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Genetically Predicted Causal Relationship between Gut Microbiota and Various Kidney Diseases

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Gut microbiota · Diabetic nephropathy · IgA nephropathy · Membranous nephropathy · Genome-wide association study · Mendelian randomization · Immune infiltration

Abstract
Introduction: Although recent research suggests that alterations in gut microbiota play a critical role in the pathophysiology of kidney diseases, the causal relationship between specific intestinal flora and the risk of kidney diseases remains unclear. Here, we investigated the causal relationship between gut microbiota and different kidney diseases through mendelian randomization analysis. ***Methods:*** Gut microbiota and three types of kidney diseases, including diabetic nephropathy, IgA nephropathy, and membranous nephropathy, were identified from large-scale genome-wide association studies summary data. Inverse variance weighted method was employed to estimate causal relationships. Cochran's *Q* test was utilized to uncover any heterogeneity. The mendelian randomization-Egger intercept test was employed to detect horizontal pleiotropy, and the leave-one-out method was used for testing the stability. In addition, the reverse, multivariable, and two-step mendelian randomization analysis was conducted to assess the causation possibilities. Furthermore, the associations between three types of kidney diseases and immune infiltration were determined. ***Results:*** We identified 1,531 single-nucleotide polymorphisms. There were 6 positive and 9 negative causal effects between gut microbiota and three types of kidney diseases. Specifically, *Dialister* was a protective factor for diabetic nephropathy while *Lachnospiraceae UCG-008* was a risk factor. *Clostridium innocuum* was a protective factor for IgA nephropathy, while *Christensenellaceae R.7*, *Clostridium sensu stricto*1, *Lachnospiraceae UCG-004*, *Lachnospiraceae UCG-010*, *Oscillospira*, *Ruminococcaceae UCG-010*, and *Terrisporobacter* were risk factors for IgA nephropathy. *Butyricicoccus*, *Catenibacterium*, *Flavonifractor*, and *Lachnospira* were associated with an increased risk of membranous nephropathy, while *Ruminococcaceae UCG-011* was associated with a decreased risk of membranous nephropathy. Sensitivity analysis indicated the results were robust. No significant pleiotropy or heterogeneity was identified. Notably, the reverse mendelian randomization analysis did not reveal any causal relationship. After adjusting for environmental confounders, including CO, PM 2.5, PM 10, and exposure to tobacco smoke at home, these causal relationships still exist. Additionally, immune infiltration analysis indicated unique immune cell distribution in each type of kidney disease, which are largely consistent with later two-step approach, emphasizing the significance of immunological processes in the

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diseases. ***Conclusion:*** This study uncovered the causal relationship between gut microbiota and three types of kidney diseases. This discovery provides fresh perspectives on how microbes contribute to kidney diseases, paving the way for more in-depth clinical studies.

Introduction

Nowadays, kidney disease ranks as the third most rapidly increasing cause of death worldwide and is the only noncommunicable disease with a continuous increase in mortality rates adjusted for age, making it a major public health concern [1]. According to estimates, chronic kidney disease (CKD) is expected to experience a significant rise in mortality rates in the coming decades, ranking the fifth leading cause of death globally by 2040 [2]. In the 2000s, studies conducted nationwide revealed that over 10% of individuals were experiencing kidney damage in Australia [3] and the USA [4]. To make matters worse, CKD is a progressive condition characterized by no cure available and high levels of morbidity and mortality. With renal function declining over time, renal replacement therapies, mainly including hemodialysis, peritoneal dialysis, and renal transplantation, would become the only choice for patients facing the end stage of the disease. Due to the unsatisfying shortage of healthy kidney donors and severe complications after renal transplantation, patients tend to select dialysis as their treatment, which in turn puts themselves at risk of heavy financial burden and diminished quality of life [5]. Among multiple types of kidney diseases, the following three types, diabetic nephropathy (DN), IgA nephropathy (IgAN), and membranous nephropathy (MN), are undoubtedly hard to treat in clinical practices for their shared similar traits of long therapy duration, complicated medical condition, and diverse complications [6–8]. For this reason, it is urgent to carry out primary prevention of such kidney diseases so as to better avoid the occurrence of kidney diseases.

In the past few years, a large amount of studies have been conducted to explore the initial etiology as well as effective therapies of kidney diseases [9–12]. Among them, intervening gut microbiota (GM) to mitigate the deterioration of kidney disease is a new research trend with the prevalence of the concept of the gut-kidney axis [13, 14]. GM has been confirmed to be concerned with the metabolism regulation in the host intestine and plays a vital role in maintaining the homeostasis of immune activities [15, 16]. Several studies have indicated that the composition and structure of intestinal flora are significantly altered in patients with DN, IgAN, and MN, which results in the imbalance of intestinal barrier [17, 18]. As the dysfunction of GM continues, there would be accumulation of systemic inflammation, oxidative stress, and waste products released by the disordered flora, which in turn will further worsen the condition of kidney function [19]. A quantity of evidence in animal models supported the common belief that various diseases and pathological processes could be modulated by the microbiome. Promising results have been observed in the treatment of DN, IgAN, and MN through fecal transplantation experiments in rodents [11, 12, 20]. These findings demonstrated the association between GM and multiple kidney diseases through transplantation of feces from human patients and healthy controls into model mice by oral gavage. Nevertheless, they are prone to biases like reverse causation and confounding and are not capable of establishing causation. The characteristics of physiological condition, lifestyle, and dietary patterns are all confounders that could influence the intricate interplay between microbiota and health [21]. Taking these limitations into consideration, it is crucial to employ innovative techniques such as mendelian randomization (MR) to study how the GM plays a causal role in multiple kidney diseases.

The integration of summary statistics of genome-wide association studies (GWASs) in MR helps to minimize the influence of confounding factors and is commonly utilized to explore the potential relationship between exposure factors and outcomes. Since the microbiome does not impact an individual's genetic blueprint [22], it is possible to investigate the causal link between GM and multiple kidney diseases through MR analysis. Under specific assumptions, MR utilizes genetic variants highly associated with exposure to deduce causation with an outcome. Here, we used the latest GM as the exposure and three types of kidney diseases as the outcomes from GWAS to conduct a comprehensive and in-depth MR analysis (Fig. 1). Our MR analysis provides direct evidence that bacterial taxa increase or decrease the risk of multiple kidney diseases (online suppl. Table S1; for all online suppl. material, see https://doi.org/10.1159/000544915).

Methods

Study Design

A two-sample MR analysis was conducted in this research using publicly available summarized data from GWAS on GM and various kidney diseases. To guarantee the validity of the outcome, the following three conditions were met: (1) Genetic variations were closely associated with the exposure. (2) The instrumental variables cannot be

