Assessing the Relationship Between Gut Microbiota and Kidney Stones: A Two-Sample Mendelian Randomization Analysis

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Purpose: Increasing evidence suggests that gut microbiota are associated with the risk of kidney stone disease; however, whether a causal relationship exists remains unclear. We used Mendelian randomization to assess the potential causal relationship between gut microbiota and kidney stone disease risk.

Materials and Methods: Genetic instrumental variables for gut microbiota were identified from a genome-wide association study of 18,340 participants. Summary statistics for kidney stone disease were derived from genome-wide association studies, including 284,598 cases and 480,873 controls. The inverse-variance weighted method was used as the primary analysis. To test the robustness of the results, we further performed the weighted-median method, MR-Egger regression, and the MR pleiotropy residual sum and outlier test. Finally, reverse Mendelian randomization analysis was performed to evaluate the possibility of reverse causation.

Results: We identified suggestive associations between 4 bacterial traits and the risk of kidney stone disease: class Lentisphaeria (odds ratio: 0.82; 95% confidence interval: 0.69-0.98; P = .032), genus Oscillibacter (odds ratio: 0.79; 95% confidence interval: 0.66-0.96; P = .018), order Victivallales (odds ratio: 0.82; 95% confidence interval: 0.68-0.98; P = .034), and genus Olsenella (odds ratio: 1.26; 95% confidence interval: 1.03-1.53; P = .022). The results of sensitivity analyses for these bacterial traits were consistent. We did not find statistically significant associations between kidney stone disease and these 4 bacterial traits in the reverse analysis.

Conclusion: This systematic analysis provides evidence supporting a potential causal relationship between 4 gut microbiota taxa and kidney stone disease risk. Further studies are needed to determine how gut microbiota influence kidney stone disease development.

Keywords: kidney stone disease; gut microbiota; mendelian randomization; single nucleotide polymorphism

INTRODUCTION

Kidney stone disease (KSD) is one of the most common diseases in urology. Kidney stones affect approximately 15% of the population, and 50% of patients experience recurrence within 5 years after the first stone episode.[1] At present, many factors are believed to affect the formation of kidney stones, including genetic factors, environmental factors, dietary habits, and others. In addition, many systemic diseases, such as diabetes, hypertension, and metabolic syndrome, are strongly associated with the risk of kidney stones.[2] Patients with kidney stones often present with back pain and hematuria, as well as nausea, vomiting, fever, hydronephrosis, and even renal insufficiency. The resulting urinary tract obstruction, infection, and other complications may promote stone formation. With the development of minimally invasive treatment, the management of renal calculi has substantially improved. However, the increasing prevalence of the disease has resulted in an economic burden on both patients and the community.[3] The trillions of microbes in the adult gut are known as the gut microbiota (GMB), a complex and evolving microbial community that functions like a metabolic organ. An imbalance in the gut microbiota can lead to metabolic disorders of the gut microbiota and subsequently affect immune function.[4] Diet, as a major factor in metabolism, is generally considered an important factor in the occurrence of KSD. GMB is also an important regulator of dietary metabolism. Recent advances in human microbiome sequencing have led to important breakthroughs showing how GMB, through the fermentation of fibers, carbohydrates, and proteins, produces a wide range of metabolites that have broad health effects.[5] Although gut microbiota have been associated with KSD, the causal nature of this relationship remains elusive.[6]

Mendelian randomization (MR) analysis is a statistical method designed to infer potential causality from observational association outcomes.[7] MR uses genetic variants associated with exposure as surrogates for exposure to assess the relationship between the surrogate and the outcome. In recent years, MR analysis has been used to assess the potential causal relationship between gut microbiota and disease-risking genes.[8-10] Although Liu et al have conducted research on the relationship between gut microbiota and kidney stones, they found no causal relationship between calcium oxalate and

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Table 1. Details of the genome-wide association studies and datasets used in the analyses.

Exposure or outcome	Sample size	Ancestry	Links for data download	PMID
Human gut microbiome	18,340 participants	Mixed	https://mibiogen.gcc.rug.nl	33462485
Kidney stone	284,598 cases; 480,873 controls	European ancestry	http://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90016001-GCST90017000/GCST90016564/	34741163

kidney stones.[11] Therefore, there is an urgent need to investigate the potential causal relationship between gut microbiota and the risk of KSD.

