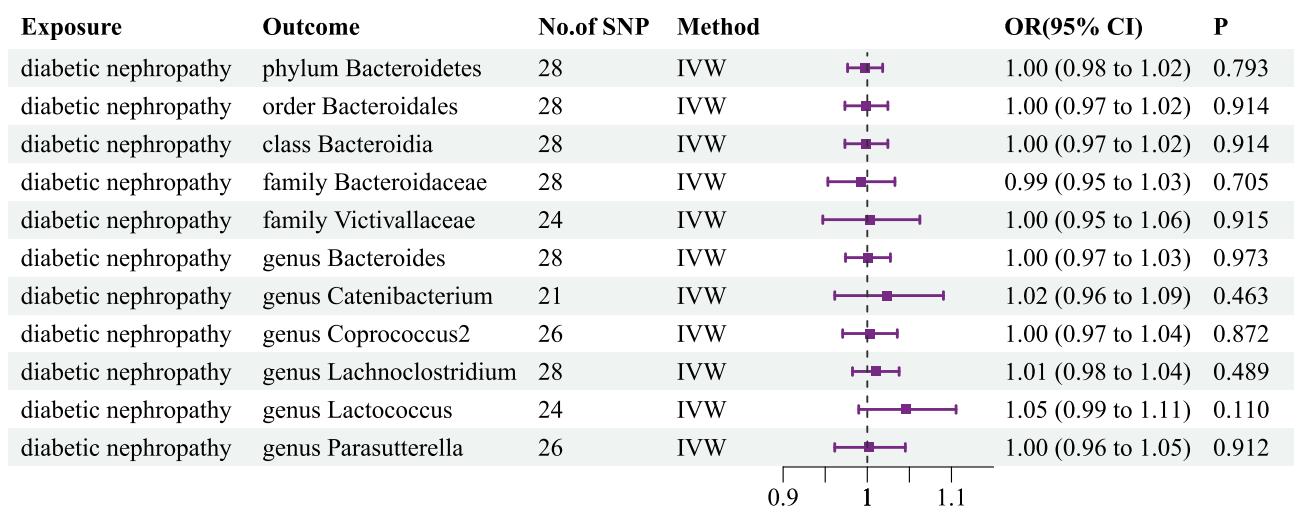
Our findings underscore the protective role of specific gut bacterial taxa. Notably, the family Bacteroidaceae and genus *Bacteroides* exhibited negative associations with the risk of DN. Conversely, the phylum Bacteroidetes, class Bacteroidia, and order Bacteroidales displayed positive correlations with the risk of DN. Previous MR analyses supported



**Table 1** Sensitivity Analysis of the Causal Association Between Gut Microbiota and DN

Exposure	Outcome	Method	Heterogeneity			Horizontal pleiotropy	MR-PRESSO
			Q	Q_df	Q_p-value	Egger_Intercept_Pvalue	P value
Phylum Bacteroidetes	Diabetic nephropathy	Inverse variance weighted	8.8427	12	0.7163	0.9066	0.8576
		MR Egger	8.0902	11	0.7051		
Order Bacteroidales	Diabetic nephropathy	Inverse variance weighted	8.8427	12	0.7163	0.4042	0.67
		MR Egger	8.0902	11	0.7051		
Class Bacteroidia	Diabetic nephropathy	Inverse variance weighted	8.8427	12	0.7163	0.4042	0.6626
		MR Egger	8.0902	11	0.7051		
Family Bacteroidaceae	Diabetic nephropathy	Inverse variance weighted	8.5839	7	0.2839	0.7379	0.335
		MR Egger	8.4117	6	0.2094		
Family Victivallaceae	Diabetic nephropathy	Inverse variance weighted	7.1589	10	0.7103	0.9958	0.717
		MR Egger	7.1589	9	0.6205		
Genus Bacteroides	Diabetic nephropathy	Inverse variance weighted	8.5839	7	0.2839	0.7379	0.3193
		MR Egger	8.4117	6	0.2094		
Genus Catenibacterium	Diabetic nephropathy	Inverse variance weighted	0.5750	3	0.9021	0.5855	0.9153
		MR Egger	0.1602	2	0.9230		
Genus Coprococcus2	Diabetic nephropathy	Inverse variance weighted	4.6598	7	0.7013	0.5895	0.7366
		MR Egger	4.3352	6	0.6314		
Genus Lachnospirillum	Diabetic nephropathy	Inverse variance weighted	8.4415	11	0.6732	0.9568	0.7023
		MR Egger	8.4384	10	0.5860		
Genus Lactococcus	Diabetic nephropathy	Inverse variance weighted	3.9804	7	0.7820	0.3890	0.8203
		MR Egger	3.1187	6	0.7938		
Genus Parasutterella	Diabetic nephropathy	Inverse variance weighted	4.2894	12	0.9776	0.8561	0.9813
		MR Egger	4.2550	11	4.2550		

