Trials

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The gut microbiota and diabetic nephropathy: an observational study review and bidirectional Mendelian randomization study

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Abstract

Background Earlier studies have implicated a crucial link between diabetic nephropathy (DN) and the gut microbiota (GM) by considering the gut-kidney axis; however, the specific cause-and-effect connections between these processes remain unclear.

Methods To compare changes in the GM between DN patients and control subjects, a review of observational studies was performed. The examination focused on the phylum, family, genus, and species/genus categories. To delve deeper into the cause–effect relationship, instrumental variables for 211 GM taxa (9 phyla, 16 classes, 20 orders, 35 families, and 131 genera), which were eligible for the mbQTL (microbial quantitative trait locus) mapping analysis, were collected from the Genome Wide Association Study (GWAS). A Mendelian randomization investigation was then conducted to gauge their impact on DN susceptibility using data from the European Bioinformatics Institute (EBI) and the FinnGen consortium. The European Bioinformatics Institute data included 1032 DN patients and 451,248 controls, while the FinnGen consortium data consisted of 3283 DN patients and 210,463 controls. Two-sample Mendelian randomization (TSMR) was utilized to determine the link between the GM and DN. The primary method for analysis was the inverse variance weighted (IVW) approach. Moreover, a reverse Mendelian randomization analysis was carried out, and the findings were validated through sensitivity assessments.

Results This review examined 11 observational studies that satisfied the inclusion and exclusion criteria. There was a significant difference in the abundance of 144 GM taxa between DN patients and controls. By employing the MR technique, 13 bacteria were pinpointed as having a causal link to DN (including 3 unknown GM taxa). Even after Bonferroni correction, the protective impact of the phylum Proteobacteria and genus Dialister (Sequeira et al. Nat Microbiol. 5:304-313, 2020; Liu et al. EBioMedicine. 90:104527, 2023) and the harmful impact of the genus Akkermansia, family Verrucomicrobiaceae, order Verrucomicrobia and class Verrucomicrobiae on DN remained significant. No noticeable heterogeneity or horizontal pleiotropy was detected in the instrumental variables (IVs). However, reverse MR investigations have failed to reveal any substantial causal relationship between DN and the GM.

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Conclusion Differences in the GM among DN patients and healthy controls are explored in observational studies. We verified the possible connection between certain genetically modified genera and DN, thereby emphasizing the connection between the "gut-kidney" axis and new insights into the GM's role in DN pathogenesis underlying DN. Investigations into this association are necessary, and novel biomarkers for the development of targeted preventive strategies against DN are needed.

Keywords Diabetic nephropathy, Gut–kidney axis, Gut microbiota, Mendelian randomization, Observational studies

Introduction

Diabetes is becoming more prevalent and will affect more than 578 million people worldwide in the next 10 years [1]. Diabetic nephropathy (DN) is a common complication of diabetes that specifically affects the microvasculature [2]. The progression of DN results from a multifaceted interplay of many different types of factors, such as genetics, immunity, inflammatory damage, stress response, and disorders in glucose and lipid metabolism [3, 4]. Consequently, researchers have proposed targeted treatments for these mechanisms. However, DN imposes a substantial burden on worldwide public health systems, and the existing treatment approaches are inadequate. It is essential to acknowledge that not all individuals with diabetes suffer from DN, and the precise reasons for this variation in susceptibility are still obscure. Furthermore, it remains uncertain whether factors beyond well-documented metabolic aspects contribute to interindividual variations.

It is widely accepted that alterations in the vigorous equilibrium of the human gut microbiota (GM) play a role among individuals [5]. Dysbiosis induced by GM in humans has been documented as a cause of multiple conditions [6], including inflammation, metabolic disorders, psychiatric illnesses, and immune dysfunctions [6]. Studies have established a connection between the GM and kidney ailments [7]. Consequently, the impact of the GM on individuals with DN remains unknown.

In their groundbreaking study, Briski et al. [8] introduced the concept of the gut-kidney axis and demonstrated the role of the GM in the regulation of chronic kidney disease (CKD). Li et al. [9] investigated the GM in diabetic mice by analyzing their plasma, kidneys, and feces. Their findings revealed that the GM significantly contributed to the damage and inflammation associated with DN. Yang et al. [10] manipulated the hyphae of Agaricus blazei mushrooms to disrupt the GM balance in mice. The results revealed that the introduction of the GM conferred protection against DN and prolonged the lifespan of the mice. In a retrospective study by Xiao Lu et al., there was a correlation between DN and the GM concentration. Nevertheless, Xiao Lu's findings revealed disparities only in the prevalence of GM among DN patients.

The study of the mechanisms linked to the gut-kidney axis in individuals with DN is considerably complicated by the presence of multiple GMs. Numerous factors, including dietary choices and rest, influence an individual's digestive system. Consequently, limited human research exists to establish a direct correlation between particular GMs and DN.

Studying the potential hyperquantization between the DN and GM has significant clinical implications. Analyzing various observational studies on the association between the GM and DN is crucial to understanding this relationship more fully. More studies are required to conclusively establish a link between the GM and DN, potentially opening up new avenues for therapeutic interventions in the management of DN. By exploring this relationship in more depth, researchers may uncover important insights that could ultimately lead to improved treatment strategies for patients with DN.

Mendelian randomization (MR) employs genetic variants as instrumental variables to determine whether a risk factor has a causal effect on a health outcome. In recent years, MR has been utilized to integrate genome-wide association study (GWAS) summary data for a substantial number of genetic variants. The heterogeneity observed among the causal estimates from multiple genetic variants suggests a potential violation of the essential assumptions underlying derived instrumental variable analysis [11]. MR trials, in comparison to randomized controlled trials, eliminate confounding factors (such as diet) and employ genetic variation instead of exposure to establish the cause and effect of an outcome. In the assessment process, we inverted the relationship between cause and effect. MR analysis is widely used in studies regarding causal connections between the GM and autoimmune diseases [12] and neuropsychiatric disorders [13].

A study was conducted to review observational research on alterations in the GM in individuals with DN. Additionally, MR forward and MR reverse analyses of 2 samples were performed to investigate the association between the two factors. Through the identification of the link between specific GMs and DN patients, this research has the potential to advance our understanding of diagnosis and treatment in the future.

Materials and methods

Literature search strategies and study selection criteria

Cross-sectional and cohort studies were conducted to compare GM changes in DN patients and controls from the earliest recording to March 6, 2024. The search terms included "intestinal microbiome," "gastrointestinal microbiota," "microbiome of the gut," "microbiota," "intestinal flora," "diabetic nephropathy," and "diabetes-related kidney disease". Using MeSH terms employed to account for variations in vocabulary. Terms employed to account for variations in vocabulary. Logical operators (e.g., AND/OR) were applied in the searches. Use OR between words with similar meanings, and use AND between GM and DN. By 2 graduate students with evidence-based experience, the documents were independently screened and cross-checked, and in case of discrepancies, a third party was used to assist in judging the documents, and the documents that met the standards were finally included. The inclusion criteria encompassed studies that (1) contrasted changes in GM between DN patients and nondiabetic individuals, specifying the subgroups studied; (2) provided essential information such as primary author, publication year, diagnostic criteria, country, study plan, age range, sample size, methodology for GM analysis, and relevant findings; (3) utilized fecal samples for GM examination; and (4) clearly described the techniques for GM identification. The exclusion criteria were studies lacking specific bacterial taxonomic data, conference presentations, reviews, systematic analyses, case reports, or a lack of raw data [14]. We will delete duplicates and studies not meeting the inclusion criteria were handled in the final confirmed inclusion literature.

Data collection and quality assessment

The information was gathered from the texts, tables, and figures in each study. The following data were collected: primary author, publication year, diagnostic criteria, country, study plan, age range, sample size, methodology for GM analysis, and relevant findings. A detailed summary of all findings from the studies is organized into tables, which present a comprehensive comparison of GM differences between DN patients and controls. These tables provide in-depth details ranging between the phyla and the species. An analysis of GM composition was conducted through a synthesis of the literature, accounting for age variations, evaluation techniques, low sample sizes, and incomplete data. Regarding Maior Microbiome Identification Method, we mainly include methods using 16S rRNA gene sequencing and Metagenomic sequencing. When the Definition of DN cannot be unified, we will review the literature and determine unified diagnostic criteria, mainly including The Microvascular Complications Group of the Chinese Diabetes Society criteria and Renal puncture pathological examination criteria and the 1999 WHO criteria. Assessment of bias risks for nonrandomized studies was carried out using the RoBANS tool, which assesses methodological quality and potential bias across six domains [15].

MR assumptions and survey depiction

We used two-sample Mendelian randomization to assess the relationships between different transgenic taxa and DN. All of the data are from the Genome-Wide Association Study (GWAS) of GM and DN. The flowchart shown in Fig. 1 shows the progress of MR research on transgenic and DN taxa. To guarantee dependable outcomes, MR analysis additionally fulfills three assumptions [16] (Fig. 1): (1) The strict relationship between the GM and the final instrumental variable (IV) used must be ensured by ensuring their alignment. Select IV in the exposure data (through correlation analysis, select SNPs that are strongly related to exposure factors as instrumental variables, and the filtering condition is p value $< 5e-08$).(2) The included IVs are in line with confounding factors that impact both GM and DN taxa, and they are mutually independent. To meet the requirements of the independence assumption, we need to remove some instrumental variables related to confounding factors. PhenoScanner V2: an expanded tool for searching human genotype–phenotype associations can search for relationships between instrumental variables and phenotypes. (3) Horizontal pleiotropy is avoided: IVs solely affect DN through transgenic taxa. If the instrumental variable affects the outcome through factors other than exposure factors, it means that the instrumental variable has pleiotropic effects. Pleiotropy would cause the assumptions of independence and exclusivity to fail. Through the MR-Egger intercept test, the pleiotropy of the data can be detected and the robustness of the results can be assessed. If p value < 0.05, it indicates that the data has pleiotropy. (If there is pleiotropy, you need to reselect the instrumental variable or reselect the exposure and outcome). Our findings are in accordance with the MR-STROBE guidelines [17].

Ethics statement

The research conducted in this study utilized openly accessible data, which were collected in an aggregated format, ensuring the protection of personal information. To guarantee adherence to ethical standards, every GWAS involved in this analysis has ethical clearance from the relevant organizations.We confirm that ethical standards mentioned for GWAS align with the Declaration of Helsinki.