In this study, to explore the potential causal relationship between gut microbiota and KSD and to identify specific pathogenic bacterial taxa, we conducted a 2-sample MR study based on summary data from genome-wide association studies (GWASs).

MATERIALS AND METHODS

Study Design

The main goal of this study was to investigate the causal relationship between gut microbiota and KSD. The overall design of the present study is presented in (**Figure 1**). This study used gut microbiota as an exposure factor and selected single nucleotide polymorphisms (SNPs) as instrumental variables (IVs) based on a threshold of $P < 1 \times 10\text{-}5$. We conducted forward MR analysis using KSD as the outcome. Then, we performed reverse MR analysis using gut microbiota as the outcome.[12,13]

In this study, MR analysis had to meet 3 main assumptions: 1) the relevance assumption: IVs are strongly associated with exposure and are independent of each other; 2) the exclusion restriction assumption: IVs are unrelated to the outcome; and 3) the independence assumption: IVs are not related to confounding factors.

Data Sources

The summary statistics for the human gut microbiome used in this study were obtained from the most recent GWAS meta-analysis, which included 18,340 participants from 24 cohorts. Details of the study have been described elsewhere.[14,15] Briefly, this study conducted association analyses by coordinating 16S rRNA gene sequencing profiles and genotyping data from diverse cohorts spanning multiple countries, including the United States, Canada, Germany, Denmark, the Netherlands, Belgium, Sweden, Finland, the United Kingdom, and others. The analyses were adjusted for various factors, such as age, sex, technical covariates, and genetic principal components, to elucidate correlations. As the present study was based on publicly available summary data, no additional ethics approval or consent to participate was required. KSD data were derived from GWASs and meta-analyses in European cohorts from EstBB, FinnGen, and Lifelines, including 284,598 patients and 480,873 controls. The KSD case definition included any participant with an International Classification of Diseases code for nephrolithiasis in the electronic health record, resulting in a cumulative incidence that reflects lifetime risk across large, population-based biobanks. Controls were defined as individuals without any such record. Details of the data sources in this MR study are shown in (**Table 1**).[16]

Selection of Instrumental Variables

We first removed 15 bacterial traits without specific names, leaving 196 bacterial traits, including 9 phyla, 16 classes, 20 orders, 32 families, and 119 genera. Then, we selected the instrumental variables at $P < 1 \times 10\text{-}5$. To obtain IVs from independent loci, we set the linkage disequilibrium threshold at $R2 < 0.001$ and the clumping distance at 10,000 kb in 1000 Genomes EUR data using the "Two Sample MR" package. SNPs with the lowest *P* value for the associated trait were retained for clumping with 196 bacterial traits.[17] A total of 2,699 independent SNPs were found to be associated with 196 bacterial traits. Finally, we also computed the F statistics for each SNP to eliminate genetic variations with weak statistical power ($F < 10$). The SNPs obtained above were used as IVs to study the effects of gut microbiota on KSD. To assess whether KSD had a causal impact on the gut microbiota, we employed a genome-wide significance threshold ($P < 5 \times 10\text{-}8$) to screen for SNPs associated with KSD. These SNPs were used as IVs in reverse MR analysis, with KSD as the exposure and gut microbiota as the outcome. The statistical methods used in reverse MR analysis were the same as those used in forward MR analysis.

Statistical Analysis

In this study, inverse-variance weighted (IVW), weighted median (WM), simple mode, and weighted mode methods were used to verify the causality between gut microbiota and KSD.[18] IVW is considered the standard analytical method. It assumes that all instrumental

Table 2. Effect estimates of the associations of KSD with class Lentisphaeria, genus Oscillibacter, order Victivallales, and genus Olsenella in the reverse MR analyses

Gut microbiome	Methods	N. SNPs	OR	95% CI	*P* value	Intercept *P* value
Class Lentisphaeria	IVW	19	0.99	0.93-1.05	0.732	
	Weighted median	19	0.99	0.90-1.08	0.766	
	MR-Egger	19	/	/	/	0.995
Genus Olsenella	IVW	18	0.99	0.92-1.06	0.728	
	Weighted median	18	0.94	0.85-1.04	0.217	
	MR-Egger	18	/	/	/	0.640
Genus Oscillibacter	IVW	19	1.00	0.96-1.05	0.945	
	Weighted median	19	1.02	0.95-1.08	0.616	
	MR-Egger	19	/	/	/	0.673
Order Victivallales	IVW	19	0.99	0.93-1.05	0.732	
	Weighted median	19	0.99	0.90-1.08	0.77	
	MR-Egger	19	/	/	/	0.995