our findings by linking class Bacteroidia to decreased renal function.<sup>30</sup> Another MR study found that phylum Bacteroidetes, class Bacteroidia, and order Bacteroidales significantly increase the risk of T1DM.<sup>31</sup> Chen et al analyzed clinical indicators and gut microbiota in 60 patients with DN, uncovering a positive correlation between genus Bacteroides and cholesterol and triglyceride levels. Conversely, they observed a negative correlation between genus Bacteroides and albumin and hemoglobin levels, suggesting potential adverse effects in the context of DN.<sup>32</sup> Similarly,



**Figure 5** Forest plot summarizing the IVW method results of diabetic nephropathy to the specific gut microbiota.

studying patients with T2DM and DN revealed elevated levels of genus *Bacteroides* in the gut microbiome.<sup>33</sup> This observation aligns with the findings of Li et al,<sup>19</sup> who found a significant increase in genus *Bacteroides* among db/db mice with renal failure. The elevation of genus *Bacteroides* could be attributed to its association with the production of p-cresyl sulfate (PCS),<sup>34</sup> which is considered a uremic toxin that increases during DN.<sup>35</sup> Its accumulation activates the immune system, leading to increased production of inflammatory factors and kidney injury.<sup>36</sup> Notably, *Bacteroides* have been implicated in kidney inflammation via the LPS-Toll-like receptor 2/4 (TLR2/4) signaling pathway.<sup>37,38</sup> By analyzing alterations in the intestinal flora of patients with DN using macro-genome sequencing technology, He et al observed a reduction in the abundance of species, including *Bacteroides coprocola*, *Bacteroides xylanisolvens*, and *Bacteroides* sp D22 in the DN group.<sup>7</sup> Additionally, another study found that the phylum Bacteroidetes and the genus *Bacteroides* are negatively correlated with the urine albumin creatinine ratio (UACR) among patients with DN.<sup>8</sup> Animal experiments have also reported a lower abundance of genus *Bacteroides* in the DN db/db mouse model compared to control db/m mice.<sup>39</sup> Bacteroidetes can ferment dietary fiber into SCFAs, which can serve as potential therapeutic options for systemic inflammatory, immune, and metabolic disorders.<sup>40</sup> SCFAs exert their effects by activating G-protein coupled receptors (eg, GPR41, GPR43, and GPR109A) and inhibiting histone deacetylase (HDAC).<sup>18,41</sup> Activation of GPRs stimulates glucagon-like peptide-1 (GLP-1) secretion, enhancing blood glucose tolerance and insulin sensitivity.<sup>41</sup> The reduction in Bacteroidetes abundance can potentially inhibit SCFA generation and promote the progression of DN. The members of Bacteroidaceae also suppress inflammation by regulating cytokine expression and lymphocyte infiltration.<sup>42</sup> Moreover, *Bacteroides fragilis* was found to mitigate renal fibrosis by reducing lipopolysaccharide (LPS) and increasing 1,5-anhydroglucitol (1,5-AG) levels.<sup>43</sup> *Bacteroides* species are promising candidates for treating immune dysregulation and metabolic disorders.<sup>42</sup> It has also been suggested that certain species of *Bacteroides* may play both beneficial and pathogenic roles based on their location in the host. Upon translocation to extraintestinal organs, they may induce inflammation, diarrhea, etc.<sup>44</sup> The roles of phylum Bacteroidetes and its subclasses remain subjects of debate due to inconsistencies among previous studies. Our results indicated divergent causal associations between various levels of *Bacteroides* and DN. Specifically, the relationship at the family and genus levels is opposite to that observed at the phylum, class, and order levels. This discrepancy may be caused by other bacterial taxa under the classification of the order Bacteroidales. The cumulative effects of multiple taxa on DN can explain the observed effects. Further studies are needed to unravel the intricate mechanisms underlying the effect of various *Bacteroides* levels on the development of DN. We propose the following recommendations: First, future studies should investigate the individual effects of distinct subclasses of *Bacteroides* and also determine the combined effects of multiple bacterial taxa. Second, the effects of varying abundances of *Bacteroides* on the disease should be explored. Third, efforts should be made to assess the effects of drugs and diet on bacterial flora in clinical studies.