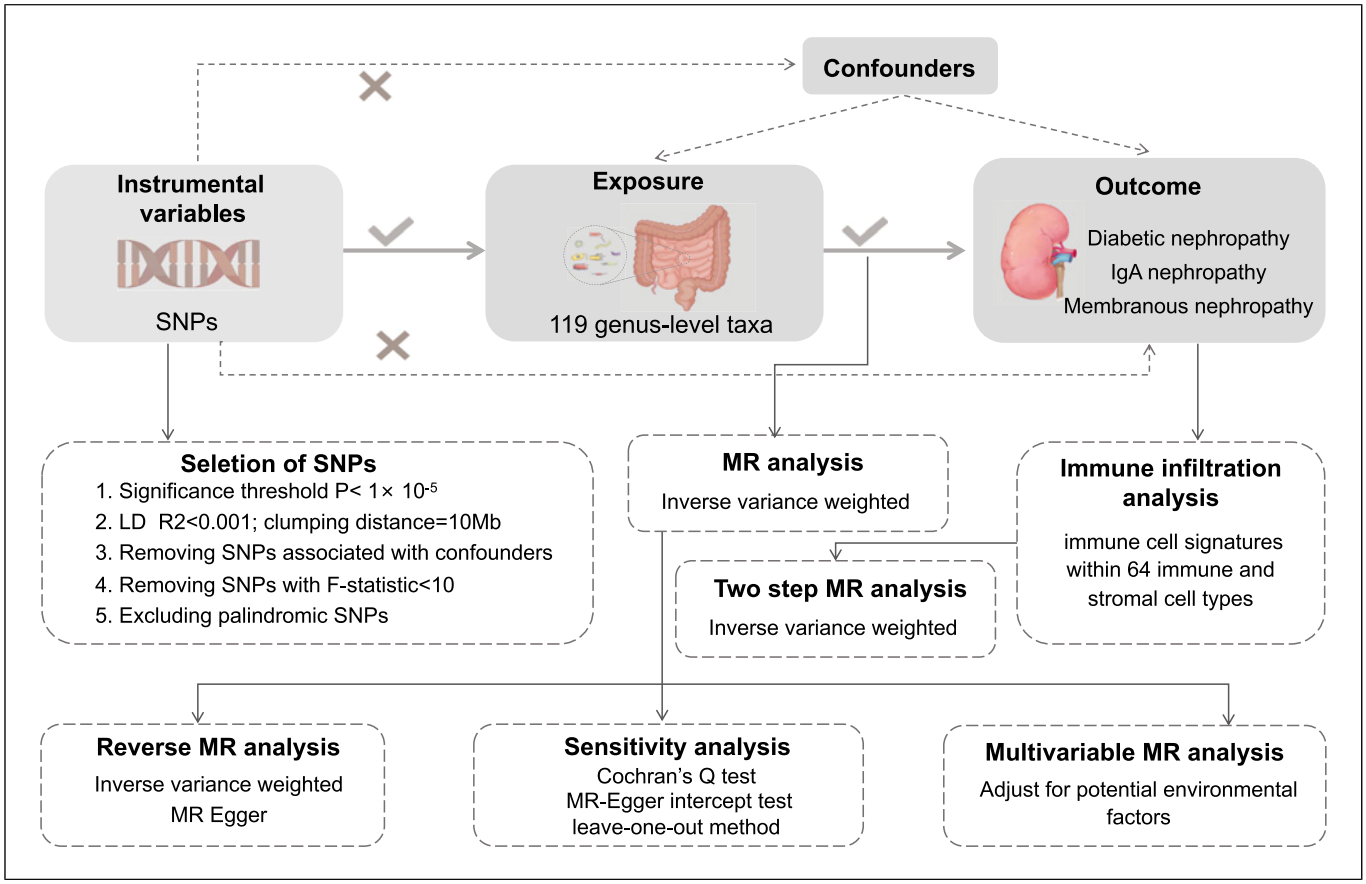


Fig. 1. Overview of the study design. SNP, single-nucleotide polymorphism; LD, linkage disequilibrium.

linked to any confounders. (3) Genetic variations did not exhibit pleiotropic effects on the outcome. By maintaining these assumptions, we effectively decreased the likelihood of systemic diseases affecting different types of kidney diseases.

Data Sources

The gut microbiome data came from the largest GWAS dataset currently available from the MiBioGen consortium [23], encompassing 16S ribosomal RNA gene profiles from 24 cohorts of 18,340 individuals predominantly of European ancestry. The known 119 genus-level taxa identified by microbiota quantitative trait loci mapping analysis were included. The data of DN were from ebi-a-GCST90018832, which includes 452,208 European individuals (1,032 cases and 451,248 controls) and 24,190,738 single-nucleotide polymorphisms (SNPs) [24]. The data of MN were from ebi-a-GCST010005, which includes 7,979 European individuals (2,150 cases and 5,829 controls) and 5,327,688 SNPs [25]. The data of IgAN were from ieu-a-1081, which includes 5,957 European individuals (977 cases and 4,980 controls) and 278,077 SNPs [26]. The data of ~22 million variants on 731 immune cell traits in a cohort of 3,757 Sardinians were from GWAS Catalog (GCST90001391~GCST90002121) [27]. The initial study has obtained approval from the relevant Ethics Committee. Thus, this study did not necessitate further ethical approval.

Instrumental Variables

To establish a strong connection between the chosen SNPs and exposure, we set the threshold at $p < 1 \times 10^{-5}$. An examination of linkage disequilibrium was carried out ($R^2 < 0.001$, clumping distance = 10 Mb) to fulfill the requirements of MR, with the elimination of palindromic and incompatible SNPs. After the process of harmonization, the F statistic value was derived as follows: $F = R^2 \times (N-2)/(1-R^2)$. We left out SNPs that had an F value of less than 10. Following this, the multi-effectiveness of SNPs was further assessed to explore their association with kidney diseases. SNPs that directly correlated with kidney disease were eliminated, while the rest were identified as potential instrumental variables. The GWASs of kidney diseases were utilized to extract the corresponding SNPs.

MR Analysis

To preliminarily explore the potential causal links between GM and kidney diseases initially, we utilized the inverse variance weighted (IVW) method. Moreover, a Bonferroni correction was employed to account for multiple comparisons, with the significance threshold at 0.05/119 = 0.0004. The odds ratio (OR) and corresponding 95% confidence intervals (CIs) were reported. We also determined the Cochran's *Q* test to evaluate result heterogeneity. In cases of heterogeneity ($Q < 0.05$), we applied the IVW random-effects model; otherwise, we opted for the fixed-effects model. The intercept obtained from MR-Egger regression was used as a measure of unbalanced pleiotropy (p_{Egger} <0.05 indicated significance) [28]. The leave-one-out method was used to analyze the sensitivity of each SNP to the outcome. All analysis was conducted with the *TwoSampleMR* package [29] (version 0.6.4) and ggplot2 (version 3.5.1) [30] was applied to draw the volcano plot.

Reverse MR Analysis

To evaluate bi-directional causation effects between GM and kidney diseases, we used IgAN, MN, and DN as "exposure" and GM previously proved to have a causal relationship with kidney disease as "outcome" to conduct the reverse MR analysis. Instrumental variable selection and statistical methods remain the same as before.

MVMR Analysis

We conducted multivariable MR (MVMR) analysis, taking into consideration potential environmental confounders that might influence kidney diseases. Specifically, four confounders, including particulate matter with an aerodynamic diameter <2.5 mm (PM 2.5), PM 10, carbon monoxide (CO), and exposure to tobacco smoke at home, were adjusted in MVMR, respectively [31]. The data of PM 2.5, PM 10, and exposure to tobacco smoke at home were extracted from ukb-b-10817 (423,796 European individuals and 9,851,867 SNPs), ukb-b-589 (455,314 European individuals and 9,851,867 SNPs), and ukb-a-19 (305,723 European individuals and 10,894,596 SNPs), respectively, in UK Biobank, while the data of CO were from FinnGen database (217,123 European individuals and 16,380,439 SNPs).

Immune Infiltration Analysis

We extracted three public microarray datasets from Gene Expression Omnibus. In detail, DN dataset was from GSE30528, which includes 9 DN patients and 13 healthy controls [32]. MN dataset was from GSE108109, which includes 44 MN patients and 6 healthy controls [33]. IgAN dataset was from GSE93798, which includes 20 IgAN patients and 22 healthy controls [34]. The infiltration of 64 immune and stromal cell types in patients with three types of kidney diseases was estimated with xCell, a novel gene signature-based method, which harmonized 1,822 pure human cell type transcriptomes from various sources and employed a curve fitting approach for linear comparison of cell types and introduced a novel spillover compensation technique for separating them [35]. The ggplot2 (version 3.5.1) [30] was used for visualization. Wilcoxon test was employed to make comparisons between kidney disease and the control groups and $p < 0.05$ was considered a statistical difference.