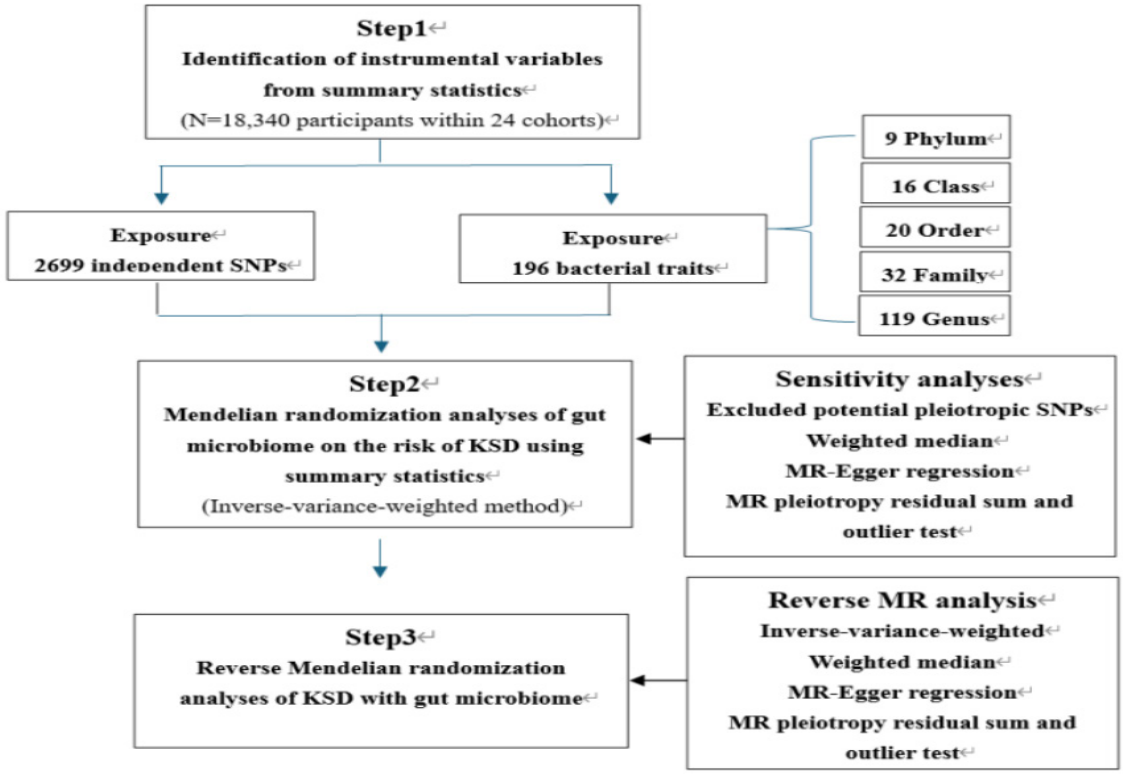

Figure 1. Overview of the analysis process of the causal relationship between the microbiota and KSD through MR analysis.

variables are valid, and the effect size of the causal exposure is calculated using the standard error of each instrumental variable as the reciprocal of the weights. However, IVW regression does not take intercept terms into account; therefore, we also adopted MR-Egger, WM, simple mode, and weighted mode analyses.[19] If the above 5 methods provide similar results for causal inference, the results are considered reliable. Heterogeneity between SNPs was detected using Cochran Q.[20] Significant heterogeneity was defined as $P < .05$. In addition, we used the MR-PRESSO method to detect SNP outliers. If outliers were detected, they were removed, and the analysis was repeated. The MR-Egger intercept was used to test for horizontal pleiotropy of SNPs, and a statistically significant test result ($P < .05$) indicated significant pleiotropy in the analysis results. Sensitivity testing using the leave-one-out method was performed to assess whether the MR results changed significantly when each IV was excluded in turn.[21]

Data Analysis

All statistical analyses were performed in R, version 4.3.1. Univariate Mendelian randomization analyses were primarily conducted using the "Two Sample MR" software package, version 0.5.7. MR-PRESSO tests were performed using the "MRPRESSO" package. $P < .05$ was considered statistically significant.

