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Causal relationship between gut microbiota and diabetic nephropathy: A bi-directional mendelian randomization study

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Abstract

In this study, we summarized the key findings and potential implications of association studies investigating the relationship between gut microbiota composition and risks for Diabetic nephropathy (DN). We used Mendelian randomization (MR) analysis to explore the relationship between gut microbiota and DN using two different publicly available DN databases. The results were also summarized using five mainstream MR analysis methods. We controlled for various possible biases in the results. The results showed that specific bacterial genera were associated with increased or decreased risk of DN. These associations can be attributed to a variety of factors, including metabolites produced by certain bacteria. Most of our findings are consistent with the existing research findings, but there are still some differences with the existing results. In addition, we also pointed out that some microbiota that may be associated with DN but remain unnoticed can bring new research directions. Our work made use of MR, a reliable technique for examining causal correlations using genetic data investigating potential processes, carrying out longitudinal studies, looking into intervention options, and using a multi-omics approach may be future research avenues. Further, our findings also point to a few unexplored possible study paths for DN in the future. These initiatives may improve our reconciliation of the internal relationships between the gut microbiota and DN and pave the way for more precise prevention and treatment methods. However, it is also critical to recognize any potential restrictions, such as those caused by sample size, population variety, and analytical techniques.

Keywords: Mendelian randomization, Gut microbiota, Diabetic nephropathy.

1. Introduction

Diabetic nephropathy (DN) is a chronic kidney disease (CKD), which is the leading cause of end-stage renal disease (ESRD) and one of the most dreaded diabetic chronic microvascular consequences [1]. Over the past ten years, both Diabetes Mellitus (DM) and DN have shown an increase in prevalence. The International Diabetes Federation reports that there will be 700.2 million diabetics worldwide by the year 2045 [2]. Thirty to forty percent of DM patients have the potential to progress to DN, and one-third of DN patients go on to develop ESRD [3,4]. People with DN have a mortality rate that is 30 times greater than people with DM who do not have kidney disease [1]. The population's health and public health are seriously jeopardized. Diabetes nephropathy places a significant strain on families and society as a whole, in addition to causing physical and emotional suffering for the sufferers themselves. This changing pattern highlights the urgent need for a thorough understanding of the pathophysiology causing DN.

The gut microbiota is a sophisticated ecosystem made up of trillions of bacteria from at least 1000 distinct species, as well as other microbial communities [5]. Although bacteria make up the majority of the gut microbiota, gut microbiota also includes other symbionts such as archaea, viruses, fungi, and protists [6,7]. They are involved in a number of physiological functions, such as immune regulation, metabolic modulation, and food digestion [8,9]. The importance of gut microbiota in preserving human health and influencing the course of disease has recently come to light thanks to the rapid advancement of gut microbiota research [8,10,11].

It is difficult and yet mostly unclear how DN develops. There is mounting evidence that the imbalances of the gut microbiota contribute to the pathophysiology of DN [12]. Fecal samples from DN patients have shown an unbalanced gut microbiota, including elevated levels of *Proteobacteria*, *Verrucomicrobia*, and *Fusobacteria* [13]. In addition, the abundance of certain organisms in the gut microbiota, such as *Escherichia coli* and *Prevotella*, is considerably different in DN patients compared to Diabetes Mellitus (DM) patients without DN [14]. Existing studies have also shown that dysbiosis can cause inflammatory reactions by rupturing the gut epithelial barrier, increasing gut permeability, allowing pathogenic bacteria to spread, and

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causing endotoxins to build up. Dysbiosis can also hasten the development of DN by affecting lipid metabolism and short-chain fatty acid metabolism [15,16]. Therefore, it is reasonable to think that there may be a causal relationship between intestinal flora and the pathogenesis of DN.

Mendelian randomization (MR) is an innovative method to investigate the relationship between the gut microbiota and DN in this situation. In order to quantify the causal relationship between exposure and disease outcome, MR constructs instrumental variables of exposure using genetic variations [17]. The distribution of genotypes from parent to child is random, therefore typical confounding variables have little impact on the correlation between genetic variations and outcome, and a causal sequence is acceptable [18]. MR has been frequently used to investigate the relationship between the gut microbiota and various diseases, such as rheumatoid arthritis [19], autoimmune diseases [20], and metabolic disorders [21].