Two-Step MR Analysis

To further determine the relationship between immune cell traits in GM and kidney diseases, we conducted two-step MR analysis. First, MR analysis was performed using IVW method with GM that had a causal relationship with kidney diseases obtained previously as exposure and immune cell traits as outcome. A Bonferroni correction was employed to account for multiple comparisons, with the significance threshold at 0.05/15 = 0.003. And then MR analysis was performed using IVW method with immune cell traits obtained in the first step that had a causal relationship with GM as exposure and kidney diseases as outcome. A Bonferroni correction was employed for IgAN to account for multiple comparisons, with the significance threshold at 0.05/459 = 0.0001.

Results

Screening of Instrumental Variables

After a series of quality control steps, we included 1,531 SNPs as instrumental variables in GM (online suppl. Table S2). The *F* value ranged from 14 to 88 with an average of 21, proving that all instrumental variables were strong enough.

Gut Microbiota and DN

Two GM (*Dialister* and *Lachnospiraceae UCG-008*) were associated with DN (Fig. 2, 3). Detailed information on 24 instrumental variables for two GM is shown in online supplementary Table S2. As shown in Figure 2, IVW method suggested that the genetic prediction of *Dialister* was associated with a decreased risk of DN (OR = 0.51, 95% CI = 0.38–0.69, $p < 0.0004$). *Lachnospiraceae UCG-008* significantly increased the risk of DN (OR = 1.45, 95% CI = 1.23–1.72, $p < 0.0004$).

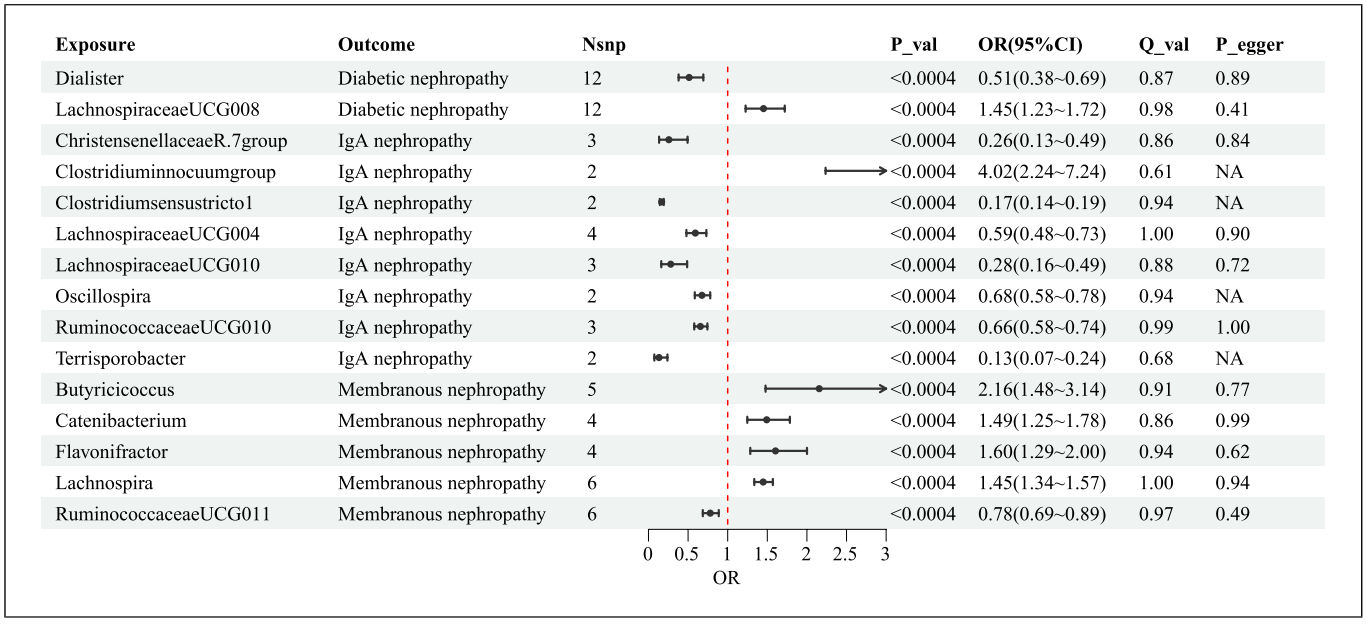


Fig. 2. Forest plots of estimates identified with IVW and the sensitivity analysis by Cochran's *Q* test and MR-Egger intercept test between GM and kidney diseases. OR, odds ratio; CI, confidence interval; NA, not applicable.

The MR-Egger regression intercepts indicated the absence of horizontal pleiotropy or outliers (p_{Egger} >0.05, Fig. 2). Furthermore, the analysis of Cochrane's *Q* test showed no obvious heterogeneity in the selected SNPs (*Q* >0.05, Fig. 2). In addition, the funnel plot showed a symmetrical distribution of instrumental variables, excluding the effect of pleiotropy (online suppl. Fig. S1A, B). Then, the leave-one-out method was applied to measure the effect of each instrumental variable, and the results showed no significant outliers (online suppl. Fig. S2A, B).

Gut Microbiota and IgAN

A total of eight GM were associated with IgAN (Fig. 2, 4). Detailed 22 instrumental variables information for eight GM is shown in online supplementary Table S2. IVW showed that *Christensenellaceae R.7* (OR = 0.26, 95% CI = 0.13–0.49, $p < 0.0004$), *Clostridium sensu stricto*1 (OR = 0.17, 95% CI = 0.14–0.19, $p < 0.0004$), *Lachnospiraceae UCG-004* (OR = 0.59, 95% CI = 0.48–0.73, $p < 0.0004$), *Lachnospiraceae UCG-010* (OR = 0.28, 95% CI = 0.16–0.49, $p < 0.0004$), *Oscillospira* (OR = 0.68, 95% CI = 0.58–0.78, $p < 0.0004$), *Ruminococcaceae UCG-010* (OR = 0.66, 95% CI = 0.58–0.74, $p < 0.0004$), and *Terrisporobacter* (OR = 0.13, 95% CI = 0.07–0.24, $p < 0.0004$) were associated with a decreased risk of IgAN, while *Clostridium innocuum* (OR = 4.02, 95% CI = 2.24–7.24, $p < 0.0004$) was associated with an increased risk of IgAN (Fig. 2).

No horizontal pleiotropy or outliers were detected in the MR-Egger regression intercepts (p_{Egger} >0.05, Fig. 2). In addition, no evident heterogeneity was found according to results from Cochrane's *Q* test (*Q* >0.05, Fig. 2). Besides, the funnel plot exhibited the distribution of SNPs, which was symmetrical and reliable (online suppl. Fig. S1C–J). After the removal of any SNP, the effects of the other SNPs remained unchanged as the leave-one-out method indicated (online suppl. Fig. S2C–F).

Gut Microbiota and MN

A total of five GM were associated with MN (Fig. 5). Detailed 25 instrumental variables information for five GM is shown in online supplementary Table S2. IVW demonstrated that *Butyricicoccus* (OR = 2.16, 95% CI = 1.48–3.14, $p < 0.0004$), *Catenibacterium* (OR = 1.49, 95% CI = 1.25–1.78, $p < 0.0004$), *Flavonifractor* (OR = 1.60, 95% CI = 1.69–2.00, $p < 0.0004$), and *Lachnospira* (OR = 1.45, 95% CI = 1.34–1.57, $p < 0.0004$) significantly increased the risk of MN. Meanwhile, the *Ruminococcaceae UCG-011* (OR = 0.78, 95% CI = 0.69–0.89, $p = 0.0002$) was associated with a decreased risk of MN.