Genus *Lachnospirillum* emerged as a risk factor for DN in our study. This finding aligns with previous studies<sup>32</sup> indicating a positive correlation between *Lachnospirillum*, serum cholesterol, and triglycerides, implying its detrimental role in DN. Another study indicated that *Lachnospirillum* is highly abundant in mice with DN. It positively correlated with the serum levels of Cr, IS, and IL-6, supporting its possible involvement in the pathogenesis of DN.<sup>45</sup> Additionally, *Lachnospirillum* was abundant in the gut microbiota of individuals with DN.<sup>46</sup> In a case-control study, patients with stage 5 CKD exhibited a higher relative abundance of *Lachnospirillum* than healthy controls.<sup>47</sup> Calorie restriction in the rat model of T2DM improved hyperglycemia, glucose tolerance, and insulin sensitivity, likely by reducing the abundance of pro-inflammatory bacteria, such as *Bacteroides*, *Lachnospirillum*, and *Bifidobacterium*.<sup>48</sup> *Lachnospirillum* has been identified as a trimethylamine (TMA)-producing genus. Specifically, *L. saccharolyticum* in the *Lachnospirillum* genus effectively converted choline to TMA in vitro experiments. Moreover, in vivo studies have shown that the administration of *L. saccharolyticum* can markedly elevate TMAO levels in the serum of ApoE<sup>-/-</sup> mice.<sup>49</sup> TMAO, a bacterial uremic toxin, increases intestinal permeability and enters the bloodstream due to the impaired function of the intestinal barrier, potentially contributing to renal dysfunction.<sup>50</sup> Thus, we hypothesized that *Lachnospirillum* may affect the development of DN by modulating TMAO levels. In addition, a recent study showed that *Lachnospirillum* may increase the risk of type 2 diabetes by producing several metabolites, such as N-acetylglucosamine and hydroxyasparagine, which increase the risk of insulin resistance and obesity.<sup>51</sup>

Furthermore, this study identified the genus *Coprococcus* as a protective factor against DN, consistent with previous studies. Tao et al observed a significant reduction in the abundance of *Coprococcus* in the gut microbiota of patients with type 2 diabetes and DN.<sup>8</sup> Similarly, two studies reported decreased abundance of *Coprococcus* in the gut microbiome of patients with DN.<sup>52,53</sup> This might be attributed to *Coprococcus* being a butyrate-producing genus,<sup>54</sup> enhancing the integrity of the intestinal barrier by increasing the production of colonic mucins and tight junction proteins (ZO-1).<sup>55</sup> Additionally, it was demonstrated to mitigate kidney injury by activating GPRs or HDACs.<sup>56,57</sup> Notably, SCFAs, particularly butyrate, alleviate DN by suppressing high glucose-induced oxidative stress and NF- $\kappa$ B signaling through GPR43.<sup>58</sup> Furthermore, our study revealed that a higher abundance of the genera *Catenibacterium* and *Parasutterella* is associated with an increased risk of DN, whereas a greater abundance of genus *Lactococcus* and family *Victivallaceae* is associated with a lower risk of DN. Nosratola et al noted an increase in operational taxonomic units from *Catenibacterium* in patients with end-stage renal disease (ESRD).<sup>12</sup> Li et al found that altered levels of the microbiota genus *Parasutterella* are associated with estimated glomerular filtration rate and other clinical indicators of disease severity in CKD.<sup>59</sup> Likewise, another study found a significantly positive correlation between *Parasutterella* abundance and the risk of type 2 diabetes.<sup>60</sup> Our findings align to some extent with previous studies, the precise mechanisms remain uncertain and warrant further studies.