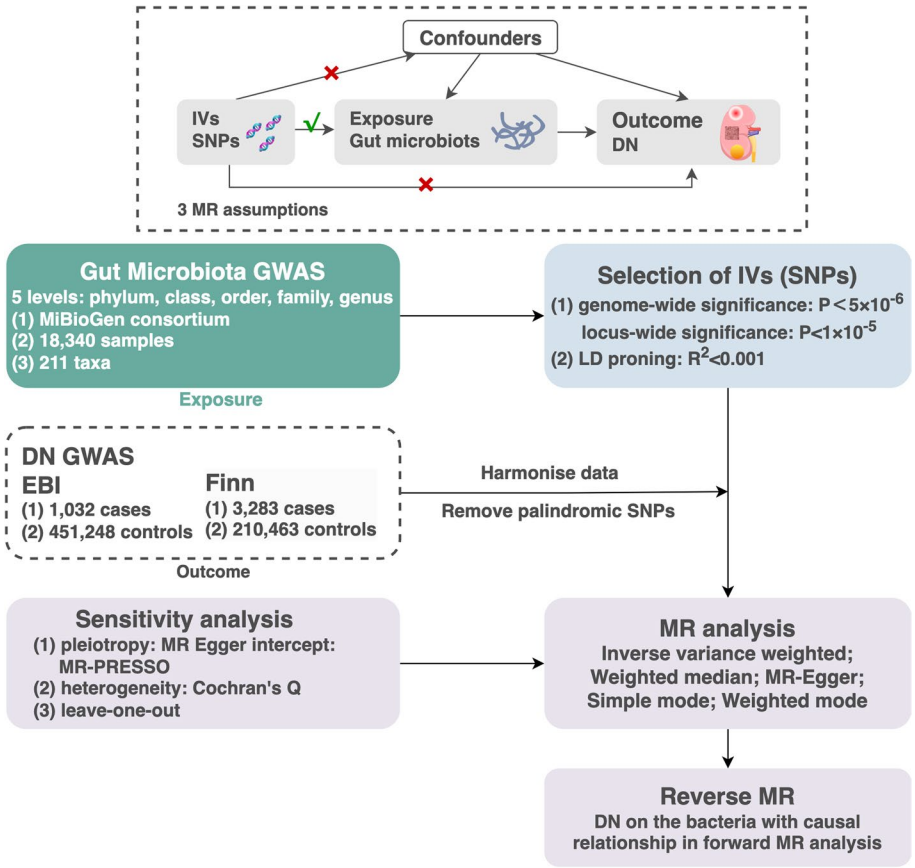


Fig. 1 Overview of the MR analysis process and major assumptions

Data source

Scientific research implemented based on MiBioGen, Kurilshikov et al. [18] performed a thorough analysis of the correlation between genetic variation and GM by examining a total of 18,340 samples. This analysis involved profiling the samples through the collection of genotyping data and 16S rRNA gene sequencing. All MiBioGen participants were of European ancestry and included 25 groups from 11 different countries. The GWAS identified a total of 122,110 mutation sites encompassing 211 taxa, ranging between phylum and genus. In this large-scale GWAS dataset, we specifically examined the IVs of five different levels of GM taxa.

The DN GWAS summary statistics were obtained from EBI (https://www.ebi.ac.uk) and FinnGen (https://r5.finngen.fi/). DN GWAS from EBI investigated 24,190,738 variables from 452,280 subjects with SAIGE (https://github.com/weizhouUMICH/SAIGE). After considering age, sex, genetic relatedness, genotyping batches, and 10 principal components, 1,032 patients with DN and 451,248 controls were used for the DN study. DN GWAS from FinnGen investigated 16,962,023 variables from 218,792 subjects with SAIGE. After adjusting for the same components as above, 14,584 patients with DN and 202,082 controls were included in the DN analysis [19].

Instrumental variables selection

To further enhance the reliability of our data and the precision of our findings, we carried out a quality assessment on single-nucleotide polymorphisms (SNPs). Our first step was to examine the SNPs in GM taxa that met the genome-wide threshold ($P<5\times10^{-8}$). However, there were no eligible IVs using this threshold. Therefore, we decided to implement a comprehensive threshold ($P<5\times10^{-6}$) [20] to obtain a wider range of results. In addition to the threshold adjustment, we also needed to ensure that our data met the assumptions of MR. An analysis of linkage disequilibrium (LD) was carried out utilizing the 1000 Genome Projects data, focusing on individuals of European descent. The clumping distance set for this analysis was 10,000 kb, with an R^2 value threshold of less than 0.001. This analysis allowed us to identify and remove any unqualified SNPs for MR. To prevent allele effects on the connection between DN and GM taxa, we eliminated palindromic SNPs from our dataset. This step was necessary to ensure that our

analysis focused solely on the connection between DN and GM taxa, without any confounding factors introduced by palindromic SNPs. Through these rigorous steps, we were able to establish a strong foundation for our analysis, ensuring the reliability of our data and the accuracy of our results.

Relevant information was extracted: chromosome, effector allele (EA), other allele (OA), effector allele frequency (EAF), effect size (β), standard error (SE), and *P*-value. Finally, we calculated explained variance (R^2) and F-statistic parameters to determine whether the identified IVs were strongly associated with exposure. In general, SNPs with F-statistic parameters less than 10 are considered weak instruments. In this study, $R^2 = 2 \times EAF \times (1 - EAF) \times \beta 2$ / $(2 \times EAF \times (1 - EAF) \times \beta 2 + 2 \times EAF \times (1 - EAF) \times N \times SE2)$, where N is the sample size of the GWAS for FI and $F = R^2 \times (N - 2)/(1 - R^2)$.

Statistical analysis

R software (version 4.1.1) was used for the purpose of conducting the statistical analysis. To investigate the connection between transgenic taxa and DN, we performed MR analysis using the R packages "TwoSampleMR" and "MR-PRESSO". To identify possible relationships, a threshold of $P < 0.05$ was established for statistical significance [21]. To obtain a more stringent interpretation of causality, Bonferroni correction based on 211 GM taxa was used as follows: $0.05/211$ (5×10^{-3}).

MR analysis

The impact of individuals on causal estimation IVs was evaluated with the Wald ratio (WR) technique. Unbiased estimates were obtained through inverse variance weighting (IVW). The IVW test employed a fixed/random effects model considering the presence or absence of heterogeneity. Effect size was measured by the 95% confidence interval (CI) and odds ratio (OR). Four other methods, the simple mode method, the weighted median (WM), the MR–Egger, and the weighted mode method, served as supplementary approaches for MR analysis. The WM method can detect significant causal relationships when the number of heterogeneous SNPs exceeds 50%, while if the number of pleiotropic SNPs exceeds 50%, MR–Egger is still effective [22].

Sensitivity analysis

We used Cochrane's *Q* test to examine heterogeneity in the data. Variables with a *P* value less than 0.05 were considered heterogeneous. We assessed potential pleiotropy in the variables by analyzing the intercept of MR–Egger regression. If *P* value greater than 0.05 indicated that horizontal pleiotropy was not present. To determine the relationship between DN and GM taxa for data accuracy, we performed additional analysis using the MR-Pleiotropy RESidual Sum and Outlier (MR-PRESSO) test. This test was conducted using the R package "MR-PRESSO" and involved removing outliers. We also used the leave-one-out approach to further test the reliability of the data [23, 24].

Reverse MR analysis

Reverse MR analysis was performed on the GM linked to the DN in forward MR analysis to explore reverse fraternization between the DN and GM. The techniques and parameters utilized in the reverse MR analysis aligned with those used in the forward MR analysis.

Results

Literature search and basic characteristics

A total of 332 research studies were identified through the search strategy employed. Following the elimination of 140 duplicate studies, the review process for the remaining 192 studies was conducted in alignment with the established inclusion and exclusion criteria. Ultimately, 11 scholarly articles were deemed suitable for inclusion in the current investigation. A graphical representation of the literature screening process can be found in Fig. 2, with a concise overview of the included studies presented in Table 1. Of the selected articles, nine were cross-sectional studies [25–33], while two were cohort studies [34, 35]. The majority of these studies utilized the Microvascular Complications Group criteria from the Chinese Diabetes Society [25, 28–30, 33, 34] along with renal puncture pathological examination criteria [26, 31, 32] for the detection of DN. A notable exception was the work by Winther and Fan, which employed the 1999 World Health Organization (WHO) criteria [27, 35]. Furthermore, a microbiome assessment approach involving 16S rRNA gene sequencing with various region specifications was employed in the majority of the studies, whereas metagenomic sequencing methods were utilized in the research by Zhang and Ji [32, 34]. Participants across two studies were categorized into DN and healthy control groups [29, 32], while other investigations segmented participants based on DM classification, DN and DM stages, and the presence or absence of DN alongside other relevant conditions. Geographically, the studies were conducted predominantly in East Asia (China, South Korea) [25, 26, 28–35], with a single study occurring in Europe (Copenhagen) [27].When including studies, we have study limitations, such as the inclusion of studies with small sample sizes.

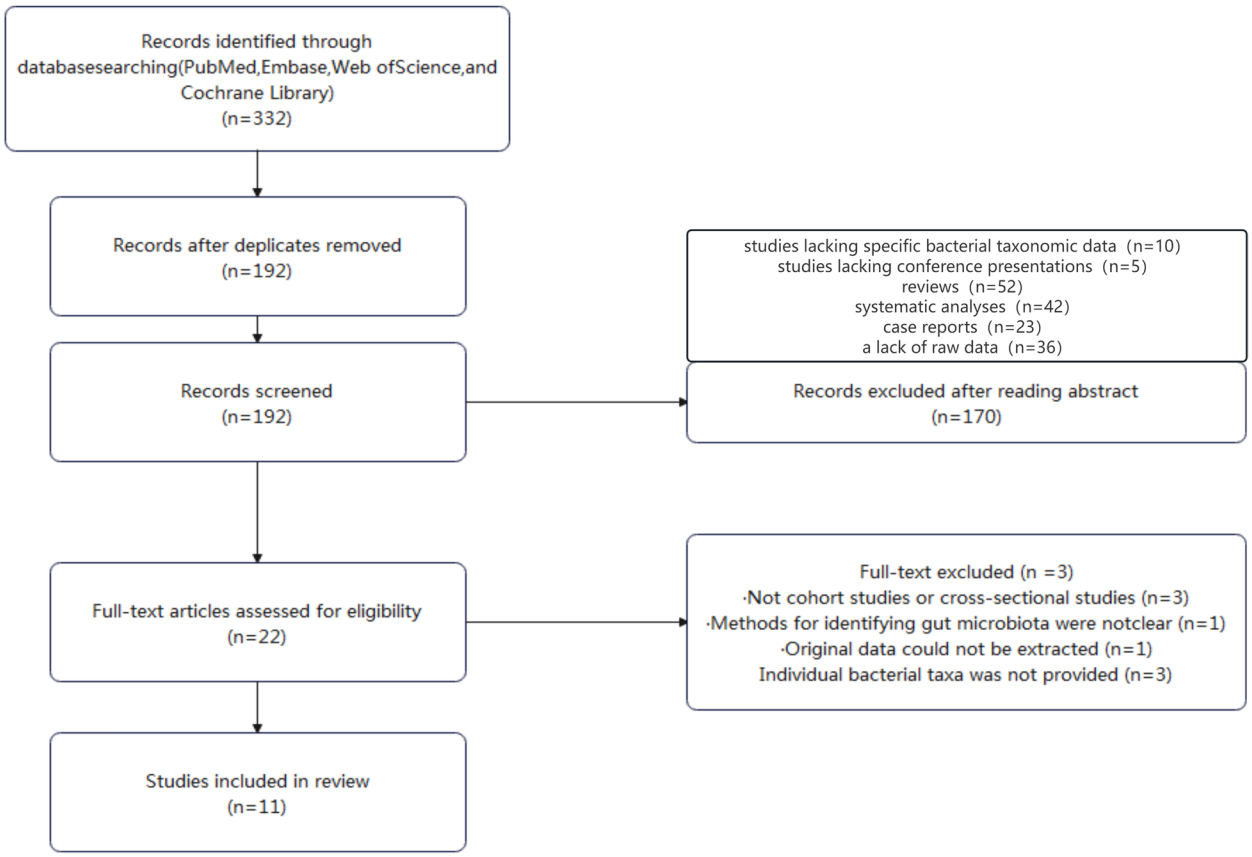


Fig. 2 Flowchart of the literature selection process

Summary of bacterial taxa changes in observational studies

Every study employed high-throughput sequencing techniques, including 16S rRNA gene sequencing and whole-genome shotgun sequencing. GM quantity in the gut tract was assessed using different criteria, such as observed operational taxonomic unit (OTU) quantities, diversity, and uniformity. Variations in the quantity of particular GM categories were established by examining notable variances ($P < 0.05$) in relative quantity at the phylum, class, order, family, species, or genus subgroup levels. The comparison groups were the DN group and the non-DN group, with or without the involved subgroups.