MR-Egger regression intercepts showed no horizontal pleiotropy or outliers (p_{Egger} >0.05, Fig. 2). Furthermore, no obvious heterogeneity was found according to results

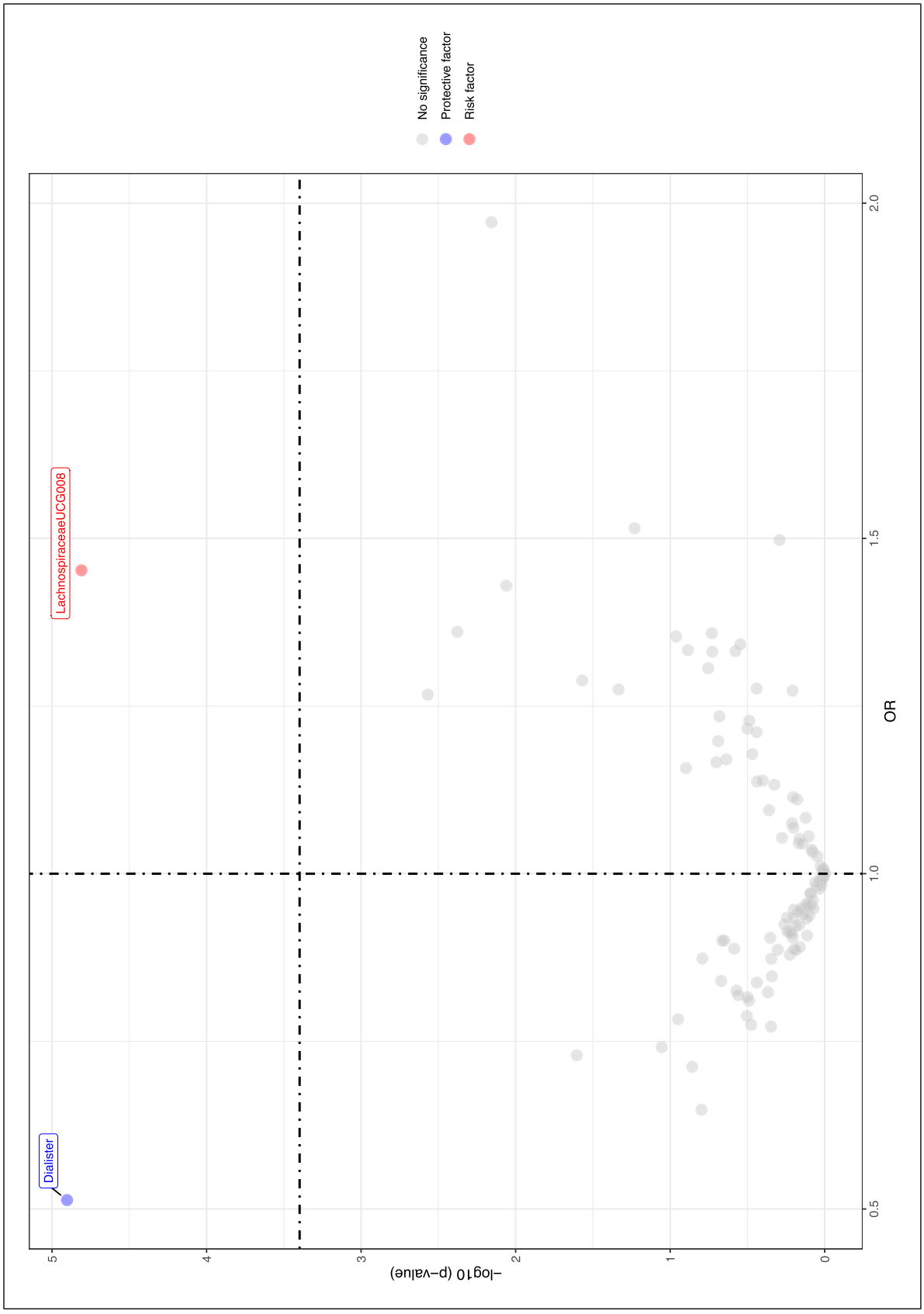


Fig. 3. Volcano plot showing the differential microbiota identification in DN. The risk factors (red), the protective factors (blue), and the microbiota of no significance (gray) are shown in the color dots.

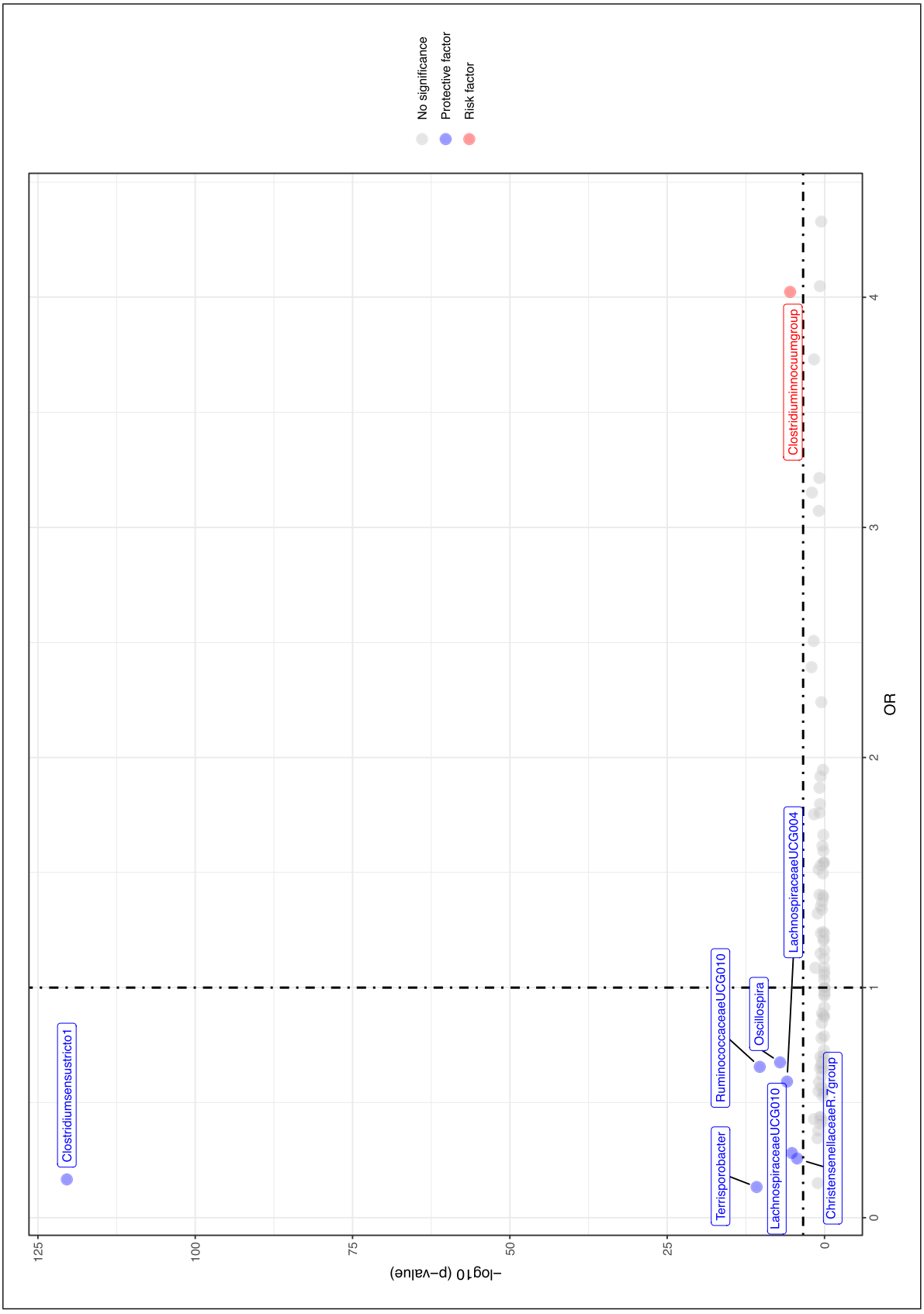


Fig. 4. Volcano plot showing the differential microbiota identification in IgAN. The risk factors (red), the protective factors (blue), and the microbiota of no significance (gray) are shown in the color dots.