Notably, our analysis did not reveal any signs of reverse causation between these specific microbiota and DN, suggesting that DN is a consequence of gut dysbiosis, not an instigating factor behind gut dysbiosis.

Unfortunately, certain gut microbial metabolites, including SCFAs, tryptophan, TMAO, and BAs, play an important role in the development of DN.<sup>18</sup> However, our study did not identify a significant association, even when relaxing the filtering conditions for instrumental variables. This lack of significance may be attributed to various factors. First, the pathogenesis of DN is associated with numerous confounding variables that can affect the outcome. Hence, establishing statistical significance for individual metabolite-gene predictions becomes challenging without accounting for these confounding factors. Second, the MR analysis considers a linear association between gut microbial metabolites and DN, potentially overlooking true associations. There may be a nonlinear relationship between gut flora metabolites and DN. Therefore, future observational studies and MR studies should unveil the intricate relationships. Thirdly, DN may act as a cause rather than a consequence of gut dysbiosis. Regrettably, the reverse MR analysis conducted in this study did not yield any significant matches between the SNPs associated with DN and gut microbial metabolites, precluding further exploration.

The strength of this study lies in the use of the most recent and extensive GWAS dataset, employing a gene prediction approach to explore the association between gut microbiota and DN. This approach effectively minimized the effect of confounding factors and overcame the issues related to reverse causality. Nevertheless, several limitations should be considered. First, the GWAS dataset mostly comprised European participants, and due to differences in genetic background, disease susceptibility genes, environment, and lifestyles of various races, further validation is needed to determine the generalizability of these findings to non-European populations. Second, the classification of gut microbial data was constrained to the genus level and beyond, not allowing the establishment of a causal relationship between gut flora at lower taxonomic levels (eg, species or strains) and DN. Third, the composition of gut microbiota relies on various factors, including antibiotic use, diet, and geographical factors. This variability leads to a high degree of microbiome heterogeneity and inter-individual variability, potentially diminishing the statistical power of microbiome GWAS analyses. Fourth, the GWAS summary data on gut microbiota did not exclusively represent European populations, causing a disparity in ethnic proportions compared to the DN dataset. This disparity might lead to some levels of inconsistency in linkage disequilibrium correlations. Both risk factors of DN and the composition of gut microbiota are affected by age and gender. Unfortunately, we could not conduct stratified analyses, potentially affecting our results. Future studies can benefit from MR analyses within subgroups of the sample. Finally, despite efforts, a causal relationship could not be established between microbiota-related metabolites and DN, and reverse MR analyses could not be conducted due to data limitations. There is an urgent need for larger GWAS datasets of metabolites in the future, as they can facilitate more robust MR analyses of specific metabolites.

In conclusion, our study suggests a plausible cause-and-effect association between gut microbiota and DN. Notably, we identified six bacterial taxa with a positive causal relationship and five bacterial taxa with a negative causal

relationship with DN. These specific microbial strains hold promise as potential biomarkers for DN and offer novel therapeutic and preventive approaches. MR analyses are based on untestable hypotheses, which need further verification through experimental and clinical studies. The molecular mechanisms underlying the interactions between intestinal microbiota and metabolites and DN, and the reasonable application of specific microbiota in the treatment phase need further exploration.

## Data Sharing Statement

All data relevant to this study were included in the article or were uploaded as supplementary information.

## Ethics Approval

This study used publicly available deidentified data from studies that were approved by an ethics committee concerning human experimentation. This study was approved by the Medical Ethics Committee of Baoding No.1 Central Hospital (No. [2022]004).