In DN patients, a massive increase in the abundance of the phylum *Bacteroidetes*, *Proteobacteria*, *Actinobacteria*, and *Fusobacteria* was reported in four studies [26, 28–30], while the abundance of the phylum *Cyanobacteria* and *Firmicutes* decreased in four studies [25–27, 34]. In patients diagnosed with DN, a notable increase in the prevalence of the following classes was documented in a previous study: *Bacilli*, *Negativicutes*, *Clostridia*, *Actinobacteria*, and *Coriobacteriia* [29]. Furthermore, a reduction in the presence of the following phyla was noted among DN patients in two separate research studies: *Alphaproteobacteria* [31]. At the order level, the abundances of *Betaproteobacteriales*, *Bifidobacteriales*, *Lactobacillales*, *Selenomonadales*, *Clostridiales*, and *Coriobacteriales* were significantly elevated in patients with DN in two studies [27, 29]. Conversely, *Chitinophagales*, *Clostridiales*, *Rhizobiales*, *Xanthomonadales*, and *Pasteurellaceae* were notably less abundant in a separate study [29]. The variation in the abundance of GM orders, including *Clostridiales*, in DN patients was inconsistent among different studies [27, 29]. At the family level, *Tannerellaceae*, *Barnesiellaceae*, *Ruminococcaceae*, *Lactobacillaceae*, *Lachnospiraceae*, *Streptococcaceae*, *Christensenellaceae*, *Erysipelotrichaceae*, *Veillonellaceae*, *Burkholderiaceae*, *Bifidobacteriaceae*, and *Atopobiaceae* were increased in DN patients in four studies [27, 29, 31, 34], while families such as *Chitinophagaceae*, *Lactobacillaceae*, *Lachnospiraceae*, and *Rhodanobacteraceae* were decreased in three studies [25, 29, 34]. The variation in the abundance of certain GM families, including *Lactobacillaceae* and *Lachnospiraceae*, was inconsistent among different studies [25, 27, 29]. Numerous significant dissimilarities were observed at the genus level. The

Table 1 Characteristics of the observational studies included in the review

First author	Year	Country	Study design	Definition of DN	Maior Microbiome Identification Method	Group	Patients, *n*	Age, years
Bao [26]	2019	China	Cross-sectional study	The Microvascular Complications Group of the Chinese Diabetes Society criteria	16S rRNA gene sequencing	DN	25	63.7 ± 13.3
						T2DM	30	62 ± 13.3
						Healthy control	30	60.2 ± 9.7
Tao [27]	2019	China	Cross-sectional study	Renal puncture pathological examination criteria	16S rRNA gene sequencing	DN	14	52.93 ± 9.98
						T2DM	14	53.29 ± 9.00
						Households	14	44.29 ± 17.31
						Healthy control	14	52.86 ± 9.91
Winther [28]	2020	Copenhagen	Cross-sectional study	the 1999 WHO criteria	16S rRNA gene sequencing	T1DM with Microalbuminuria	50	62 ± 9
						T1DM with Macroalbuminuria	61	60 ± 10
						T1DM with normoalbuminuria	50	59 ± 11
						Healthy control	50	59 ± 13
Chen [29]	2021	China	Cross-sectional study	The Microvascular Complications Group of the Chinese Diabetes Society criteria	16S rRNA gene sequencing	Early DN	13	61.23 ± 12.56
						Established DN	35	60.51 ± 8.63
						Advanced DN	12	59.83 ± 9.66
						DM	20	55.20 ± 14.77
						Healthy control	20	55.15 ± 13.77
Du [30]	2021	China	Cross-sectional study	The Microvascular Complications Group of the Chinese Diabetes Society criteria	16S rRNA gene sequencing	DN	43	60.86 ± 5.69
						Healthy control	37	61.78 ± 6.40
Yang [31]	2022	China	Cross-sectional study	The Microvascular Complications Group of the Chinese Diabetes Society criteria	16S rRNA gene sequencing	DKD	8	58.75 ± 7.40
						T2DM	9	57.67 ± 4.61
						Healthy control	8	57.13 ± 2.80
Zhang [32]	2022	China	Cohort study	The Microvascular Complications Group of the Chinese Diabetes Society criteria	Metagenomic sequencing	DN	12	61.67 ± 8.75
						T2DM	12	57.08 ± 8.59
						Healthy control	14	58.86 ± 7.36
Lu [35]	2023	China	Cross-sectional study	Renal puncture pathological examination criteria	16S rRNA gene sequencing	DN	35	54.09 ± 6.39
						DM	40	58.83 ± 3.71
						Healthy control	40	54.44 ± 7.21

Table 1 (continued)

First author	Year	Country	Study design	Definition of DN	Maior Microbiome Identification Method	Group	Patients, *n*	Age, years
Ji [33]	2023	South Korea	Cross-sectional study	Renal puncture pathological examination criteria	Metagenomic sequencing	DMN	15	56.8 ± 11.1
						Healthy control	22	51.8 ± 9.6
Fan [36]	2023	China	Cohort study	the 1999 WHO criteria	16S rRNA gene sequencing	DN	41	58.0 (49.5–62.5)
						T2DM without DN	49	51.0 (45.0–58.5)
						Healthy control	42	52.5 (47.0–56.3)
Huo [34]	2023	China	Cross-sectional study	The Microvascular Complications Group of the Chinese Diabetes Society criteria	16S rRNA gene sequencing	T2DM patients with microalbuminuria	26	52.92 ± 9.19
						T2DM	26	53.65 ± 9.22
						Healthy control	15	48.73 ± 7.04

DN group exhibited considerable increases in the following genera: *Bacteroides*, *Bifidobacterium*, *Prevotella*, *Lachnoclostridium*, *Alistipes*, *Faecalibacterium*, *Ruminococcus*, *Peptostreptococcus*, *Megasphaera*, *Subdoligranulum*, *Lactobacillus*, *Enterococcus*, *Coprobacillus*, *Blautia*, *Anaerococcus*, *Fusicatenibacter*, *Solobacterium*, *Lachnospiraceae*, *Escherichia*, *Shigella*, *Klebsiella*, *Slackia*, *Rothia*, and *Eisenbergiella* [25–28, 30, 31, 33, 34]. Conversely, the DN group displayed notable reductions in the following genera: *Prevotella*, *Alloprevotella*, *Lachnoclostridium*, *Mitsuokella*, *Faecalibacterium*, *Clostridium*, *Megasphaera*, *Acidaminococcus*, *Eubacterium*, *Lactobacillus*, *Bacillus*, *Tyzzerella*, *Blautia*, *Roseburia*, *Romboutsia*, *Coprococcus*, *Turicibacter*, *Olsenella*, *Anaerotruncus*, *Sutterella*, *Gemmiger*, *Fusobacterium*, *Flavonifractor*, *Fusicatenibacter*, and *Trichospira* [25–27, 29–31, 33, 34]. Notably, six genera, *Prevotella*, *Lachnoclostridium*, *Faecalibacterium*, *Megasphaera*, *Lactobacillus*, and *Blautia*, exhibited contrasting changes in abundance across various studies [25, 26, 29–31, 33, 34]. Five studies investigated changes in number at the species or genus subgroup level. The genera *Prevotella MSX73*, *Bacteroides stercoris*, *Bacteroides stercoris CAG_120*, *Bacteroides caccae*, *Prevotella_6*, *Odoribacter splanchnicus*, *Tannerella* sp. *CAG_51*, *Alistipes ihumii*, *Alistipes onderdonkii*, *Alistipes shahii*, *Alistipes Communis*, *B. intestinalis*, *Clostridium-XIVa*, *Clostridium-XVIII*, *Ruminococcus_1*, *Parabacteroides* sp. *20_3*, and *Ruminococcus* sp. *JE7A12* were significantly increased in DN patients [31–35]. The obviously decreased genera or species included the genus *Prevotella copri*, species *Clostridium* sp. *CAG_768*, species *Eubacterium* sp. *AF22_9*, species *Clostridium* sp. *CAG_715*, species *Clostridium* sp.*26_22*, genus *Roseburia intestinalis*, species *Roseburia* sp. *AM23_20*, genus *Coprococcus_3*, genus *Bacteroides plebeius CAG_211*, genus *Intestinibacter*, genus *Eligens_group*, genus *Ruminum_group*, genus *Lachnospiraceae_NC2004_group*, genus *Enterobacter* and genus *Fusobacterium varium* [31, 33, 34]. It is found that there are many inconsistencies in GM in different studies. For example, it is found that there are inconsistencies in Lachnospiraceae and Lactobacillaceae variations in different studies. Table 2 presents a compilation of the gut microorganism categories at the six levels exhibiting notable variances across the included research populations from diverse regions exhibiting varying dietary patterns, leading to disparities in GM species and abundance. Western dietary patterns are characterized by high calorie content, rich in animal protein, saturated fats, simple sugars, and ultra-processed foods, and low in fiber, fruits, and vegetables. Compared to other dietary patterns, the Western diet was associated with a significant reduction in gut microbiota diversity, with a shift in gut characteristics toward Bacteroides. Other enriched bacteria genera include Ruminococcus, Faecalis, Bifidobacterium, allocladobacterium, Brautella, and Jelia [36]. To investigate the variations in the GM among DN populations across different regions, we compiled abundance data on the GM in various countries (Supplementary Table 1).