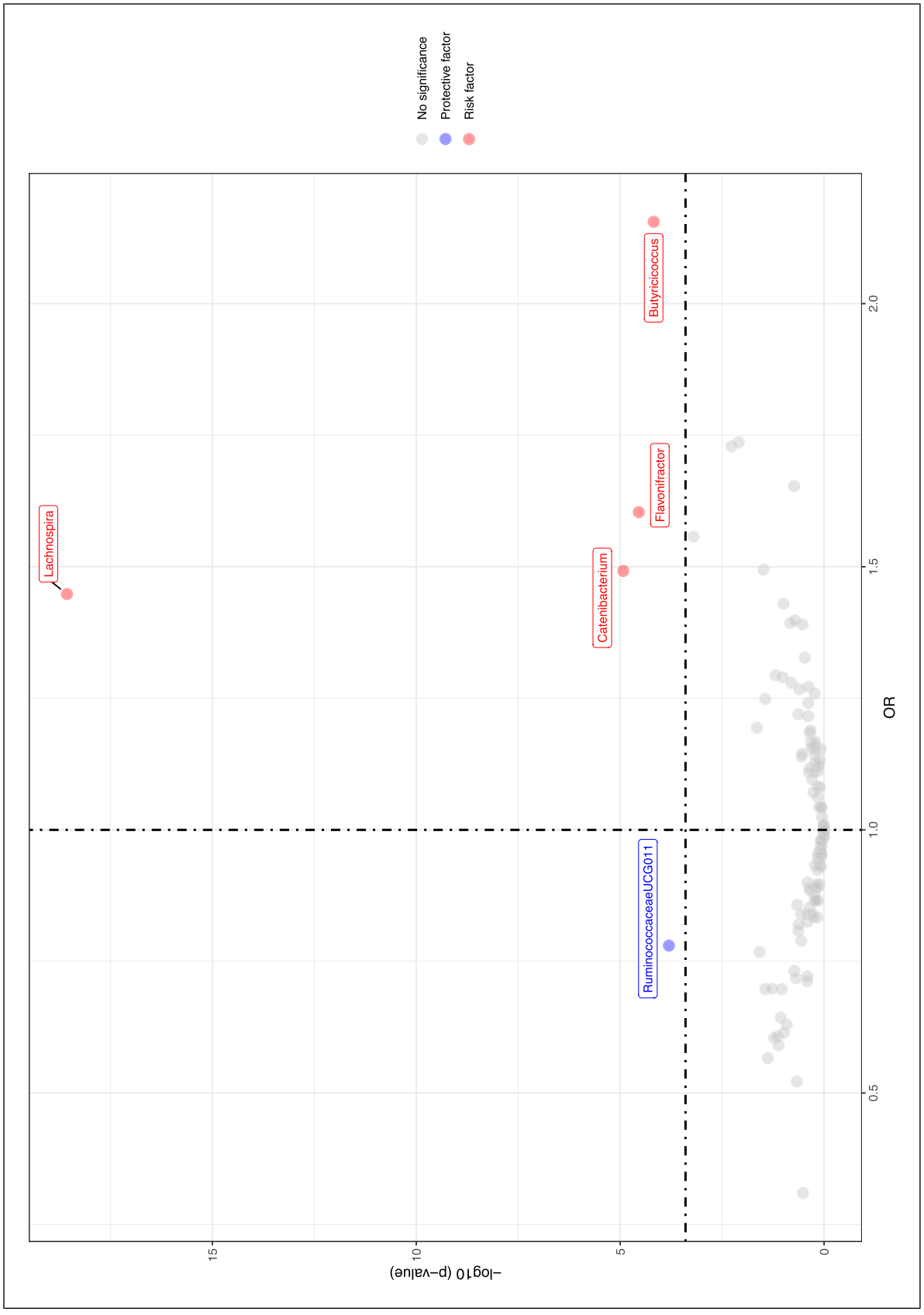


Fig. 5. Volcano plot showing the differential microbiota identification in MN. The risk factors (red), the protective factors (blue), and the microbiota of no significance (gray) are shown in the color dots.

from Cochrane's *Q* test (*Q* >0.05, Fig. 2). In addition, the funnel plot showed a symmetrical distribution of SNPs, emphasizing the relative stability of the results (online suppl. Fig. S1K–O). Moreover, the leave-one-out method showed no single SNPs might dominate the positive results (online suppl. Fig. S2G–K).

Causal Effects of Multiple Kidney Diseases on GM

We conducted reverse MR on the findings that achieved nominal significance to explore whether the genetically predicted kidney diseases would be causal for GM. Given that there was only one instrumental variable between *Lachnospira* and MN, the relevant MR analysis was not applied. Altogether, no causal relationships were found in the analysis between three kidney diseases and the remaining GM (without *Lachnospira*) ($p > 0.05$) (online suppl. Fig. S3).

MR-Egger tests showed no horizontal pleiotropy or outliers (*p*Egger >0.05, online suppl. Fig. S3). Except for the heterogeneity between MN and *Flavonifractor* ($Q < 0.05$), no obvious heterogeneity was found according to results from Cochrane's *Q* test (online suppl. Fig. S3). The funnel plot showed the symmetrical distribution (online suppl. Fig. S4). In addition, the leave-one-out method showed that vast majority of results are robust (online suppl. Fig. S5).

Multivariable MR

In MVMR, the causal effect of *Dialister* on DN remained after adjusting for environmental confounders, including PM 2.5, PM 10, and exposure to tobacco smoke at home, which indicated the robustness of its impact on DN (online suppl. Fig. S6). Compared with the univariable MR analysis, the observed causalities between *Lachnospiraceae UCG-008*, *Christensenellaceae R.7*, *Clostridium innocuum*, *Lachnospiraceae UCG-004*, *Lachnospiraceae UCG-010*, *Terrisporobacter*, *Catenibacterium*, and specific type of kidney disease were slightly attenuated after adjusting for CO, but the causal estimates were still statistically significant (online suppl. Fig. S6). However, after adjusting for PM 2.5 only or exposure to tobacco smoke at home only, the association between *Christensenellaceae R.7*, *Clostridium sensu stricto*1, *Lachnospiraceae UCG-004*, *Ruminococcaceae UCG-010*, *Oscillospira*, and risk of kidney disease was not significant (online suppl. Fig. S6).