In conclusion, this study investigates the complex link between gut microbiota and DN using MR as a research paradigm to identify the causative factor. The findings of this work have the potential to significantly improve our understanding of the pathophysiology behind DN, paving the way to creative recommendations and well-planned strategic interventions for disease prevention, detection, and treatment.

2. Materials and Methods

2.1. Exposure data source

The worldwide cooperative MiBioGen contributed to the Genome-wide Association investigation (GWAS) dataset, from which the genetic information for the gut microbiota used in this investigation was chosen [22]. 18340 people from 24 cohorts from 18 different nations—including the USA, Canada, Israel, South Korea, Germany, Denmark, the Netherlands, Belgium, Sweden, Finland, and the UK—were a part of this extensive GWAS. The dataset included genotyping and sequencing profiles for the 16S ribosomal RNA gene [22]. The goal of the study was to look at the relationship between human autosomal genetic variations and the make-up of the gut microbiota. A large collection of 211 taxa was examined, comprising 131 genera, 35 families, 20 orders, 16 classes, and 9 phyla.

2.2 Outcome data source

Two DN GWAS summary data were taken from publically accessible GWAS analyses (IEU [MRC Integrative Epidemiology Unit] OpenGWAS Project, https://gwas.mrcieu.ac.uk/) during the discovery phase. Europeans made up the locals. Table 1 here offers comprehensive details on the datasets.

2.3. Instrument variable selection

This study looked at the five hierarchical levels of phylum, class, order, family, and genus for bacterial species. Each unique taxon was regarded as a feature. Several quality control procedures were used to choose the most suitable instrumental variables (IVs) in order to guarantee the accuracy and validity of the findings on the causal link between gut microbiota and DN risk.

Single nucleotide polymorphisms (SNPs) with measurable links to the gut microbiota were first selected as IVs. The selection of the IV was done using two criteria. The first threshold included choosing SNPs as IVs that were less significant than the genome-wide threshold of 5×10^{-8} [23]. But because of the initial selection, only a few gut microbiotas were given serious consideration as IVs. To get more thorough data and investigate further connections between cancer and gut microbiota, a second threshold was used. As the second batch of IVs, SNPs below the locus-wide significance threshold of 1×10^{-5} [23] were chosen to look for probable causal relationships.

To guarantee the IVs utilized in the MR analysis were of high quality, several measures were performed. First, a minor allele frequency (MAF) threshold of 0.01 was applied to the variations of interest [24]. It was also critical to determine whether linkage disequilibrium (LD) existed among the IVs because severe LD might generate bias. The LD between the chosen SNPs was assessed using a clumping procedure with settings $r2 < 0.01$ and clumping distance = 10,000 kb [25].

Ensuring that the effects of the SNPs on the exposure are consistent with the same allele effects on the outcome is an important additional step in MR analysis. Palindromic SNPs (such as those with A/T or G/C alleles) were eliminated to prevent any distortion brought on by strand orientation or allele coding. Alleles were matched with the human genome reference sequence during the harmonization phase, and ambiguous or redundant SNPs were eliminated.

We used the Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) [26] and Mendelian randomization-Egger (MR-Egger) [27] regression tests to evaluate the potential horizontal pleiotropy effect. Each SNP's pleiotropy significance was determined using the MR-PRESSO outlier test, while the MR-PRESSO global test determined the p-value for the total horizontal pleiotropy. SNPs were successively eliminated in ascending order according to their MR-PRESSO outlier test p-values. The MR-PRESSO global test was performed on the

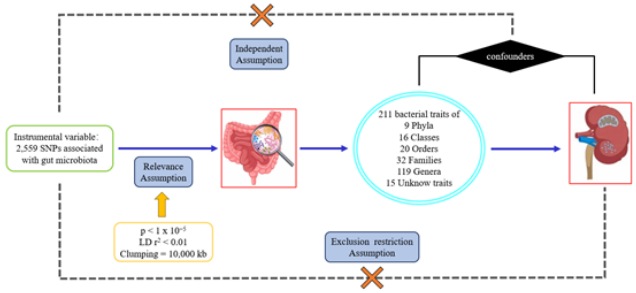

Fig. 1. Instrumental variable selection process.