Risk of bias assessment

The studies' quality was evaluated with the RoBANS tool (Supplementary Table 2). There was no indication of exposure measurement bias in the included studies, and

Table 2 Summary of representative taxa in diabetic nephropathy (DN) patients compared to healthy controls in the included observational studies

Phylum	Increase	Decrease	Class	Increase	Decrease	Order	Increase	Decrease	Family	Increase	Decrease	Genus	Increase	Decrease	Species or Genus Subgroups	Increase	Decrease
Bacteroidetes	Chen 2021					Betaproteobacteriales	Du 2021		Bacteroidaceae			Bacteroides	Chen 2021		Bacteroides stercoris	Zhang 2022	
													Zhang 2022		Bacteroides stercoris CAG_120	Zhang 2022	
															Bacteroides plebeius CAG_211		Zhang 2022
															Bacteroides caccae	Fan 2023	
						Bifidobacteriales	Du 2021					Bifidobacterium	Chen 2021				
									Prevotellaceae			Prevotella	Chen 2021	Tao 2019	Prevotella stercorea		
														Du 2021	Prevotella copri		Zhang 2022
														Zhang 2022	Prevotella MSX73	Zhang 2022	
															Prevotella_6	Huo 2023	
												Alloprevotella		Yang2022			
									Odoribacteraceae			Odoribacter			Odoribacter splanchnicus	Ji 2023	
									Tannerellaceae	Du 2021		Parabacteroides			Tannerella sp. CAG_51	Zhang 2022	
															Parabacteroides sp. 20_3	Zhang 2022	
									Barnesiellaceae	Zhang 2022							
												Lachnoclostridium	Chen 2021	Du 2021			
						Chitinophagales		Du 2021	Chitinophagaceae		Du 2021	Alistipes	Chen 2021		Alistipes ihumii	Zhang 2022	
															A. onderdonkii	Ji 2023	
															A. shahii	Ji 2023	
															A. communis	Ji 2023	
												Mitsuokella		Du 2021			

Table 2 (continued)

Phylum	Increase	Decrease	Class	Increase	Decrease	Order	Increase	Decrease	Family	Increase	Decrease	Genus	Increase	Decrease	Species or Genus Subgroups	Increase	Decrease
															Intestinibacter		Zhang 2022
															B. intestinalis	Ji 2023	
Firmicutes		Bao 2019	Negativicutes	Du 2021					Ruminococcaceae	Winther 2020		Faecalibacterium	Chen 2021	Bao 2019	FaecalibacteriumPrausnitsi		
		Tao 2019												Huo 2023	Ruminococcus sp. JE7A12	Ji 2023	
		Zhang 2022	Clostridia	Du 2021		Clostridiales	Winther 2020	Du 2021				Ruminococcus	Chen 2021		Ruminococcus bromi.		
		Winther 2020										Clostridium		Zhang 2022	Clostridium sp. CAG_768,		Zhang 2022
															Clostridium sp. CAG_715		Zhang 2022
															Clostridiumsp.26_22		Zhang 2022
															Clostridium-XIVa	Lu 2023	
															Clostridium-XVIII	Lu 2023	
												Peptostreptococcus	Huo 2023				
															Ruminococcus_1	Huo 2023	
												megasphaera	Bao 2019	Du 2021			
														Yang2022			
												Subdoligranulum	Chen 2021				
												Acidaminococcus		Du 2021			
												Eubacterium		Zhang 2022	Eubacterium sp. AF22_9		Zhang 2022
															eligens_group		Huo 2023
															ruminantium_group		Huo 2023

Table 2 (continued)

Phylum	Increase	Decrease	Class	Increase	Decrease	Order	Increase	Decrease	Family	Increase	Decrease	Genus	Increase	Decrease	Species or Genus Subgroups	Increase	Decrease
			Bacilli	Du 2021		Lacto-bacillales	Du 2021		Lactobacil-laceae	Du 2021	Bao 2019	Lactoba-cillus	Bao 2019	Du 2021			
													Chen 2021				
												Bacillus		Lu 2023			
												Tyzzerella		Du 2021			
									Streptococ-cus			Entero-coccus	Yang2022				
									Oscillo-spiraceae			Oscil-libacter					
												Coproba-cillus	Bao 2019				
									Lachno-spiraceae	Winther 2020	Bao 2019	Blautia	Chen 2021	Yang2022	Blautia spp		
											Du 2021	Roseburia		Bao 2019	Roseburia spp		
											Zhang 2022			Du 2021	Roseburia intestinalis		Zhang 2022
														Zhang 2022	Roseburia sp. AM23_20		Zhang 2022
														Huo 2023			
												Lachno-spira			Lachno-spiraceae_ NC2004_ group		Huo 2023
												Rom-boutsia		Zhang 2022			
												laclno-spirg					
												Coproc-occus		Bao 2019	Coprococ-cus_3		Huo 2023
														Yang2022			
														Huo 2023			
												Turicibac-ter		Bao 2019			
									Peptoniphi-laceae			Anaero-coccus	Bao 2019				
									Streptococ-caceae	Du 2021		Lactococ-cus					

Table 2 (continued)

Phylum	Increase	Decrease	Class	Increase	Decrease	Order	Increase	Decrease	Family	Increase	Decrease	Genus	Increase	Decrease	Species or Genus Subgroups	Increase	Decrease
						Selenomonadales	Du 2021										
									Christensenellaceae	Lu 2023							
												Fusicatenibacter	Huo 2023				
									Erysipelotrichaceae	Winther 2020		Solobacterium	Winther 2020				
												lachnospiraceae	Bao 2019				
									Veillonellaceae	Du 2021							
												Olsenella		Du 2021			
Tenericutes												Anaerotruncus		Winther 2020			
Proteobacteria	Tao 2019		Alphaproteobacteria		Du 2021	Rhizobiales		Du 2021	Enterobacteriaceae			Escherichia	Tao 2019				
						Xanthomonadales		Du 2021					Chen 2021				
													Yang2022				
												Shigella	Chen 2021				
												Klebsiella	Chen 2021				
									Pasteurellaceae			Haemophilus					
									Burkholderiaceae	Du 2021							
												Sutterella		Du 2021			
						Hyphomicrobiales			Hyphomicrobiaceae			Gemmiger		Lu 2023			
			Gammaproteobacteria			Enterobacteriaceae			Enterobacteriaceae			Enterobacter			Enterobacter		Lu 2023

Table 2 (continued)

Phylum	Increase	Decrease	Class	Increase	Decrease	Order	Increase	Decrease	Family	Increase	Decrease	Genus	Increase	Decrease	Species or Genus Subgroups	Increase	Decrease
Actinobacteria	Du 2021		Actinobacteria	Du 2021					Bifidobacteriaceae	Du 2021							
	Yang2022		Coriobacteriia	Du 2021		Coriobacteriales	Du 2021		Coriobacteriaceae			Slackia	Bao 2019				
									Micrococcaceae			Rothia	Bao 2019				
									Atopobiaceae	Du 2021							
												Eisenbergiella	Lu 2023				
Fusobacteria	Chen 2021											Fusobacterium		Zhang 2022	Fusobacterium varium		Zhang 2022
												Flavonifractor		Lu 2023			
												Fusicatenibacter		Huo 2023			
Cyanobacteria		Bao 2019															
Flavobacteria									Rhodanobacteraceae		Du 2021						
Basidiomycota			Blastomycetes			Cryptococcaceae			Cryptococcaceae			Trichospira		Lu 2023			

they provided comprehensive outcome data. Out of the five studies, participant selection was deemed to carry a high risk of bias, while confounding variables were addressed in four studies. Furthermore, outcome blinding risk was not evaluated in 11 of the studies.

Selection of IVs related to GM

A total of 2744 SNPS in intestinal flora were examined for quality (Supplementary Table 3). After a quality check was conducted using LD effects [37] and the palindromic sequence, 1479 SNPs were identified as IVs linked to 211 GM taxa for DN (P < 5(P < a). Please mention Supplementary Table 4 for essential information regarding the identified IVs (Supplementary Table 4).

Results of MR analysis at 5 levels from the MiBioGen consortium (locus-wide significance, $P < 1 \times 10^{-5}$)

We found the predicted relative number of genes for 1 phylum, 2 classes, 1 order, 1 family and 8 genera. Since three of the genes are unknown, we excluded them. Among the remaining 1 phylum, 2 classes, 1 order, 1 family and 5 genera, 95 SNPs agreed with the quality inspection and were subjected to IV ($P < 1 \times 10^{-5}$) (Supplementary Table 5). The results of the MR analysis of the causal relationships between the 211 GM taxa and DN are shown in Supplementary Tables 6 and 7. The IVW results indicated that genetic increases in the genus *Dialister* (OR, 0.484; 95% CI, 0.317 d DN are shownidentifiphylum *Proteobacteria* (OR, 0.439; 95% CI, 0.272–0.710; $P = 7.7e-04$) and class *Bacilli* (OR, 0.710; 95% CI, 0.532–0.949; $P = 0.021$) in the host genetics-driven region had a protective effect on DN risk. The MR estimates of IVW indicated that the genes *Lachnospiraceae_UCG_008* (OR, 1.421; 95% CI, 1.045–1.932; $P = 2.5e-02$), *Terrisporobacter* (OR, 1.972; 95% CI, 1.204 − 3.229; $P = 7.0e-03$), *Sellimonas* (OR, 1.197; 95% CI, 1.013–1.415; $P = 0.035$), *Verrucomicrobia* (OR, 1.463; 95% CI, 1.124–1.903; $P = 0.010$), *Akkermansia* (OR, 1.463; 95% CI, 1.124–1.903; $P = 0.010$), *Verrucomicrobiaceae* (OR, 1.463; 95% CI, 1.124–1.903; $P = 0.010$), and *Verrucomicrobiales* (OR, 1.463; 95% CI, 1.124–903; $P = 0.010$) were risk factors for DN (Fig. 3). For example, Lachnospiraceae_UCG_008 found in the analysis of MR that by selecting instrumental variables from exposure data (SNP strongly related to exposure factors was selected as instrumental variables through correlation analysis, and the filtering condition was p value < 5e − 08), we found that nSNP was strongly correlated with GM and DN. And OR > 1, but Lachnospiraceae UCG010 did not show strong correlation. Details can be found in the supplementary document. After Bonferroni correction, the IVW analysis results for the protective impact of the phylum *Proteobacteria* and genus *Dialister* and the harmful impact of the genus *Akkermansia,* family *Verrucomicrobiaceae*, order *Verrucomicrobia*, and class *Verrucomicrobiae* remained significant (adjusted $P = 5 \times 10^{-3}$).

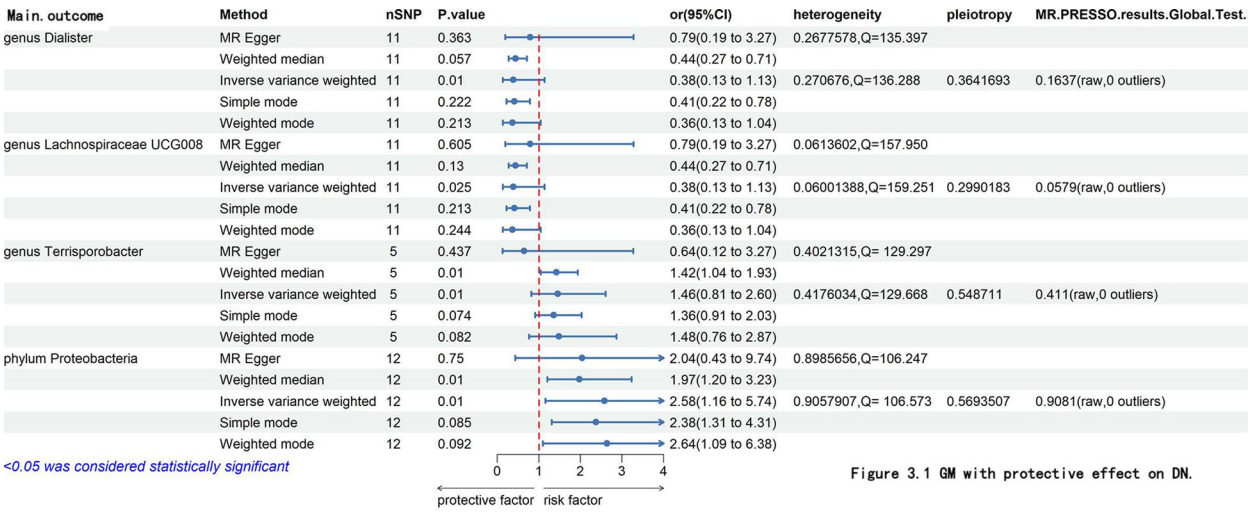
Sensitivity analysis

We sustained the impact of MR on the DNs of 1 phylum, 2 classes, 1 order, 1 family, and 5 genera. No horizontal pleiotropy was detected in the genera *Dialister* ($P = 0.874$), *Proteobacteria* ($P = 0.412$), *Lachnospiraceae_UCG_008* ($P = 0.355$), *Terrisporobacter* ($P = 0.966$), *Bacilli* ($P = 0.860$), *Sellimonas* ($P = 0.578$), *Verrucomicrobiae* ($P = 0.767$), *Akkermansia* ($P = 0.764$), *Verrucomicrobiaceae* ($P = 0.764$), or *Verrucomicrobiales* ($P = 0.767$) for DN. No heterogeneity was found in genus *Dialister* (IVW: $P = 0.873$; MR Egger: $P = 0.814$), phylum *Proteobacteria* (IVW: $P = 0.406$; MR Egger: $P = 0.383$), genus *Lachnospiraceae_UCG_008* (IVW: $P = 0.973$; MR Egger: $P = 0.984$), genus *Terrisporobacter* (IVW: $P = 0.304$; MR Egger: $P = 0.184$), class *Bacilli*(IVW: $P = 0.628$; MR Egger: $P = 0.530$), genus *Sellimonas* (IVW: $P = 0.977$; MR Egger: $P = 0.980$), class *Verrucomicrobiae* (IVW: $P = 0.453$; MR Egger: $P = 0.360$), genus *Akkermansia* (IVW: $P = 0.452$; MR Egger: $P = 0.359$), family *Verrucomicrobiaceae* (IVW: $P = 0.452$; MR Egger: $P = 0.359$), and order *Verrucomicrobiales* (IVW: $P = 0.453$; MR Egger: $P = 0.360$) for DN (Supplementary Table 8).