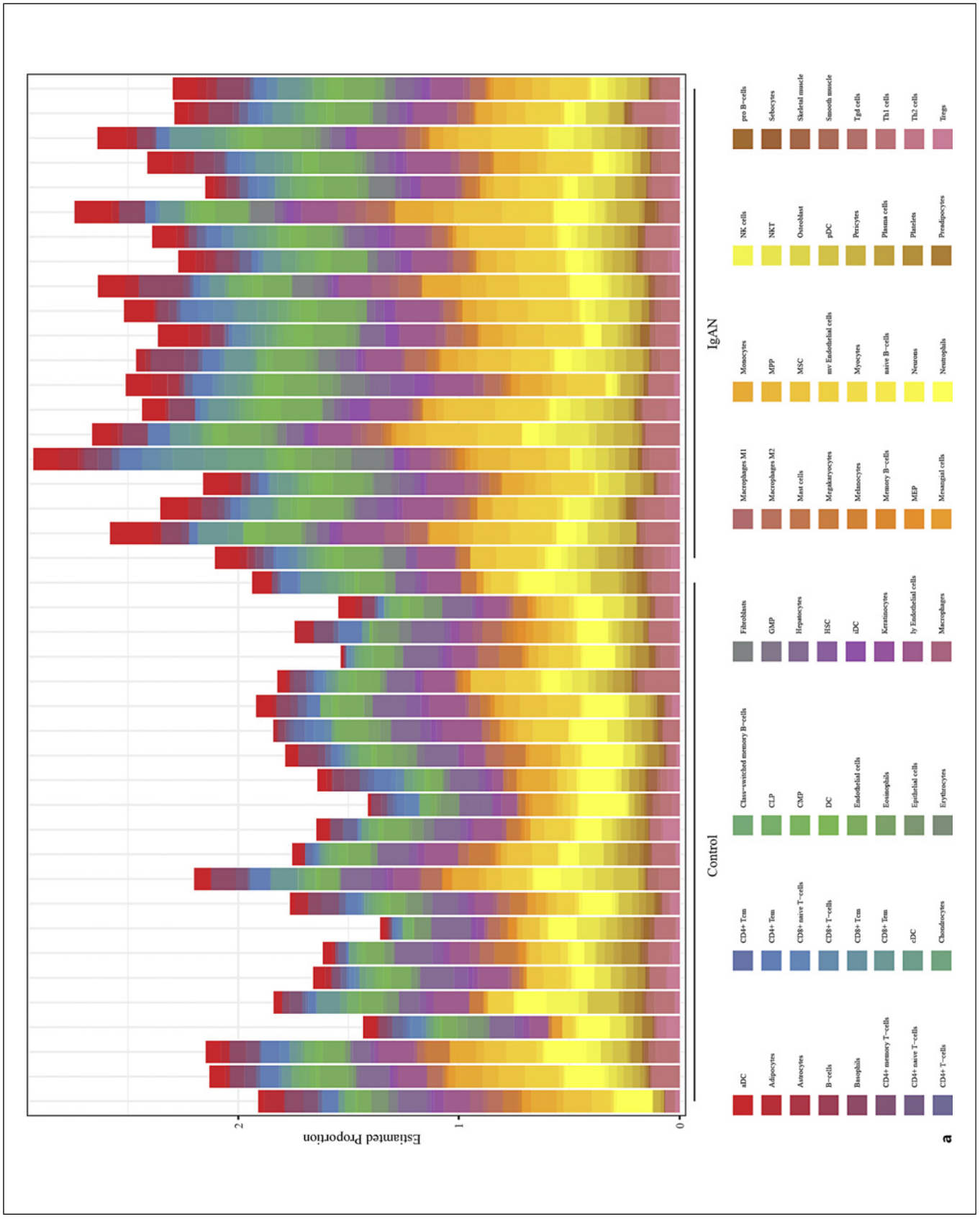
Assessment of Immune Cell Infiltration in Multiple Kidney Diseases

More recent studies have illuminated that the onset of renal disorders demonstrated a close relationship with the immune system [36]. Figure 6a exhibited the estimated proportion of 64 immune and stromal infiltration cells in the control and IgAN groups, while Figure 6b showed the estimated proportion of each immune infiltration cell in all the samples. Through comparison of the proportion of cells in samples from control and IgAN groups, we observed a significant difference in specific immune cell subtypes between the IgAN and control group samples. The IgAN group exhibited more significantly elevated expression of dendritic cells (DC), activated DC (aDC), conventional DC (cDC), immature DC, astrocytes, $CD8^+$ effective memory T cells (Tem), common myeloid cells, endothelial cells, ly endothelial cells, mv endothelial cells, macrophages, mast cells, fibroblasts, multipotent progenitors, mesenchymal stem cells, osteoblast, and pericytes among the total of 28 kinds of high-expression immune cells (Fig. 6c). Conversely, the control group demonstrated more highly expressed epithelial cells, hepatocytes, keratinocytes, megakaryocyte erythroid progenitors, neutrophils, and preadipocytes among the total of 11 kinds of high-expression immune cells (Fig. 6c).

As for DN, the proportion of $CD4^+$ Tem, $CD8^+$ central memory T cells, $CD4^+$ Tem, cDC, epithelial cells, macrophages, M1 macrophages, mast cells, megakaryocyte erythroid progenitors, natural killer T cells, sebocytes, and Tgd cells was higher, while the proportion of ly endothelial cells and myocytes was lower in patients with DN (online suppl. Fig. S7). After comparison with the control group, three immune cell subtypes (aDC, endothelial cells, and granulocyte monocyte progenitors) obviously showed elevated proportion in MN group (online suppl. Fig. S8). However, five immune cell subtypes including keratinocytes, M2 macrophages, megakaryocytes, neurons, and platelets displayed a lower proportion (online suppl. Fig. S8). Collectively, the immune cell infiltration played a significant role in the development of multiple kidney diseases.

Immune Cell Traits Served as Mediators

Through two-step MR analysis, we confirmed that GM that had a causal relationship with DN had shared a causal relationship with 123 immune cell traits, GM that had a causal relationship with IgAN had shared a causal relationship with 459 immune cell traits, and GM that had a causal relationship with MN had shared a causal relationship with 272 immune cell traits. Among these immune cell traits, 14 immune cell traits were genetically associated with DN (online suppl. Fig. S9), 18 immune cell traits were genetically associated with IgAN (Fig. 7), and 19 immune cell traits were genetically associated with IgAN (online suppl. Fig. S10).



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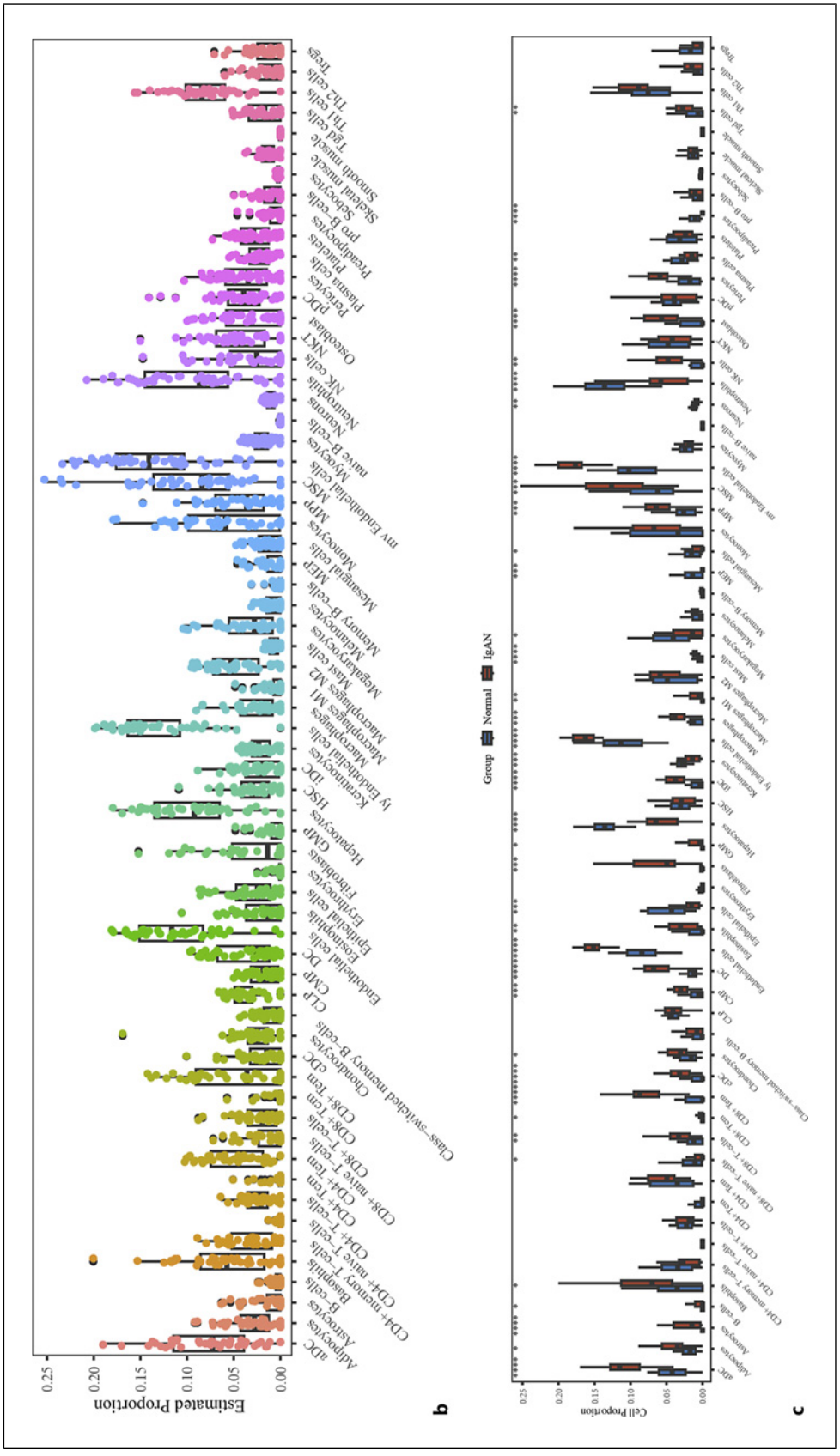