Table 1. DN GWAS datasets were used in this study.

GWAS-ID*	$N_{control}$	N_{case}	No. SNPs	Ethnicity
finn-b-DM_NEPHROPATHY	210,463	3,283	16,380,453	European
finn-b-DM_NEPHROPATHY_EXMORE	181,704	3,283	16,380,453	European

* The GWAS ID in the IEU OpenGWAS project refers to the distinctive identification for each individual GWAS research. It makes a distinction between various studies and offers access to the data and outcomes related to them.

remaining SNPs after each SNP was eliminated. Until the P-value for the overall test was not significant (P > 0.05), this recursive process was repeated. The final list of SNPs was used for the subsequent MR analysis and was free of pleiotropic SNPs [26]. Figure 1 illustrates the detail of instrumental variable selection.

2.4. MR analysis

We used a range of statistical approaches, including the fixed/random-effects inverse variance weighted (IVW) test [28], weighted mode [29], MR-Egger regression [27], weighted median estimation (WME), and MR-PRESSO [26], to quantify the probable causal link between the gut microbiota and DN. Since the lVW technique offers the most precise effect estimate, we utilized it as the primary analysis. The IVW test was almost always the primary methodology in meta-analyses. In order to get the principal cause estimate, the lVW approach first computes the ratio estimates of each SNPs using the Wald estimator and Delta technique [28]. The heterogeneity between the chosen SNPs will be evaluated using Cochran's Q-test [30]. The random effects IVW approach was used if there was heterogeneity among these SNPs (p< 0.05); otherwise, the fixed effect IVW method was applied.

We first performed a sensitivity analysis to evaluate the robustness of the association before estimating the association using the weighted median method because it can give a more accurate estimate of causal effects in the absence of effective tools. The results of the IVW method are susceptible to effective tools and potential pleiotropic effects. Effective causal impact estimates can be produced when the information derived through invalid instruments accounts for less than 50% of the data. The possibility of horizontal pleiotropy of SNPs exists if the P-value of the intercept is less than 0.05.

We searched the GWAS Catalog (http://www.ebi.ac.uk/gwas, last accessed on August 27, 2023) for the potential secondary phenotypes of each SNP used as an IV in order to further evaluate the impact of potential directional pleiotropy. After excluding these SNPs, the analysis would be redone if the overlapping SNPs were discovered. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to show the relationships between the microbiota in the human gut and the risk of DN. R version 4.3.1 (https://www.r-project.org/) and the "Mendelian Randomization", "TowSampleMR", and "MRInstruments" packages were used for all MR studies.

3. Results

After eliminating palindromic SNPs, we discovered 937, 1,576, 1,583, 2,390, 6,525 and 739 SNPs connected to the gut microbiota at the phylum, class, order, family, genus, and species levels, respectively. The suggestive significance threshold of p < 1.0×10-5 was used to determine the relevance of these connections. The full MR results obtained through different methods are shown in Figure 2.

3.1. The unadjusted MR analysis results

We used MR analysis to look at the relationship between two DN databases and gut microbial communities following a set of quality control procedures. The DN data from finn-b-DM_NEPHROPATHY demonstrated significant relationships with 7 genera of gut bacteria (78 SNPs) without adjusting for multiple testing. Eight genera of gut bacteria (90 SNPs) were associated with causal links in the DN data from finn-b-DM_NEPHROPATHY_EXMORE. There was no sign of weak instrument bias, according to the F-statistic values for the IVs, which varied from 22.0953 to 23.1333 and were all more than 10. Additionally, the MR-PRESSO test finds the evidence of pleiotropy ($P_{Cochrane\ Q}$ > 0.05) of *class Gammaproteobacteria* in finn-b-DM_NEPHROPATHY database and we removed it from this research.