Statistically significant MR findings were additionally supported by MR-PRESSO to verify the precision of MR–Egger analysis. No horizontal pleiotropy was demonstrated for the genera *Dialister* ($P = 0.431$), the phylum *Proteobacteria* ($P = 0.317$), the genus *Lachnospiraceae_UCG_008* ($P = 0.982$), the genus *Terrisporobacter* ($P = 0.205$), the class *Bacilli* ($P = 0.860$), the genus *Sellimonas* ($P = 0.578$), the class *Verrucomicrobiae* ($P = 0.767$), the genus *Akkermansia* ($P = 0.764$), the family *Verrucomicrobiaceae* ($P = 0.764$), or the order *Verrucomicrobiales* ($P = 0.767$) (Supplementary Table 9). The leave-one-out results further explicited the lustiness of the data (Fig. 4). There was no heterogeneity or pleiotropy in the IVW results, and the findings are reliable. Therefore, the genera *Dialister* and *Proteobacteria*, the genus *Lachnospiraceae_UCG_008*, the genus *Terrisporobacter*, the class *Bacilli*, *the* genus *Sellimonas*, the class *Verrucomicrobiae*, the genus *Akkermansia*, the family *Verrucomicrobiaceae*, and the order *Verrucomicrobiales* were causally related to DN. The forest plot, funnel plot, and scatter plot all confirmed the reliability of the results. (Figs. 5, 6, and 7).

Reverse MR analysis

No significant causal relationship was found in the reverse MR analysis between DN and any of the five GMs based on the results (Supplementary Tables 10 and 11).



Main. outcome	Method	nSNP	P.value	or(95%CI)	heterogeneity	pleiotropy	MR.PRESSO.results.Global.Test.
genus Dialister	MR Egger	11	0.363	0.79(0.19 to 3.27)	0.2677578,Q=135.397		
	Weighted median	11	0.057	0.44(0.27 to 0.71)			
	Inverse variance weighted	11	0.01	0.38(0.13 to 1.13)	0.270676,Q=136.288	0.3641693	0.1637(raw,0 outliers)
	Simple mode	11	0.222	0.41(0.22 to 0.78)			
	Weighted mode	11	0.213	0.36(0.13 to 1.04)			
genus Lachnospiraceae UCG008	MR Egger	11	0.605	0.79(0.19 to 3.27)	0.0613602,Q=157.950		
	Weighted median	11	0.13	0.44(0.27 to 0.71)			
	Inverse variance weighted	11	0.025	0.38(0.13 to 1.13)	0.06001388,Q=159.251	0.2990183	0.0579(raw,0 outliers)
	Simple mode	11	0.213	0.41(0.22 to 0.78)			
	Weighted mode	11	0.244	0.36(0.13 to 1.04)			
genus Terrisporobacter	MR Egger	5	0.437	0.64(0.12 to 3.27)	0.4021315,Q= 129.297		
	Weighted median	5	0.01	1.42(1.04 to 1.93)			
	Inverse variance weighted	5	0.01	1.46(0.81 to 2.60)	0.4176034,Q=129.668	0.548711	0.411(raw,0 outliers)
	Simple mode	5	0.074	1.36(0.91 to 2.03)			
	Weighted mode	5	0.082	1.48(0.76 to 2.87)			
phylum Proteobacteria	MR Egger	12	0.75	2.04(0.43 to 9.74)	0.8985656,Q=106.247		
	Weighted median	12	0.01	1.97(1.20 to 3.23)			
	Inverse variance weighted	12	0.01	2.58(1.16 to 5.74)	0.9057907,Q= 106.573	0.5693507	0.9081(raw,0 outliers)
	Simple mode	12	0.085	2.38(1.31 to 4.31)			
	Weighted mode	12	0.092	2.64(1.09 to 6.38)			

Figure 3.1 GM with protective effect on DN.

Main. outcome	Method	nSNP	P.value	or(95%CI)	heterogeneity	pleiotropy	MR.PRESSO.results.Global.Test.P
class Bacilli	MR Egger	10	0.301	0.67(0.33 to 1.36)	0.2677578,Q=135.397		
	Weighted median	10	0.105	0.72(0.49 to 1.07)			
	Inverse variance weighted	10	0.021	0.71(0.53 to 0.95)	0.270676,Q=136.288	0.3641693	0.1637(raw,0 outliers)
	Simple mode	10	0.388	0.75(0.41 to 1.39)			
	Weighted mode	10	0.231	0.71(0.42 to 1.20)			
genus Sellimonas	MR Egger	6	0.369	1.55(0.66 to 3.60)	0.0613602,Q=157.950		
	Weighted median	6	0.058	1.22(0.99 to 1.49)			
	Inverse variance weighted	6	0.035	1.20(1.01 to 1.42)	0.06001388,Q=159.251	0.2990183	0.0579(raw,0 outliers)
	Simple mode	6	0.213	1.23(0.92 to 1.65)			
	Weighted mode	6	0.198	1.24(0.93 to 1.65)			
class Verrucomicrobiae	MR Egger	9	0.583	1.29(0.54 to 3.04)	0.4021315,Q= 129.297		
	Weighted median	9	0.086	1.35(0.96 to 1.90)			
	Inverse variance weighted	9	<0.01	1.46(1.12 to 1.90)	0.4176034,Q=129.668	0.548711	0.411(raw,0 outliers)
	Simple mode	9	0.201	1.43(0.86 to 2.37)			
	Weighted mode	9	0.202	1.39(0.88 to 2.20)			
genus Akkermansia	MR Egger	9	0.586	1.28(0.54 to 3.04)	0.8985656,Q=106.247		
	Weighted median	9	0.098	1.35(0.95 to 1.93)			
	Inverse variance weighted	9	<0.01	1.46(1.12 to 1.90)	0.9057907,Q= 106.573	0.5693507	0.9081(raw,0 outliers)
	Simple mode	9	0.185	1.43(0.88 to 2.33)			
	Weighted mode	9	0.183	1.39(0.89 to 2.15)			
family Verrucomicrobiaceae	MR Egger	9	0.586	1.28(0.54 to 3.04)	0.0613602,Q=157.950		
	Weighted median	9	0.108	1.35(0.94 to 1.95)			
	Inverse variance weighted	9	<0.01	1.46(1.12 to 1.90)	0.06001388,Q=159.251	0.2990183	0.0579(raw,0 outliers)
	Simple mode	9	0.22	1.43(0.84 to 2.43)			
	Weighted mode	9	0.223	1.39(0.85 to 2.26)			
order Verrucomicrobiales	MR Egger	9	0.583	1.29(0.54 to 3.04)	0.4021315,Q= 129.297		
	Weighted median	9	0.097	1.35(0.95 to 1.93)			
	Inverse variance weighted	9	<0.01	1.46(1.12 to 1.90)	0.4176034,Q=129.668	0.548711	0.411(raw,0 outliers)
	Simple mode	9	0.193	1.43(0.87 to 2.34)			
	Weighted mode	9	0.217	1.39(0.86 to 2.24)			

Fig. 3 Cause and effect analysis of GM and DN (locus-wide significance, $P < 1 \times 10^{-5}$). MR results of the GM with respect to the DN

The Cochran's Q test also indicated no significant heterogeneity in the IVs among patients with DN (Supplementary Table 12). MR–Egger regression in the reverse MR analysis did not yield significant results for horizontal pleiotropy (Supplementary Table 13).

Discussion

The intricate ecosystem of the GM is essential for immunity and metabolism. Various studies have shown that DN is linked to alterations in the GM [38]. This shift can potentially result in disruptions in lipid and glucose metabolism, inflammation, and immune function [39]. Moreover, external factors such as diet and medication can worsen imbalances in the GM, ultimately contributing to the progression of DN [40–43]. This finding underscores the connection between the GM and the development of DN.

Several observational studies have yielded varied and conflicting results, as outlined in Table 2. The notable disparities in results could stem from the differences in