Fig. 6. Analysis of immune cell infiltration in IgAN. **a** Stacked histogram of the estimated proportion of immune cells between the IgAN and control groups. **b** Box plot showing the general proportion of 64 immune and stromal cell types in all the samples. **c** Box plot showing the comparison of 64 immune and stromal cell types between the IgAN group and the control group.

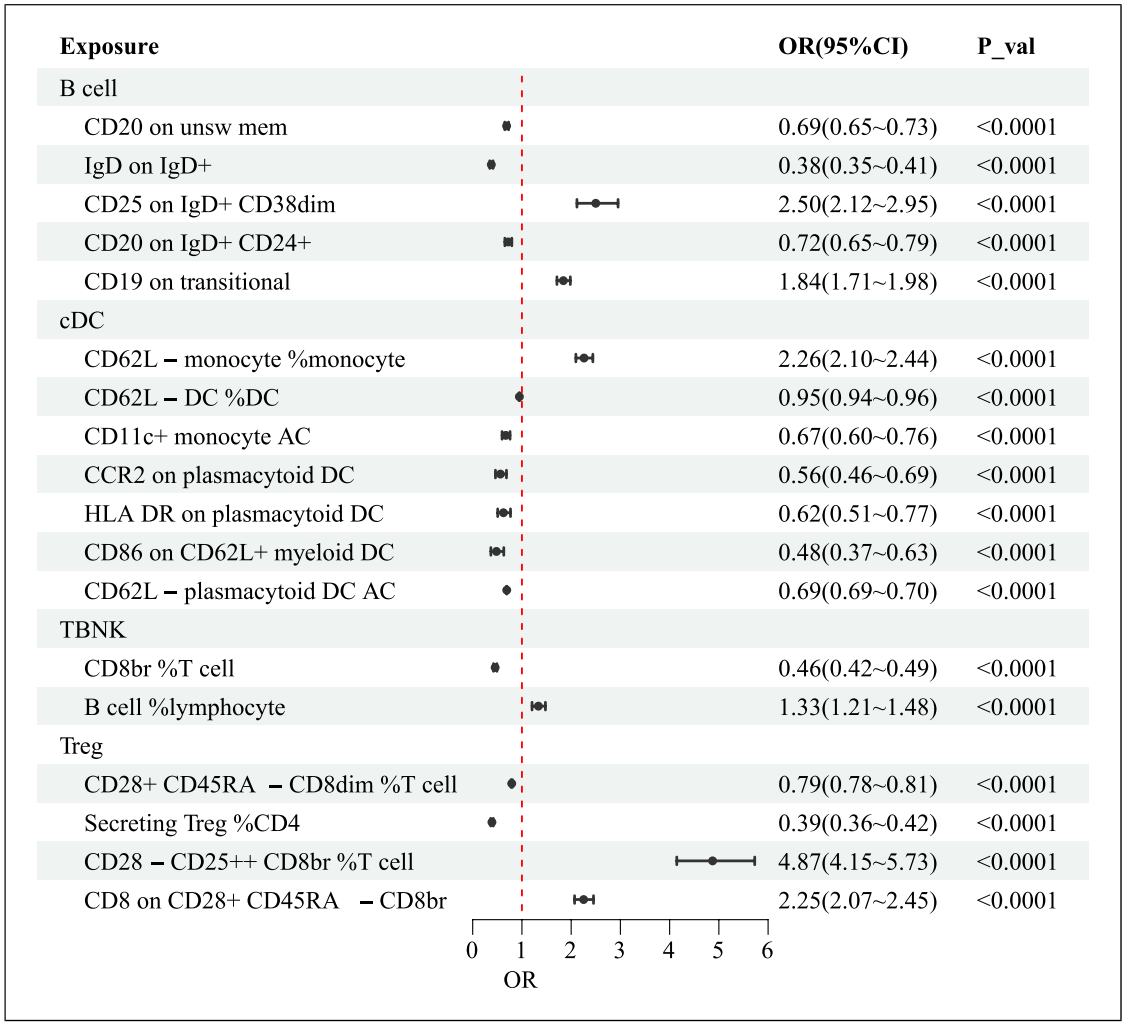

Fig. 7. Forest plots of estimates identified with IVW between immune cell traits and IgAN. OR, odds ratio; CI, confidence interval.

Discussion

In this study, we examined the causality between GM and three types of kidney diseases by utilizing large-scale gene data from the GM at the gene prediction level. By analyzing large GWAS datasets from European subjects, this research identified 15 bacterial taxa that might play a causal role in the susceptibility to DN, IgAN, and MN. This causality was further confirmed by the reverse MR analysis and MVMR analysis adjusting for environmental factors (PM 2.5, PM 10, CO, and exposure to tobacco smoke at home). The discovery highlighted the significant impact of GM on the development of kidney diseases and served as a valuable resource for future studies.

Apart from the similar feather in stepping into the end-stage renal disease in a terrible way, the etiologies of DN, IgAN, and MN are apparently different. DN progression is impacted by a range of risk factors, some of which can be altered, while others cannot be modified, such as gender, ethnicity, family history of diabetes [6, 37]. The onset of DN is complicated and starts with renal cells being exposed to excessive glucose. While IgAN, regarded as an immune-complex-mediated glomerulonephritis [38], is distinguished by pathological features including the accumulation of IgA in the mesangial regions of the kidney glomeruli [39], the proliferation of glomerular mesangial cells, and the increase in the mesangial matrices [40]. As for another type of kidney disease, the cause of MN is obviously different from that of DN and IgAN. Recent research has

shown that MN can be caused by autoimmune antibodies, infections, malignancies, drugs like NSAIDs, and other factors. As the most common cause of adult-onset nephrotic syndrome worldwide, MN is an immune-mediated glomerular disease [41], with muscle-type phospholipase A2 receptor and thrombospondintype-1 domain-containing 7A identified as the target antigens [42, 43].