## Acknowledgments

We appreciate the efforts of the authors in data collection, paper compilation, etc. We want to acknowledge the participants and investigators of the FinnGen study.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

## Funding

This study was supported by the Hebei Province Medical Applicable Technology Tracking Program (GZ2021055) and Natural Science Foundation of Hebei Province(H2023104011).

## Disclosure

The authors report no conflicts of interest in this work.

## References

1. Nicholas MS, Maarten WT. An updated overview of diabetic nephropathy: diagnosis, prognosis, treatment goals and latest guidelines. *Diabetes Obes Metab.* 2020. doi:10.1111/dom.14007
2. Saeedi P, Petersohn I, Salpea P, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Res Clin Pract.* 2019;157. doi:10.1016/j.diabres.2019.107843
3. Gheith O, Farouk N, Nampoory N, et al. Diabetic kidney disease: world wide difference of prevalence and risk factors. *Journal of Nephro pharmacology.* 2016;5(1):49–56.
4. Qichao H, Yuan C, Xinyu D, et al. Diabetic nephropathy: focusing on pathological signals, clinical treatment, and dietary regulation. *Biomed Pharmacother.* 2023;159. doi:10.1016/j.biopha.2023.114252
5. Feyzi Sinan T, Yeliz D, Cüneyt T, et al. Novel acetic acid derivatives containing quinazolin-4(3H)-one ring: synthesis, in vitro, and in silico evaluation of potent aldose reductase inhibitors. *Drug Dev Res.* 2023;84(2). doi:10.1002/ddr.22031
6. Wang Y, Zhao J, Qin Y, et al. The Specific Alteration of Gut Microbiota in Diabetic Kidney Diseases-A Systematic Review and Meta-Analysis. *Front Immunol.* 2022;13. doi:10.3389/fimmu.2022.908219
7. He X, Sun J, Liu C, et al. Compositional Alterations of Gut Microbiota in Patients with Diabetic Kidney Disease and Type 2 Diabetes Mellitus. *Diabetes Metab Syndr Obes.* 2022;15:755–765. doi:10.2147/DMSO.S347805
8. Tao S, Li L, Li L, et al. Understanding the gut-kidney axis among biopsy-proven diabetic nephropathy, type 2 diabetes mellitus and healthy controls: an analysis of the gut microbiota composition. *Acta Diabetologica.* 2019;56(5):581–592. doi:10.1007/s00592-019-01316-7
9. Larsen N, Vogensen F, van den Berg F, et al. Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. *PLoS One.* 2010;5(2):e9085. doi:10.1371/journal.pone.0009085
10. Han S, Chen M, Cheng P, et al. A systematic review and meta-analysis of gut microbiota in diabetic kidney disease: comparisons with diabetes mellitus, non-diabetic kidney disease, and healthy individuals. *Front Endocrinol.* 2022;13:1018093. doi:10.3389/fendo.2022.1018093