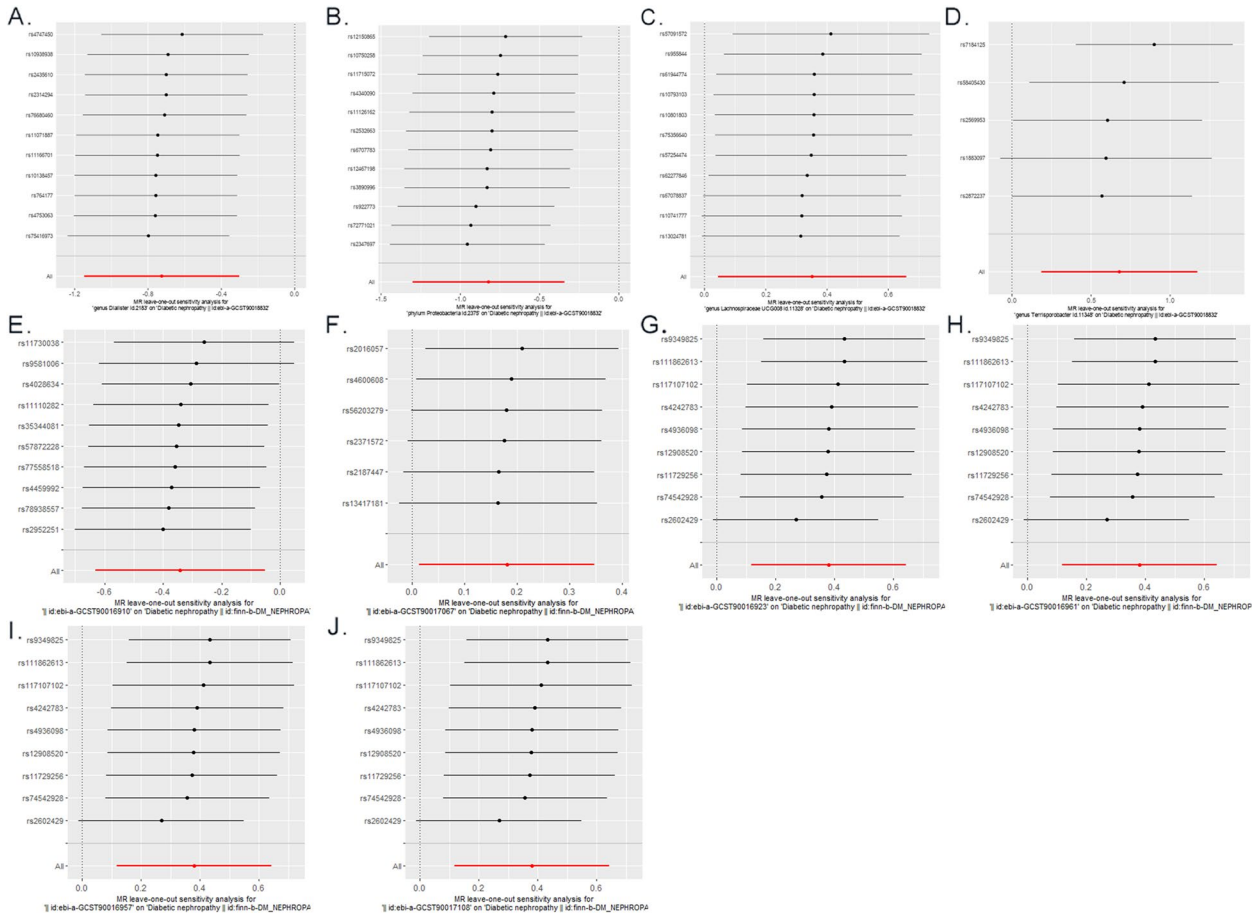


Fig. 4 Leave-one-out results for the GM and DN. **A** Leave-one-out analysis of the genus Dialister on EBI DN. **B** Leave-one-out analysis of the phylum Proteobacteria in EBI DN. **C** Leave-one-out analysis of the effect of the genus Lachnospiraceae_UCG_008 on EBI DN. **D** Leaf-one-out analysis of the genus Terrisporobacter on EBI DN. **E** Leave-one-out analysis of the class Bacilli on FinnGen DN. **F** Leave-one-out analysis of the genus Sellimonas on FinnGen DN. **G** Leave-one-out analysis of the class Verrucomicrobiae on FinnGen DN. **H** Leave-one-out analysis of the genus Akkermansia id.4037 on FinnGen DN. **I** Leave-one-out analysis of the family Verrucomicrobiaceae on FinnGen DN. **J** Leave-one-out analysis for the order Verrucomicrobiales on FinnGen DN

sample sizes, grouping criteria, and methods for identifying microbiological entities used in various observational studies. It is imperative to highlight that populations in distinct regions exhibit diverse dietary habits, which may influence the inconclusive results [41]. Subsequent studies should focus on developing more effective approaches for comparing the composition of the GM among individuals hailing from different geographical areas. Research advancements in the "gut-kidney" axis have revealed numerous complicating factors (e.g., dietary patterns), making it challenging to examine the connection between the GM and DN through observational studies.

To address this, we employed MR analysis and publicly available EBI data and FinnGen data to evaluate the association between the GM and DN from the gene. The analysis verified the impact of GM taxa on modifying susceptibility to DN.

In contrast to previous studies on GM and DN, due to the inclusion of data from the FinnGen consortium in our study, we identified one phylum, one class, one order, and one genus that connected with a reduced DN risk. One class, one family, and three genera are related to elevated DN risk. These discoveries have potential for identifying novel biomarkers for future DN studies. Concomitantly, our results offer innovative avenues for DN prevention and therapeutic strategies. Nonetheless, insufficient renal research evidence exists to validate the exact underlying mechanism involved.

More than 90% of the GM contained 2 GM phyla, namely, the phylum *Proteobacteria* and the phylum *Firmicutes* [44]. The phylum *Proteobacteria* is a gram-negative GM [45]. Vatanen T et al. conducted an analysis on a total of 10,913 metagenomes obtained from stool samples of 783 predominantly Caucasian non-Hispanic children.

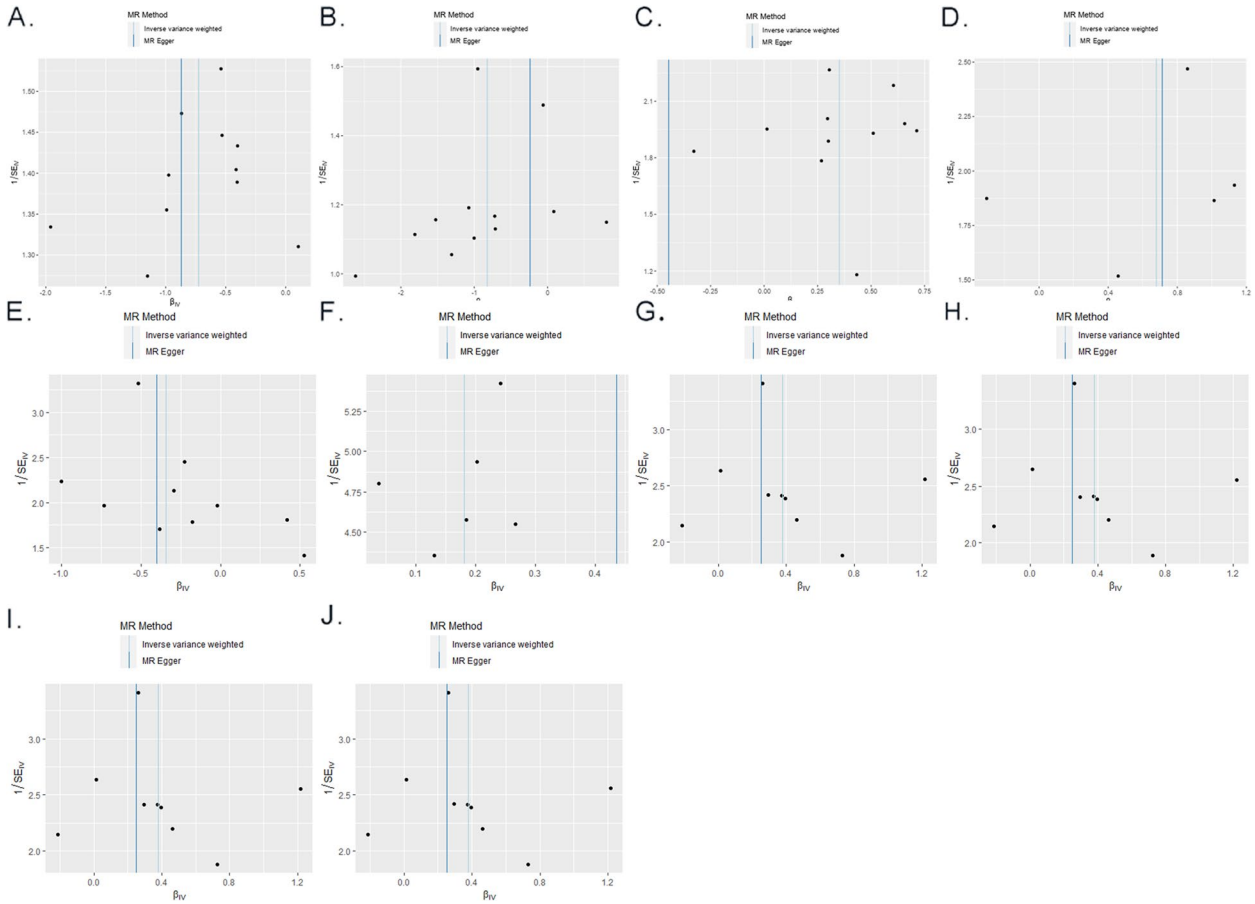


Fig. 5 Scatter plot of the GM and DN. **A** Scatter plot of the effect of the genus Dialister on EBI DN. **B** Scatter plot of the effect of the phylum Proteobacteria on EBI DN. **C** Scatter plot of the effect of the genus Lachnospiraceae_UCG_008 on EBI DN. **D** Scatter plot of the effect of the genus Terrisporobacter on EBI DN. **E** Scatter plot of the class Bacilli on FinnGen DN. **F** Scatter plot of the genus Sellimonas on FinnGen DN. **G** Scatter plot of the class Verrucomicrobiae on FinnGen DN. **H** Scatter plot of the effect of the genus Akkermansia id.4037 on FinnGen DN. **I** Scatter plot of the family Verrucomicrobiaceae on FinnGen DN. **J** Scatter plot of the order Verrucomicrobiales on FinnGen DN

Their findings indicate that the presence of the phylum *Proteobacteria* is essential for protecting short-chain fatty acids, particularly in the context of early-onset type 1 diabetes in humans [46]. Bastos et al. [47] revealed that fecal microbiota transplantation (FMT) increased the abundance of *Proteobacteria* and minimized the risk of DN by reducing albuminuria and tumor necrosis factor. Transgenic dysbiosis within the gut can result in disruptions in both glucose and lipid metabolism, along with the onset of immune and neurological disorders [12, 13, 48]. Nevertheless, the role of GM dysbiosis in the progression of DN is still unclear. Candela et al. [49] reported that the levels of *Proteobacteria* were lower in fecal bacteria samples obtained from 40 obese patients diagnosed with type 2 diabetes than in those obtained from the control group. DN exhibited similar correlations with diabetes. Our MR findings are consistent with those of the study by Candela et al. After the Bonferroni correction, the beneficial effect of the phylum *Proteobacteria* on DN increased.

Interestingly, Cai et al. [50] demonstrated that an increase in *the abundance of the* phylum *Proteobacteria* is associated with increased levels of serum creatinine, urinary albumin excretion, and inflammatory factors, indicating that a decrease in inflammation is a critical mechanism through which the phylum *Proteobacteria* safeguards renal function in DN patients. Additionally, *Proteobacteria* are also closely associated with aging [51]. Scheithauer et al. showed that an imbalance in the GM is often caused by a chronic increase in *Proteobacteria* [48]. These results are also inconsistent with our MR study.