RESULTS

Main Results of the 196 Bacterial Traits With the Risk of KSD

The F statistics for the 196 bacterial traits were all above 10, suggesting a lower possibility of weak instrument bias. The MR results for the associations between all 196 bacterial traits and the risk of KSD are presented in Additional file 1: Table S1. Briefly, we observed suggestive evidence that 5 bacterial traits were associated with the risk of KSD using the IVW method.

In particular, we found that genetically predicted class Lentisphaeria was negatively associated with KSD using the IVW method (odds ratio [OR]: 0.84; 95% confidence interval [CI]: 0.70-1.00; $P = .049$) (**Figure 2A**). The association between class Lentisphaeria and KSD remained stable in the weighted-median method (OR: 0.89; 95% CI: 0.70-1.13; $P = .341$). Furthermore, the MR-PRESSO test detected no outliers, and the results were consistent with those of the primary method ($P = .590$). In the MR-Egger regression, there was no evidence of directional pleiotropic effects (intercept P value = .613).

Genus Oscillibacter was also negatively associated with the risk of KSD using the IVW method (OR: 0.80; 95% CI: 0.67-0.96; $P = .017$) (**Figure 2B**). The results from the weighted-median method were consistent (OR: 0.82; 95% CI: 0.63-1.06; $P = .132$). Additionally, no evidence of directional pleiotropy was found in MR-Egger regression (intercept P value = .089), and no outliers were detected with the MR-PRESSO test; the effect estimate was similar ($P = .035$).

Order Victivallales was also negatively associated with the risk of KSD using the IVW method (OR: 0.84; 95% CI: 0.70-1.00; $P = .049$) (**Figure 2C**). The results from the weighted-median method were consistent (OR: 0.89; 95% CI: 0.70-1.14; $P = .363$). The absence of outliers in the MR-PRESSO test, along with results consistent with the primary method ($P = .611$), further sup-