11. Lehto M, Groop PH. The Gut-Kidney Axis: putative Interconnections Between Gastrointestinal and Renal Disorders. *Front Endocrinol.* 2018;9:553. doi:10.3389/fendo.2018.00553
12. Vaziri ND, Wong J, Pahl M, et al. Chronic kidney disease alters intestinal microbial flora. *Kidney Int.* 2013;83(2):308–315. doi:10.1038/ki.2012.345
13. Wu X, Zhao L, Zhang Y, et al. The role and mechanism of the gut microbiota in the development and treatment of diabetic kidney disease. *Front Physiol.* 2023;14:1166685. doi:10.3389/fphys.2023.1166685
14. Mercer K, Yeruva L, Pack L, et al. Xenometabolite signatures in the UC Davis type 2 diabetes mellitus rat model revealed using a metabolomics platform enriched with microbe-derived metabolites. *Am J Physiol Gastrointest Liver Physiol.* 2020;319(2):G157–G69. doi:10.1152/ajpgi.00105.2020
15. Chen P, Zhang J, Li X, et al. Outer membrane vesicles derived from gut microbiota mediate tubulointerstitial inflammation: a potential new mechanism for diabetic kidney disease. *Theranostics.* 2023;13(12):3988–4003. doi:10.7150/thno.84650
16. Pedersen HK, Gudmundsdottir V, Nielsen HB, et al. Human gut microbes impact host serum metabolome and insulin sensitivity. *Nature.* 2016;535(7612):376–+. doi:10.1038/nature18646
17. C-c L, Z-b H, Wang R, et al. Gut microbiota dysbiosis-induced activation of the intrarenal renin-angiotensin system is involved in kidney injuries in rat diabetic nephropathy. *Acta Pharmacol Sin.* 2020;41(8):1111–1118. doi:10.1038/s41401-019-0326-5
18. Mao Z-H, Gao Z-X, Liu D-W, et al. Gut microbiota and its metabolites - molecular mechanisms and management strategies in diabetic kidney disease. *Front Immunol.* 2023;14. doi:10.3389/fimmu.2023.1124704
19. Li YJ, Chen X, Kwan TK, et al. Dietary Fiber Protects against Diabetic Nephropathy through Short-Chain Fatty Acid-Mediated Activation of G Protein-Coupled Receptors GPR43 and GPR109A. *J Am Soc Nephrol.* 2020;31(6):1267–1281. doi:10.1681/asn.2019101029
20. Fang Q, Zheng B, Liu N, et al. Trimethylamine N-Oxide Exacerbates Renal Inflammation and Fibrosis in Rats With Diabetic Kidney Disease. *Front Physiol.* 2021;12. doi:10.3389/fphys.2021.682482
21. Davey Smith G, Hemani G. Mendelian randomization: genetic anchors for causal inference in epidemiological studies. *Hum Mol Genet.* 2014;23(R1):R89. doi:10.1093/hmg/ddu328
22. Skrivankova VW, Richmond RC, Woolf BAR, et al. Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization: the STROBE-MR Statement. *JAMA J Am Med Assoc.* 2021;326(16):1614–1621. doi:10.1001/jama.2021.18236
23. Kurilshikov A, Medina-Gomez C, Bacigalupe R, et al. Large-scale association analyses identify host factors influencing human gut microbiome composition. *Nat Genet.* 2021;53(2):156–165. doi:10.1038/s41588-020-00763-1
24. Rhee EP, Ho JE, Chen MH, et al. A genome-wide association study of the human metabolome in a community-based cohort. *Cell Metab.* 2013;18(1):130–143. doi:10.1016/j.cmet.2013.06.013
25. Guo Z, Pan J, Zhu H, et al. Metabolites of Gut Microbiota and Possible Implication in Development of Diabetes Mellitus. *J Agric Food Chem.* 2022;70(20):5945–5960. doi:10.1021/acs.jafc.1c07851
26. Kurki MI, Karjalainen J, Palta P, et al. FinnGen provides genetic insights from a well-phenotyped isolated population. *Nature.* 2023;613(7944):508. doi:10.1038/s41586-022-05473-8