The disparities in the results can be attributed to several factors. First, our study, along with the work of Candela et al. focused on people, whereas Cai et al. conducted their research on mice, which unavoidably led to

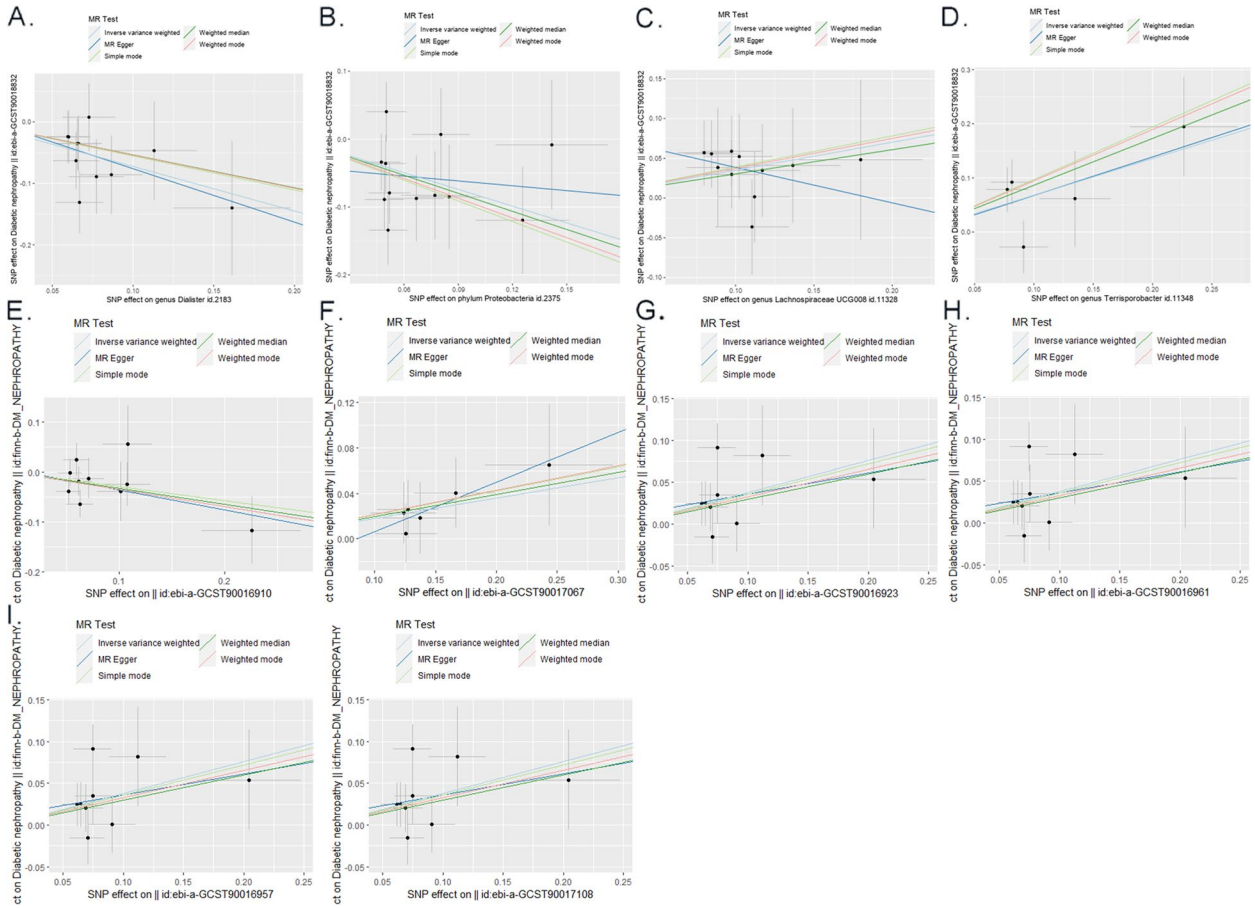


Fig. 6 The forest plot of GM and DN. **A** Forest plot of the effect of the genus Dialister on EBI DN. **B** Forest plot of the effect of the phylum Proteobacteria on EBI DN. **C** Forest plot of the effect of the genus Lachnospiraceae_UCG_008 on EBI DN. **D** Forest plot of the effect of the genus Terrisporobacter on EBI DN. **E** Forest plot of the class Bacilli on FinnGen DN. **F** Forest plot of the genus Sellimonas on FinnGen DN. **G** Forest plot of the class Verrucomicrobiae on FinnGen DN. **H** Forest plot of the effect of the genus Akkermansia id.4037 on FinnGen DN. **I** Forest plot of the family Verrucomicrobiaceae on FinnGen DN. **J** Forest plot of the order Verrucomicrobiales on FinnGen DN

variations in GM abundance. Moreover, analyzing GM at the genus level encompasses numerous taxa. The complex interactions among different taxa at more refined levels, such as phylum and genus interactions, may have influenced the observations of their influence.

According to the findings of Scheithauer et al. [48], the presence of diabetes-associated GM disrupts the level of inflammation, thereby impacting the progression of DN. Cai et al. [50] reported that an increase in the abundance of the phylum *Proteobacteria* is associated with lower levels of kidney inflammatory factors, indicating that a reduction in inflammation is a critical mechanism through which renal function is safeguarded, which is similar to our results. However, research conducted on patients with early-stage DN [52] has reported an increase in the abundance of the phylum *Proteobacteria*, which worsens the chronic low-grade inflammatory state. This observation might be linked to the different stages of DN, emphasizing the necessity for further exploration of DN at various stages in subsequent investigations. Cai et al. [48] also emphasized the impact of the phylum *Proteobacteria* on the development of DN by stimulating macrophage activation in the immune system, especially in innate immunity. Hence, we postulate that *proteobacteria* have the potential to mitigate inflammation-induced harm and enhance renal immunity via the gut-kidney pathway, thus influencing the progression of DN.

Our findings revealed that two taxa of the GM, genus *Dialister* and *Lachnospiraceae_UCG_008*, belong to the phylum *Firmicutes*. Genus *Dialister* is a protector in DN, and the defensive effect of the genus Dialister on DN remained prominent after Bonferroni correction. Genus *Lachnospiraceae_UCG_008* is a high risk factor for DN. Genus *Dialister* metabolizes carbohydrates, produces acetic acid and butyric acid, and produces histamine and catalase [53]. A systematic review by Letchumanan

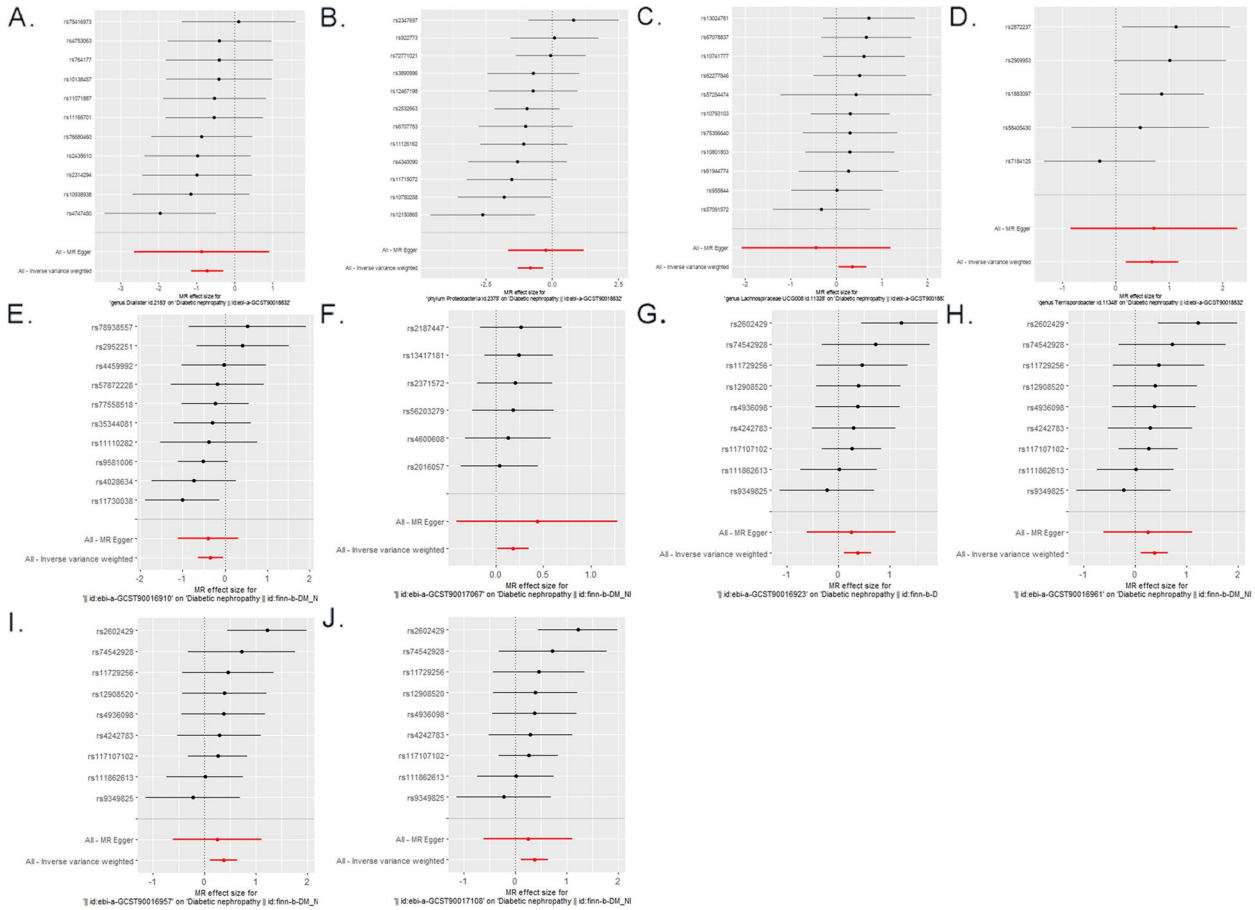


Fig. 7 Funnel plot of the GM and DN. **A** Funnel plot of the genus Dialister on EBI DN. **B** Funnel plot of the effect of the phylum Proteobacteria on EBI DN. **C** Funnel plot of the effect of the genus Lachnospiraceae_UCG_008 on EBI DN. **D** Funnel plot of the effect of the genus Terrisporobacter on EBI DN. **E** Funnel plot of the effect of the class Bacilli on FinnGen DN. **F** Funnel plot of the genus Sellimonas on FinnGen DN. **G** Funnel plot of the class Verrucomicrobiae on FinnGen DN. **H** Funnel plot of the genus Akkermansia id.4037 on FinnGen DN. **I** Funnel plot of the family Verrucomicrobiaceae on FinnGen DN. **J** Funnel plot of the order Verrucomicrobiales on FinnGen DN

et al. [54] revealed that at the genus and species levels, the *Diallist* abundance decreased, while the *Lactobacillus* abundance increased in the type 2 diabetes group.

Quiroga et al. [55] assessed the impact of 12 weeks of training on the GM and inflammation among obese pediatric patients. It was observed that engaging in physical activity tended to enhance the presence of *Dialister*, resulting in an introduction to the microbiome comparable to that of a child who is in good health. This effect was achieved by suppressing obesity-related NLRP3. Byrd et al. [56] showed that increased *dialister* abundance was associated with improved overall survival, which was associated with immune genes in colorectal cancer patients.

Lachnospiraceae_UCG_008, as one of the subgroups of Lachnospiraceae, has been poorly researched in the literature. Zhu et al. [57] showed that in a mouse model of PCOS-IR, increased fasting insulin levels were correlated with increased inflammation, while *Lachnospiraceae UCG-008* conspicuously enhanced the release of provoked inflammatory indicators. Hence, additional investigations focusing on this topic are warranted to elucidate the underlying mechanisms and causal impacts on DN.

Despite the absence of specific findings regarding the genus *Dialister*, genus *Lachnospiraceae_UCG_008*, and DN, our hypothesis is that *Dialister* could enhance renal functionality, whereas *Lachnospiraceae_UCG_008* could hinder renal function during the progression of DN as a result of the immune response and inflammation.

The class *Bacilli* belongs to the phylum *Firmicutes.* Research on class *Bacilli* and DN is scarce, however, current research on the genus *Bacillus*, a subset of the class *Bacilli*, and DN has shown that the genus *Bacillus* possesses the ability to improve insulin activity, regulate lipid metabolism, and reduce inflammation in the kidney. These results coincide with our MR investigation, which

is inconsistent with the results of our literature review [29], suggesting that class *Bacilli* might be advantageous microbes with properties that protect the kidneys, but further study is needed [58, 59].