According to the results of the MR analysis, the gut microbiota linked to DN risk was nearly identical in the two datasets. For instance, the *genus Intestinimonas* was linked to a lower incidence of DN in the finn-b-DM_NEPHROPATHY dataset (OR=0.494, 95%CI=0.283-0.863) and the finn-b-DM_NEPHROPATHY_EXMORE dataset (OR=0.494, 95%CI=0.282-0.868). The *genus Marvinbryantia*, however, was linked to a higher risk of DN in the finn-b-DM_NEPHROPATHY dataset (OR=1.369, 95% CI=1.045-1.794) and the finn-b-DM_NEPHROPATHY_EXMORE dataset (OR=1.353, 95% CI=1.030-1.777). The *family Peptostreptococcaceae* (OR=1.277, 95%CI=1.005-1.622) and *genus Lachnospiraceae UCG001* (OR=1.249, 95%CI=1.012-1.542) were shown to increase the risk of DN in the finn-b-DM_NEPHROPATHY_EXMORE dataset, although these associations were not seen in the finn-b-DM_NEPHROPATHY dataset. Additionally, *order Lactobacillales* (OR=0.748, 95%CI=0.563-0.993) was seen in the finn-b-DM_NEPHROPATHY dataset to reduce the incidence of DN, however this was not seen in the finn-b-DM_NEPHROPATHY_EXMORE dataset. The entire unadjusted MR analysis findings from the two datasets are shown in Table 2 (in the end of the document).

3.2. The adjusted MR analysis results

In order to identify bacterium species with numerous SNPs, we used the widely used MR analysis approach for species while taking into account different correction strategies. The significance thresholds at various taxonomic levels were established as follows in the SNP set with a genome-wide significance threshold (1×10^{-6}) as IVs: phylum $P = 5 \times 10^{-2}$ (0.05/1), class $P = 5 \times 10^{-2}$ (0.05/1), order $P = 2.5 \times 10^{-2}$ (0.05/2), family $P = 1.25 \times 10^{-2}$ (0.05/4), and genus $P = 4.54 \times 10^{-3}$ (0.05/11). In the end, 10 different gut microbiota showed causative relationships with DN.

The gut microbiota associated with DN risk was still almost same in the two datasets. According to the findings of the MR study, the *class Bacteroidia* (OR=1.384,

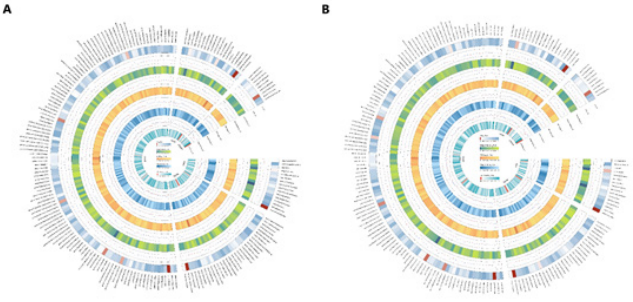

Fig. 2. Circular heat map of full MR result. * Part A is the result from finn-b-DM_NEPHROPATHY database and part B is the result from finn-b-DM_NEPHROPATHY_EXMORE database.

Table 2. Complete MR analysis results without adjustment for significance (should be inserted at line 249).