27. Tziomalos K, Athyros VG. Diabetic Nephropathy: new Risk Factors and Improvements in Diagnosis. *The Review of Diabetic Studies: RDS.* 2015;12(1–2):110. doi:10.1900/rds.2015.12.110
28. Lizicarova D, Krahulec B, Hirnerova E, et al. Risk factors in diabetic nephropathy progression at present. *Bratislava Med J Bratisla Lekarske Listy.* 2014;115(8):517–521. doi:10.4149/blm\_2014\_101
29. Shuxiang Y, Hua W, Baiyu F, et al. Causal relationship between gut microbiota and diabetic nephropathy: a two-sample Mendelian randomization study. *Front Immunol.* 2024;15. doi:10.3389/fimmu.2024.1332757
30. Li N, Wang Y, Wei P, et al. Causal Effects of Specific Gut Microbiota on Chronic Kidney Diseases and Renal Function-A Two-Sample Mendelian Randomization Study. *Nutrients.* 2023;15(2). doi:10.3390/nu15020360
31. Manjun L, Mengting S, Tingting W, et al. Gut microbiota and type 1 diabetes: a two-sample bidirectional Mendelian randomization study. *Front Cell Infect Microbiol.* 2023;13. doi:10.3389/fcimb.2023.1163898
32. Chen W, Zhang M, Guo Y, et al. The Profile and Function of Gut Microbiota in Diabetic Nephropathy. *Diabetes Metabolic Syndr Obes Targ Therapy.* 2021;14:4283–4296. doi:10.2147/dmso.S320169
33. Zhang L, Wang Z, Zhang X, et al. Alterations of the Gut Microbiota in Patients with Diabetic Nephropathy. *Microbiology Spectrum.* 2022. doi:10.1128/spectrum.00324-22
34. Wing MR, Patel SS, Ramezani A, et al. Gut microbiome in chronic kidney disease. *Exp Physiol.* 2016;101(4):471–477. doi:10.1113/ep085283
35. Kikuchi K, Saigusa D, Kanemitsu Y, et al. Gut microbiome-derived phenyl sulfate contributes to albuminuria in diabetic kidney disease. *Nat Commun.* 2019;10. doi:10.1038/s41467-019-09735-4
36. Sun C-Y, Hsu -H-H, Wu M-S. p-Cresol sulfate and indoxyl sulfate induce similar cellular inflammatory gene expressions in cultured proximal renal tubular cells. *Nephrol Dial Transplant.* 2013;28(1):70–78. doi:10.1093/ndt/gfs133
37. Li F, Yang N, Zhang L, et al. Increased Expression of Toll-Like Receptor 2 in Rat Diabetic Nephropathy. *Am j Nephrol.* 2010;32(2):179–186. doi:10.1159/000317023
38. Yang M, Gan H, Shen Q. Effect of LPS on the level of TLR4 and on the expression of NF-kappaB and Notch1 in monocytes from patients with type 2 diabetic nephropathy. *Zhong Nan Da Xue Xue Bao Yi Xue Ban.* 2012;37(6):578–585. doi:10.3969/j.issn.1672-7347.2012.06.007
39. Cai -T-T, Ye X-L, Li -R-R, et al. Resveratrol Modulates the Gut Microbiota and Inflammation to Protect Against Diabetic Nephropathy in Mice. *Front Pharmacol.* 2020;11. doi:10.3389/fphar.2020.01249
40. Kimura I, Ichimura A, Ohue-Kitano R, et al. FREE FATTY ACID RECEPTORS IN HEALTH AND DISEASE. *Physiol Rev.* 2020;100(1):171–210. doi:10.1152/physrev.00041.2018
41. Lin J-R, Wang Z-T, Sun -J-J, et al. Gut microbiota and diabetic kidney diseases: pathogenesis and therapeutic perspectives. *World J Diab.* 2022;13(4):308–318. doi:10.4239/wjcd.v13.i4.308
42. Tan H, Zhai Q, Chen W. Investigations of Bacteroides spp. towards next-generation probiotics. *Food Res Int.* 2019;116:637–644. doi:10.1016/j.foodres.2018.08.088
43. Zhou W, Wu WH, Si ZL, et al. The gut microbe Bacteroides fragilis ameliorates renal fibrosis in mice. *Nat Commun.* 2022;13(1):6081. doi:10.1038/s41467-022-33824-6
44. Hassan Z, Milton H. Gut Bacteroides species in health and disease. *Gut Microbes.* 2021;13(1). doi:10.1080/19490976.2020.1848158