Some experts have recently brought attention to the link between GM and the susceptibility to these three types of kidney diseases [11, 20, 44]. Several studies speculated that GM influences kidney disease in the following ways [45]. First, the imbalance of GM can disturb the intestinal mucosal barrier and accelerate the absorption of intestinal toxins into blood, which exerts a negative impact on other organs, especially the kidney [46]. Conversely, certain GM can counteract the adverse effects of intestinal toxins and antigens on the kidneys by enhancing the release of antimicrobial peptides [16]. Second, GM could regulate innate and adaptive immune responses by inducing intestinal epithelial cells to express nucleotide-binding oligomerization domain-like receptor 1 and toll-like receptors on the intestinal mucosal surface, which in turn fosters the formation and maturation of gut-associated lymphocytes tissue [47]. Therefore, it is a valid assumption that GM is linked to the pathogenesis of multiple kidney diseases, but this correlation is still unclear. In this study, we conducted MR analysis to validate the genetic causation between GM and multiple kidney diseases as well as to discover unique bacterial taxa that can serve as new predictive markers for multiple kidney diseases.

Given that the majority of genetic variations contribute minimally to the overall risk factor variability, MR studies require a substantial sample size and sufficient magnitude [48]. Our data included large numbers of participants, encompassing 452,208 individuals for studying DN, 7,979 individuals for MN, and 5,957 individuals for IgAN.

Several previous MR studies have recognized the negative or protective effect of GM on three types of kidney diseases [49–51]. However, the causality between GM and diverse kidney diseases is still largely unknown. In our results, we suggested two GM, eight ones and five ones associated with DN, IgAN, and MN, respectively, at the genus level. To be exact, our study revealed that the *Dialister* was a protective factor while the *Lachnospiraceae UCG-008* was a risk factor for DN. In line with our study, the decreased abundance of the bacterial genus *Dialister* showed a significant association with the risk of IgAN and the progression of CKD [52, 53]. *Dialister* is characterized by producing propionate through a succinate pathway [54]. Propionate plays a vital role in the gut-kidney axis as some studies have shown that propionate can activate G protein-coupled receptors expressed in both the kidney and renal arteries, and the activation of G protein-coupled receptor-41 and G protein-coupled receptor-43 has the potential to regulate blood pressure and boost cell immune responses, respectively [55, 56]. Therefore, we can speculate that the *Dialister* may lower the risk of DN by increasing propionate production or strengthening the intestinal mucosal barrier. As a result, based on these findings, controlling the quantity of *Dialister* by employing techniques such as fecal transplantation therapy or specialized probiotics could potentially be a therapy for DN.

Few studies explored the association between GM and IgAN. In this study, *Christensenellaceae R.7*, *Clostridium sensu stricto*1, *Lachnospiraceae UCG-004*, *Lachnospiraceae UCG-010*, *Oscillospira*, *Ruminococcaceae UCG-010*, and *Terrisporobacter* may be protective factors for IgAN and the *Clostridium innocuum* seemed to be a risk factor for IgAN. Among them, the genus *Clostridium* has been discovered that it can influence the development of T regulatory cells by supplying bacterial antigens and short-chain fatty acids [57]. These variables influence T regulatory cell activity and contribute to lowering levels of pro-inflammatory cytokines [58]. Thus, the *Clostridiuminnocuum* may contribute to the risk of IgAN by aggravating the disturbance of autoimmune response. Moreover, a previous study showed that the abundance of *Clostridiuminnocuum* was enriched in CKD patients [59]; however, the patients had a significant decrease in 24-h proteinuria after 4 months of the Yi-Shen-Hua-Shi intervention (a traditional Chinese medicine that treats CKD), accompanying the decline of *Clostridiuminnocuum* [60]. This discovery further indicated the negative impact of *Clostridiuminnocuum* on kidney disease. Consequently, it is crucial to introduce preventive measures that are directly related, such as incorporating probiotics or targeted antibiotics, modifying dietary behaviors, and improving unhealthy lifestyles. For example, individuals at high risk of IgAN could consider taking specific probiotics to increase beneficial gut bacteria or selecting antibiotics to lower levels of *Clostridiuminnocuum*.

As for MN, we suggested that high abundance of *Butyricicoccus*, *Catenibacterium*, *Flavonifractor*, and *Lachnospira* may increase the risk of MN, while the *Ruminococcaceae UCG-011* seems to be a protective factor. The *Ruminococcaceae UCG-011* is a Gram-positive anaerobic bacterium belonging to the *Ruminococcaceae* family and the *Firmicutes* phylum, which are recognized for their capability to hydrolyze and ferment numerous types of polysaccharides, leading to the generation of short-chain fatty acids, such as butyrate [61, 62]. Recent studies found that short-chain fatty acid produced by GM-mediated fermentation have been shown to be nephroprotective [63, 64]. There is no direct

evidence for the role of *Ruminococcaceae UCG-011* in mitigating the development of MN in past research. In our study, we first discovered that the genus *Ruminococcaceae UCG-011* is a protective factor for MN.

It is widely acknowledged that immunotherapy holds great promise as a treatment modality for various kidney diseases. To identify the immune cell characteristic in kidney diseases, we determined the associations between three types of kidney diseases and immune infiltration. Our immunoinfiltration analysis revealed significant discrepancies in the proportions of infiltration among 28 kinds of high-expression immune cells in IgAN, including aDC, B cells, $CD8^+$ T cells, $CD8^+$ Tem, macrophages, NK cells, and so on. As illuminated in a recent review article, macrophages/DC capture antigens and present them to helper T cells. Once activated, helper T cells promote the stimulation and activation of mature B cells located in the tonsillar germinal center, resulting in the production of Gd-IgA1. This substance subsequently enters the systemic circulation via the lymphatic system, contributing to renal injury [65]. Besides, the proportion of $CD4^+$ Tem, $CD8^+$ central Tem, $CD8^+$ Tem, cDC, M1 macrophages, and mast cells was found to be elevated in DN group, which is in line with the previous study [66]. Interestingly, these results are largely consistent with our later two-step MR approach, indicating that immune cells may act as mediating factors for GM affecting kidney diseases. Nevertheless, more in-depth exploration, such as the identification of differentially expressed immune-related genes, machine learning, and protein-protein interaction network analysis, is still needed to further unveil the pathologic mechanism of kidney diseases.

However, there are still some limitations in our study. First, the cases of kidney disease subtypes, especially MN and IgAN, were relatively insufficient, which may affect the generalizability and reliability of the study results. Second, all GWAS data used in this research were mainly derived from European individuals, so it is uncertain whether the findings can be applied to non-European populations. Future large-scale and multiethnic clinical studies will enrich our research results. Third, it is essential to conduct additional experimental and clinical validation studies to assess the clinical relevance of microbial species, as the MR analysis relies on untestable assumptions. Last but not least, despite our investigation into the key factors between GM and multiple kidney diseases, the mechanisms how GM influenced the onset of kidney diseases remained to be studied. In spite of these potential limitations, we ascertained through a series of sensitivity assessments that the causal results in this study were sound. That is to say, this study accurately reflects the strong association between GM and the risk of three types of kidney diseases.

Conclusions

Through MR analysis of the causal relationship between 119 intestinal microflora and three types of kidney diseases, we identified 6 positive and 9 negative causal associations, which offers a theoretical foundation to direct clinical practice and potentially indicates directions for upcoming studies. It is desired that medical professionals and scientists increase their focus on observing GM for prevention of multiple kidney diseases, with the aim of identifying additional predictors and beneficial microbiota for renal function, which is of great clinical significance.

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Statement of Ethics

Ethics approval was not required.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

B.L. and J.-H.Z. conceived, designed, and planned the study and contributed to the critical revision of the manuscript. B.L., Z.-J.C., and R.W. acquired the data. Z.-J.C., M.-Y.Y., and R.W. analyzed the data. Z.-J.C. drafted the manuscript. All authors interpreted the results and read and approved the final manuscript.

Data Availability Statement

The data in this study were obtained from MiBioGen, IEU Open GWAS Project, UK Biobank, FinnGen, GWAS Catalog, and Gene Expression Omnibus.

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