Gut microbiota	Method	NSNPs*	Odds Ratio	95% CI†	P-value	F-value	R2	PCochrane_Q‡
finn-b-DM_NEPHROPATHY								
genus Intestinimonas	MR Egger	16	0.494	0.283-0.863	0.0266	22.1363	0.0242	0.3692
genus Marvinbryantia	IVW	10	1.369	1.045-1.794	0.0226	22.3123	0.0154	0.8396
genus Ruminococcus gauvreauii group	IVW	11	0.735	0.551-0.981	0.0365	22.4558	0.0170	0.2388
class Verrucomicrobiae	IVW	11	1.444	1.135-1.836	0.0028	22.4720	0.0170	0.5696
order Bacteroidales	WM	13	1.582	1.052-2.377	0.0275	21.3743	0.0191	0.1993
order Bacteroidales	IVW	13	1.384	1.004-1.908	0.0475	21.3743	0.0191	0.1993
order Lactobacillales	IVW	15	0.748	0.563-0.993	0.0448	22.2733	0.0228	0.1972
order Rhodospirillales	MR Egger	14	2.714	1.317-5.593	0.0191	21.7400	0.0209	0.3142
order Verrucomicrobiales	IVW	11	1.444	1.135-1.836	0.0028	22.4720	0.0170	0.5696
phylum Proteobacteria	IVW	12	0.714	0.542-0.941	0.01665	21.3675	0.0176	0.9827
class Bacteroidia	WM	13	1.582	1.054-2.374	0.0270	21.3743	0.0191	0.1993
class Bacteroidia	IVW	13	1.384	1.004-1.908	0.0475	21.3743	0.0191	0.1993
family Rhodospirillaceae	MR Egger	15	3.036	1.449-6.359	0.0114	21.6679	0.0222	0.3161
family Verrucomicrobiaceae	IVW	11	1.444	1.135-1.836	0.0028	22.4606	0.0170	0.5688
genus Akkermansia	IVW	11	1.443	1.135-1.836	0.0028	22.4832	0.0170	0.5687
genus Catenibacterium	IVW	4	1.278	1.023-1.596	0.0306	21.3812	0.0059	0.9751
genus Coprococcus1	WM	11	1.509	1.065-2.140	0.0208	22.3817	0.0169	0.8857
genus Coprococcus1	IVW	11	1.368	1.046-1.789	0.0222	22.3817	0.0169	0.8857
genus Eubacterium ventriosum group	IVW	15	0.767	0.604-0.975	0.0301	21.9701	0.0225	0.9707
finn-b-DM_NEPHROPATHY_RXMORE								
class Gammaproteobacteria	WM	6	0.486	0.277-0.855	0.0123	22.0953	0.0091	0.4506
genus Intestinimonas	MR Egger	16	0.494	0.282-0.868	0.0278	22.1363	0.0242	0.3328
genus Lachnospiraceae UCG001	IVW	12	1.249	1.012-1.542	0.0382	22.5828	0.0186	0.5706
genus Marvinbryantia	IVW	10	1.353	1.030-1.777	0.0297	22.3123	0.0154	0.8224
genus Ruminococcus gauvreauii group	IVW	11	0.733	0.540-0.993	0.0452	22.4558	0.1699	0.1771
class Verrucomicrobiae	IVW	11	1.457	1.143-1.857	0.0024	22.4720	0.0170	0.5056
order Bacteroidales	WM	13	1.594	1.080-2.352	0.0188	21.3743	0.0191	14.6092
order Bacteroidales	IVW	13	1.412	1.025-1.945	0.0350	21.3743	0.0191	14.6092
order Rhodospirillales	MR Egger	14	2.458	1.187-5.093	0.0323	21.7400	0.0209	0.4004
order Verrucomicrobiales	IVW	11	1.457	1.143-1.857	0.0024	22.4720	0.0170	0.5056
phylum Proteobacteria	IVW	12	0.713	0.540-0.941	0.0170	21.3675	0.0176	0.9689
family Peptostreptococcaceae	IVW	13	1.277	1.005-1.622	0.0451	23.1333	0.0206	0.3599
class Bacteroidia	WM	13	1.594	1.089-2.335	0.0166	21.3743	0.0191	0.2154
class Bacteroidia	IVW	13	1.412	1.025-1.945	0.0350	21.3743	0.0191	0.2154
family Rhodospirillaceae	MR Egger	15	2.765	1.313-5.826	0.0191	21.6679	0.0222	0.3531
family Verrucomicrobiaceae	IVW	11	1.457	1.143-1.857	0.0024	22.4606	0.0170	0.5049
genus Akkermansia	IVW	11	1.457	1.143-1.857	0.0024	22.4832	0.0170	0.5052
genus Catenibacterium	IVW	4	1.298	1.037-1.624	0.0227	21.3812	0.0059	0.9963
genus Coprococcus1	WM	11	1.560	1.090-2.234	0.0151	22.3817	0.0169	0.8736
genus Coprococcus1	IVW	11	1.392	1.061-1.825	0.0168	22.3817	0.0169	0.8736
genus Eubacterium ventriosum group	IVW	15	0.756	0.594-0.963	0.0233	21.9701	0.0225	0.9868

*NSNPs: Number of SNPs. †95%CI: The 95% Confidence Interval of odd ratio. ‡ $P_{Cochrane\_Q}$: P value for the Cochrane Q test.