The genus *Akkermansia* belongs to *the* family *Verrucomicrobiaceae*, order *Verrucomicrobia*, class *Verrucomicrobiae*, and is a gram-negative bacterium. According to Vanessa Fernandes Rodrigues, who studied the order *Verrucomicrobia* and DM, it can be speculated that the genus *Akkermansia* can play a role in delaying the progression of DM, even DN [60], which is not consistent with our findings. After Bonferroni correction, the negative effects of the genus *Akkermansia*, family *Verrucomicrobiaceae*, order *Verrucomicrobia*, and class *Verrucomicrobiae* on DN were still notable. Current research shows that order *Verrucomicrobia* can improve the intestinal barrier [61], inflammation [62], immunity [63], and glucose and lipid levels [60, 64] and can be used as a probiotic to treat metabolic disorders such as DN [65]. The relationship between the genus *Akkermansi* and DN needs further research. There are few studies on the class *Verrucomicrobiae*, order *Verrucomicrobia*, family *Verrucomicrobiaceae*, genus *Akkermansia* and DN. The present IVW analysis did not support this observation, which may be attributed to the distinct group specificity of GM taxa for the FinnGen consortium [66].

The genus *Terrisporobacter* belongs to the gastric Streptococcus family [67] and is an acetone-producing bacterium [68]. The findings of this MR analysis concur with those of Ho et al. An investigation involving children diagnosed with type 1 diabetes revealed an elevated presence of *Terrisporobacter* in the placebo group [69]. Luo et al. [70] reported that *Terrisporobacter* exhibited a positive correlation with IL-1 but a negative correlation with IL-10. *Terrisporobacter* exhibited a greater abundance in the CP-H than in the lower-altitude pigs in a high-altitude hypoxic environment. This increased abundance of *Terrisporobacter* was found to contribute to inflammation, which is linked to the production of acetic acid.

The genus *Sellimonas* is a gram-positive and anaerobic bacterium from the family *Lachnospiraceae.* There has been minimal research conducted on the genera Sellimonas and DN. Studies have shown an inverse relationship between the abundance of the genus Sellimonas and the healthy plant-based diet index [71], which is consistent with our magnetic resonance study. This is associated with a decrease in favourable health-promoting GM characteristics. The genus Sellimonas can aid in reestablishing harmony in the gut and may serve as a probiotic in T2DM [72, 73]. This finding may imply that the kidney-related role of the genus *Sellimonas* in DN needs to be revealed through further studies.

Research has examined the gut-kidney axis as a possible mechanism underlying this cause-and-effect connection [74, 75]. Probiotics and prebiotics have demonstrated promise in improving renal deterioration in DM through the gut-kidney axis through significant alterations in typical renal indicators, including serum creatinine, serum urea nitrogen/urea, and microalbuminuria [76].

The GM can also improve inflammation and oxidative stress by affecting diet, thereby ameliorating kidney damage in DN patients [77]. Inflammation and oxidative stress lead to GM disorders and disruption of the gut barrier [78]. Pomegranin (PU) in pomegranate can improve DN kidney damage by increasing the concentration of caecal SCFAs, which suppresses inflammation and inhibits serum lipopolysaccharide (LPS) and diamine oxidase (DAO) levels [79]. Hong et al. found that oral administration of *Ruminococcus* verrucosa (R. gnavus) to DN mice resulted in increased expression of inflammatory factors such as inflammasome (NLRP3) and interleukin (IL)-6 and decreased expression of connexins such as claudin-1, occludin, and ZO-1, leading to increased levels of urea nitrogen (UN), creatinine (Cr), and urinary protein and aggravated kidney damage [80].

In DN, changes in the GM and its metabolites affect the progression of immunity and DN and lead to an increase in toxic metabolites, which further leads to the transport of the GM and its metabolites into the circulation, inducing local and systemic immunity [81]. The systemic induction of Th1 responses by *Bacteroides fragilis* can protect the kidney [82, 83]. However, the presence of *Escherichia coli-Shigella* species in the gut of patients with DN is elevated, resulting in the translocation of the GM. This translocation leads to immune system dysfunction, heightened susceptibility to infections, and kidney damage in DN patients [84].

Glycolipid metabolism can potentially affect the GM, leading to DN [85]. Dyslipidemia is a common complication of DN [86]. Shen et al. demonstrated that Astragalus membranaceus and Salvia miltiorrhiza have the potential to enhance DN through the 'gut-kidney axis'. *Lactobacillus murinus* was identified as the key bacteria involved and is linked to glycolipid metabolism, particularly sphingolipid metabolism and glycerophospholipid metabolism [87]. Dietary fiber supplemented with inulin-type fructans (ITFs) can protect the kidneys of db/db mice, and fecal microbiota transplantation (FMT) confirmed this effect. GM changes induced by ITF treatment lead to an enrichment of short-chain fatty acid-producing GM, thereby replenishing fecal and serum acetate concentrations and reducing glomerular injury and renal fibrosis [88].

The current research on the relationship between the GM and DN has potential clinical significance. Initially,

modifications in the GM can be utilized as an indication for the onset of DN, suggesting that the GM could be utilized for DN diagnosis. A practical prognostic evaluation carried out by Zhang et al. revealed noteworthy variances in fecal bacteria among DN individuals, T2DM individuals, and healthy persons [30], emphasizing significant disparities in the intestinal microbiota and its anticipated functions in DN and T2DM without causing kidney harm. The favourable bacteria recognized in the current MR research exhibit promising potential as diagnostic bacteria for the incidence and aftermath of DN in the future.

Additionally, changes in the GM are linked with numerous GM-associated clinical aspects, including lipid metabolic elements, immunity, inflammatory agents, and regulators of the gut-kidney axis [89–92]. Treatment of DN based on the GM is receiving increasing attention, with animal experiments showing success with FMT leading to significant improvements in DN. The potential of using FMT as a treatment for DN has sparked optimism [93]. Microbial agents such as probiotics have displayed therapeutic potential for DN [94, 95]. The GM identified in the study could serve as a valuable source for future microbial agent research.

Furthermore, specific drugs used in DN treatment, such as metformin, glucagon-like peptide-1 (GLP-1) receptor agonists, sodium-dependent glucose transporter-2 (SGLT-2) inhibitors, and traditional Chinese medicine (TCM), may influence the GM [94, 96]. Therefore, the impact of the GM on mediating DN treatment effects should not be overlooked.

In addition to therapeutic interventions targeting the gut-kidney axis, GM can also potentially apply for other microbiota and organ disease such as H. pylori -gastric. Their findings suggest that Helicobacter pylori (HP) infection may enhance the migratory potential of gastric cancer cells, and that these genes may be associated with both immunity and drug sensitivity in gastric cancer. In human subjects diagnosed with gastric cancer, the presence of HP within tumors may influence migration, immune response, and drug sensitivity [97].

Limitations

This study possesses numerous advantages. First, the existing examination of the link between GM and kidney disease has centered on the classification of the genus. However, this study provides a more elaborate understanding of GM taxa, investigating the impact of each category on DN at various levels, extending from the genus level to the phylum level. This foundational knowledge provides a basis for exploring the subsequent mechanisms by which specific bacterial strains affect DN and enhances the identification of novel biomarkers. Second, the utilization of the latest vast GWAS enables the acquisition and examination of genetic data in extensive distribution populations. MR can be used to eradicate any confusion and represents a novel approach for exploring the "gut-kidney axis."

There are numerous constraints to this study. One major obstacle in evaluating observational studies is the challenge of adjusting for potential confounders and other variables due to substantial heterogeneity among studies. The complexity of the populations included limited our capacity to conduct a more thorough quantitative systematic review of these studies. In addition, due to the lack of explicit confounding variables and selection of participants in some articles, patients who do not meet the inclusion criteria may be included in the process of participant inclusion, resulting in deviations in the study conclusions. Furthermore, our research encompassed a smaller range of population varieties in various geographic areas, and the diverse GM patterns influenced by dietary practices in different regions further complicate the interpretation of the summarized findings using MR. The potential confounding factors or biases in SNP selection of MR also lead to the limitations of the MR method itself. The GWAS data employed in the present MR originated from 24 cohorts in different nations. Compared with other previous MR studies on GM in other chronic diseases, we also used the GWAS database and included 211 GM [98].Variations in polymorphisms among human populations may yield disparate outcomes in GWAS results. Genetic diversity within each population could also impact the reliability of GWAS findings, potentially affecting their interpretability. In MR investigations, completely eliminating LDs can be challenging. Although conforming to the assumptions of MR and having IVs closely associated with GM, we cannot guarantee that the instrument will not undergo slight distortion. This study also encountered limitations in establishing a potential bidirectional link between the GM and DN, as the number of IVs available for reverse MR analysis was insufficient. Furthermore, the results could not be applied to other people, as the GWAS was conducted solely on individuals of European descent. The many stat fixes employed in the study were conservative and stringent, potentially overlooking GM taxa that may actually have a causal association with DN. Therefore, different test results were not considered, and the focus was on biological plausibility. Additionally, a previous study by Kurilshikovetal et al. reported no species-level investigations. Future research will explore the relationships between the GM and DN at the species level to significantly increase the sample size and provide stronger

clinical evidence for studying the gut-kidney axis. In the current MR analysis, the Bonferroni correction was employed as a multiple testing correction method. While this approach effectively controls type I errors, it has the potential to be overly cautious, leading to higher type II error rates [99]. Moreover, the stringent nature of the Bonferroni correction may eliminate results that could have significant implications.

Conclusion

The present review included 11 observational studies that met the inclusion and exclusion criteria. The abundance of 144 GM taxa significantly differed between DN patients and controls. We validated the cause-and-effect association between DN and GM, encompassing the phylum *Proteobacteria*, class *Bacilli*, class *Verrucomicrobiae*, order *Verrucomicrobia*, family *Verrucomicrobiaceae*, genus *Akkermansia*, *Dialister*, *Lachnospiraceae_UCG_008*, *Sellimonas* and *Terrisporobacter*. These bacterial types potentially serve as innovative indicators, providing insights into DN management and prophylaxis. We hope to further explore GM-targeted therapies or dietary interventions in future research. By intervening in GM, various clinical diseases such as endocrine diseases or cardiovascular diseases can be improved to a certain extent. and add references [100].

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-025-08755-4.

Additional file 1: Table S1. Summary of gut microbiota abundances in populations from different countries. Table S2. Quality assessment of included non-randomized studies based on RoBANS tool. Table S3. 2774 SNPs for the 211 gut microbiota taxa. Table S4. Instrumental variables used in MR analysis of the association between gut microbiota and DN. Table S5. SNPs comply with quality inspection between gut microbiota and DN. Table S6. Full results of MR analysis for the association between gut microbiota and DN form FinnGen. Table S7. Full results of MR analysis for the association between gut microbiota and DN form EBI. Table S8. The heterogeneity of gut microbiota instrumental variables. Table S9. Directional horizontal pleiotropy assessed by intercept term in MR-Egger analysis and MR-PRESSO of the association between gut microbiota and DN. Table S10. The reverse MR analysis between DN and GM. Table S11. Full results of MR analysis for the association between DN and gut microbiota. Table S12. The heterogeneity of DN instrumental variables. Table S13. Directional horizontal pleiotropy assessed by intercept term in MR-egger of the association and MR-PRESSO of the association between DN and gut microbiota.

Additional file 2.

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Authors' contributions
The study was designed by Z.H., L.W., and H.Y., W.Y., Z.X., D.B., W.Y., Z.X., and J.J. were responsible for the analysis of the information and preparation of the figures. H.Y. and W.Y. are the common first authors of this article. All authors played an active role in the careful revision of the article.

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Data availability
The research findings described in the study are available in the article/supplementary material. If you require further clarifications, feel free to directly reach out to the corresponding author.

Declarations

Ethics approval and consent to participate
Not required.

Consent for publication
Not required.

Competing interests
The authors declare that they have no competing interests.

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