45. Jinni H, Tingting F, Weizhen L, et al. Jiangtang Decoction Ameliorates Diabetic Kidney Disease Through the Modulation of the Gut Microbiota. *Diabetes Metab Syndr Obes.* 2023;16. doi:10.2147/dmso.S441457
46. Bai J, Wan Z, Zhang Y, et al. Composition and diversity of gut microbiota in diabetic retinopathy. *Front Microbiol.* 2022;13. doi:10.3389/fmicb.2022.926926
47. Li Y, Su X, Zhang L, et al. Dysbiosis of the gut microbiome is associated with CKD5 and correlated with clinical indices of the disease: a case-controlled study. *J Transl Med.* 2019;17. doi:10.1186/s12967-019-1969-1
48. Zhang L, Zhang T, Sun J, et al. Calorie restriction ameliorates hyperglycemia, modulates the disordered gut microbiota, and mitigates metabolic endotoxemia and inflammation in type 2 diabetic rats. *J Endocrinol Invest.* 2023;46(4):699–711. doi:10.1007/s40618-022-01914-3
49. Cai YY, Huang FQ, Lao X, et al. Integrated metagenomics identifies a crucial role for trimethylamine-producing *Lachnoclostridium* in promoting atherosclerosis. *NPJ Biofilms Microbiomes.* 2022;8(1):11. doi:10.1038/s41522-022-00273-4
50. Nallu A, Sharma S, Ramezani A, et al. Gut microbiome in chronic kidney disease: challenges and opportunities. *Transl Res.* 2017;179:24–37. doi:10.1016/j.trsl.2016.04.007
51. Zheng W, P BA, Bing Y, et al. Gut Microbiota and Blood Metabolites Related to Fiber Intake and Type 2 Diabetes. *Circ Res.* 2024;134(7). doi:10.1161/circresaha.123.323634
52. Jiang S, Xie S, Lv D, et al. Alteration of the gut microbiota in Chinese population with chronic kidney disease. *Sci Rep.* 2017;7. doi:10.1038/s41598-017-02989-2
53. Yasuno T, Takahashi K, Tada K, et al. Dysbiosis of Gut Microbiota in Patients with Chronic Kidney Disease. *Intern Med.* 2023. doi:10.2169/internalmedicine.1602-23
54. Fujio-Vejar S, Vasquez Y, Morales P, et al. The Gut Microbiota of Healthy Chilean Subjects Reveals a High Abundance of the Phylum Verrucomicrobia. *Front Microbiol.* 2017;8. doi:10.3389/fmicb.2017.01221
55. Gonzalez A, Krieg R, Massey HD, et al. Sodium butyrate ameliorates insulin resistance and renal failure in CKD rats by modulating intestinal permeability and mucin expression. *Nephrol Dial Transplant.* 2019;34(5):783–794. doi:10.1093/ndt/gfy238
56. Lu Y, Fan C, Li P, et al. Short Chain Fatty Acids Prevent High-fat-diet-induced Obesity in Mice by Regulating G Protein-coupled Receptors and Gut Microbiota. *Sci Rep.* 2016;6. doi:10.1038/srep37589
57. Lin MY, de Zoete MR, van Putten JPM, et al. Redirection of epithelial immune responses by short-chain fatty acids through inhibition of histone deacetylases. *Front Immunol.* 2015;6. doi:10.3389/fimmu.2015.00554
58. Huang W, Man Y, Gao C, et al. Short-Chain Fatty Acids Ameliorate Diabetic Nephropathy via GPR43-Mediated Inhibition of Oxidative Stress and NF-kappaB Signaling. *Oxid Med Cell Longev.* 2020;2020:4074832. doi:10.1155/2020/4074832
59. Li F, Wang M, Wang J, et al. Alterations to the Gut Microbiota and Their Correlation With Inflammatory Factors in Chronic Kidney Disease. *Front Cell Infect Microbiol.* 2019;9. doi:10.3389/fcimb.2019.00206
60. Henneke L, Schlicht K, Andreani NA, et al. A dietary carbohydrate - gut Parasutterella - human fatty acid biosynthesis metabolic axis in obesity and type 2 diabetes. *Gut Microbes.* 2022;14(1). doi:10.1080/19490976.2022.2057778

## International Journal of Nephrology and Renovascular Disease

Dovepress

### Publish your work in this journal

The International Journal of Nephrology and Renovascular Disease is an international, peer-reviewed open-access journal focusing on the pathophysiology of the kidney and vascular supply. Epidemiology, screening, diagnosis, and treatment interventions are covered as well as basic science, biochemical and immunological studies. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/international-journal-of-nephrology-and-renovascular-disease-journal>