95%CI=1.004-1.908 in finn-b-DM_NEPHROPATHY database; OR=1.412, 95%CI=1.025-1.945 in finn-b-DM_NEPHROPATHY_EXMORE database by IVW method), *class Verrucomicrobiae* (OR=1.444, 95%CI=1.135-1.836 in finn-b-DM_NEPHROPATHY database; OR=1.457, 95%CI=1.143-1.857 in finn-b-DM_NEPHROPATHY_ EXMORE database), *order Verrucomicrobiales* (OR=1.444, 95%CI=1.135-1.836 in finn-b-DM_NEPHROPATHY database; OR=1.457, 95%CI=1.143-1.857 in finn-b-DM_NEPHROPATHY_EXMORE database), *order Bacteroidalesa* (OR=1.594, 95%CI=1.080-2.352 in finn-b-DM_NEPHROPATHY_ EXMORE database), *order Rhodospirillales* (OR=2.714, 95%CI=1.317-5.593 in finn-b-DM_NEPHROPATHY database), *family Verrucomicrobiaceae* (OR=1.444, 95%CI=1.135-1.836 in finn-b-DM_NEPHROPATHY database; OR=1.457, 95%CI=1.143-1.857 in finn-b-DM_NEPHROPATHY_ EXMORE database), *family Rhodospirillales* (OR=3.036, 95%CI=1.449-6.359 in finn-b-DM_NEPHROPATHY database) and *genus Akkermansia* (OR=1.443, 95%CI=1.135-1.836 in finn-b-DM_NEPHROPATHY database; OR=1.457, 95%CI=1.143-1.857 in finn-b-DM_NEPHROPATHY_EXMORE database) among them showed possible risk factors for the emergence and progression of DN. On the other hand, the *phylum Proteobacteria* (OR=0.714, 95%CI=0.542-0.941 in finn-b-DM_NEPHROPATHY database; OR=0.713, 95%CI=0.540-0.941 in finn-b-DM_NEPHROPATHY_EXMORE database) and *class Gammaproteobacteria* (OR=0.486, 95%CI=0.277-0.855 in finn-b-DM_NEPHROPATHY_EXMORE database) revealed a specific defense against DN. The full findings of the modified MR analysis are as shown in Figure 3.

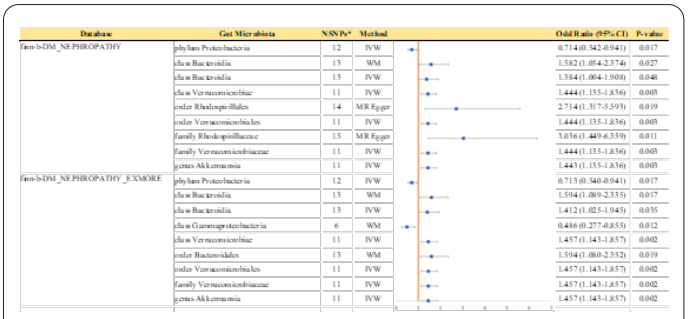

Fig. 2. Forest plot of the adjusted MR analysis result.

4. Discussion

The purpose of this study was to look into the connection between certain gut flora and the risk of getting DN. We have uncovered many critical findings that suggest a specific causal association between gut microbiota and the progression of DN by a rigorous MR analysis and meta-analysis of DN-related gut microbiota data from two publicly accessible GWAS databases.

In our analysis results, there were 8 risk factors and 2 beneficial factors for DN. Among them, *class Bacteroidia*, *order Bacteroidales*, *family Verrucomicrobiaceae* and *genus Akkermansia* were suggested as a risk factor for DN, which is coincident to the existing experiment results [13,31-36].

Furthermore, based on our findings, Bacteroides is a risk factor. It could result in an increase in trimethylamine-N-oxide, Lipopolysaccharide (LPS), phenyl sulfate, and indoxyl sulfatec, which have been linked to insulin resistance, inflammation, oxidative stress, and fibrosis as well as renal dysfunction by activating renin-angiotensin-aldosterone system and the endothelin system [32,33].

However, the finding that *phylum Proteobacteria* is a risk factor is in conflict with the existing conclusion [13,31,37]. The study done by Hu et al. indicated that the severity of DN is highly correlated with the quantity of LPS produced by Proteobacteria, a Gram-negative bacterium, which raises the oxygen level in the lumen and causes an unbalanced structure in the gut [38]. This difference may be caused by the insufficient sample size of the data we used and the single race.

In addition, our results suggest that *class Gammaproteobacteria* is a protective factor for DN while *class Verrucomicrobiae*, *order Verrucomicrobiales*, *order Rhodospirillales* and *family Rhodospirillaceaeare* are also risk factors for DN. However, there is no relevant research. Therefore, our findings provide a new direction and new ideas for the subsequent study of DN.

It is vital to stress that our work made use of MR, a reliable technique for examining causal correlations using genetic data. To clarify the precise molecular pathways by which these gut microbiota genera affect the risk of DN, more mechanistic researches are required. Future studies can further investigate the discrepancies between our findings on the *genus Akkermansia* and those of other studies, as well as the unstudied areas that we have pointed out.

It is also to recognize any potential limitations of this study, though. Limitations in sample size, demographic variety, or generalizability are a few examples of these. While useful for determining causal linkages, the study's use of Mendelian randomization analysis may also have some inherent drawbacks. To confirm the results and give a more thorough knowledge of the gut microbiota's function in MR, more research with bigger sample numbers, various demographics, and other analytical techniques are required.

5. Conclusion

In conclusion, research examining the connection between DN and gut microbiota has shed light on important issues. These findings draw attention to particular bacterial genera that are either more or less likely to cause DN. Numerous variables, such as the metabolites that these bacteria generate, might be blamed for these relationships.

Most of our findings are consistent with the existing research findings, but there are some differences with the existing results on the association between *phylum Proteobacteria* and DN, which means that more research is still required to broaden and confirm these findings. Investigating potential processes, carrying out longitudinal studies, looking into intervention options, and using a multi-omics approach may be future research avenues. Furthermore, our findings also point to a few unexplored possible study paths for DN in the future. These initiatives may improve our comprehension of the intricate relationships between gut microbiota and DN and pave the way for more precise prevention and treatment methods.

It is critical to recognize any potential restrictions, such as those caused by sample size, population variety, and analytical techniques. To improve the evidence and correct any weaknesses, more studies of various populations and alternative methodologies are required.

Abbreviations
DN: Diabetic nephropathy; MR: Mendelian randomization; CKD: chronic kidney disease; ESRD: end-stage renal disease; DM: Diabetes Mellitus; GWAS: Genome-wide Association investigation; IV: instrumental variable; SNP: Single nucleotide polymorphism; MAF: minor allele frequency; LD: linkage disequilibrium; MR-PRESSO: Mendelian randomization pleiotropy residual sum and outlier; IVW: inverse variance weighted; WME: weighted median estimation; OR: Odds ratios; CI: confidence intervals; LPS: Lipopolysaccharide.

Declarations
Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Availability of data and materials
The datasets analyzed during the current study are publicly available.

Competing interests
All the authors did not have any competing interests.

Funding
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Author's contributions
CLY, YJC and ZJG contributed to the study conception and design, revised the manuscript, and provided research funding. YJC organized the database. YJC, XYH and QC performed the statistical analysis. WC wrote the first draft of the manuscript. All authors commented on previous versions of the manuscript. All authors consented to the publication of the manuscript and agreed to be responsible for the manuscript.

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