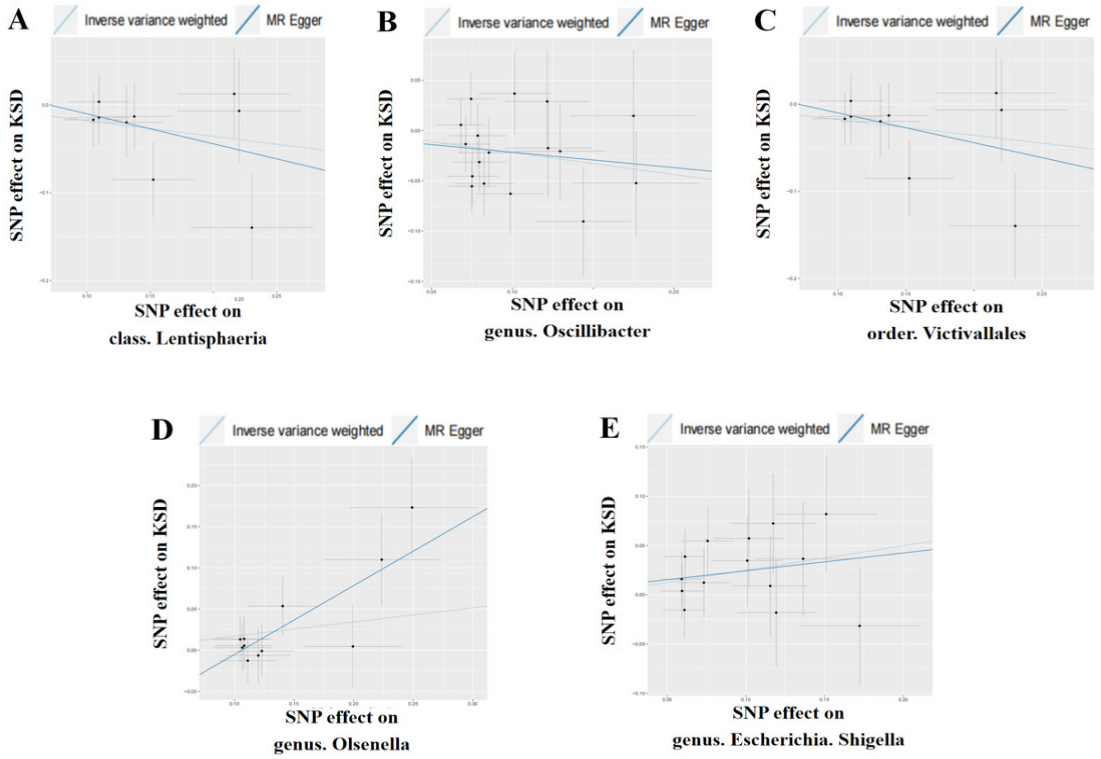

Figure 2. Scatter plot of the associations of genetic variants with 4 bacterial traits and the risk of KSD.

ports the robustness of the findings. In the MR-Egger regression, there was no evidence of directional pleiotropic effects (intercept *P* value = .613).

In contrast, genus Olsenella was positively associated with KSD risk using the IVW method (OR: 1.19; 95% CI: 1.02-1.39; *P* = .029) (Figure 2D). In sensitivity analyses, the weighted-median method produced similar estimates (OR: 1.05; 95% CI: 0.85-1.30; *P* = .655), although with wider confidence intervals. Additionally, little evidence of directional pleiotropy was found in MR-Egger regression (intercept P value = .043), and no outliers were detected with the MR-PRESSO test; the effect estimate was similar (*P* = .449).

Genus Escherichia-Shigella was also positively associated with the risk of KSD using the IVW method (OR: 1.28; 95% CI: 1.02-1.61; *P* = .034) (**Figure 2E**). The results from the weighted-median method were consistent (OR: 1.31; 95% CI: 0.95-1.81; *P* = .106). Furthermore, the MR-PRESSO test detected no outliers, with results aligning with the primary method (P = .883). In the MR-Egger regression, there was no evidence of directional pleiotropic effects (intercept *P* value = .832).

To further assess the influence of potential directional pleiotropy on the causal effect estimates, we used the GWAS Catalog to scan the SNPs associated with these 5 bacterial traits, and some SNPs were found to be associated with other traits. After excluding these pleiotropic SNPs, we recalculated the updated IV sets, and the associations of class Lentisphaeria, genus Oscillibacter, order Victivallales, and genus Olsenella with the risk of KSD remained stable using the IVW method (OR: 0.82; 95% CI: 0.69-0.98; *P* = .032 for class Lentisphaeria; OR: 0.79; 95% CI: 0.66-0.96; *P* = .018 for genus Oscillibacter; OR: 0.82; 95% CI: 0.68-0.98; *P* = .034 for order Victivallales; OR: 1.26; 95% CI: 1.03-1.53; *P* = .022 for genus Olsenella) (Figure 3). However, the relationship between genus Escherichia-Shigella and KSD was unstable (OR: 1.31; 95% CI: 0.99-1.73; *P* = .061).

Results of Reverse MR Analysis

Finally, we evaluated the potential reverse associations between the 4 bacterial traits and KSD using reverse MR analyses. We did not find statistically significant associations between KSD and any of these 4 bacterial traits using the IVW method (OR: 0.99; 95% CI: 0.93-1.05; *P* = .732 for class Lentisphaeria; OR: 1.00; 95% CI: 0.96-1.05; *P* = .945 for genus Oscillibacter; OR: 0.99; 95% CI: 0.93-1.05; *P* = .732 for order Victivallales; OR: 0.99; 95% CI: 0.92-1.06; *P* = .728 for genus Olsenella). The results were stable across sensitivity analyses, which are listed in (**Table 2**).

DISCUSSION

As a Mendelian randomization study, our findings are primarily hypothesis-generating and represent the first step in establishing causal inference from gut microbiota to KSD. This study confirmed that genus Olsenella is a risk factor for KSD, whereas class Lentisphaeria, genus Oscillibacter, and order Victivallales have potential protective effects against KSD.

Kidney stone disease is a complex disease that can be caused by genetic and environmental factors. Given that 75% of kidney stones are composed of calcium oxalate, it is noteworthy that oxalate serves as an end product of amino acid metabolism, potentially exerting

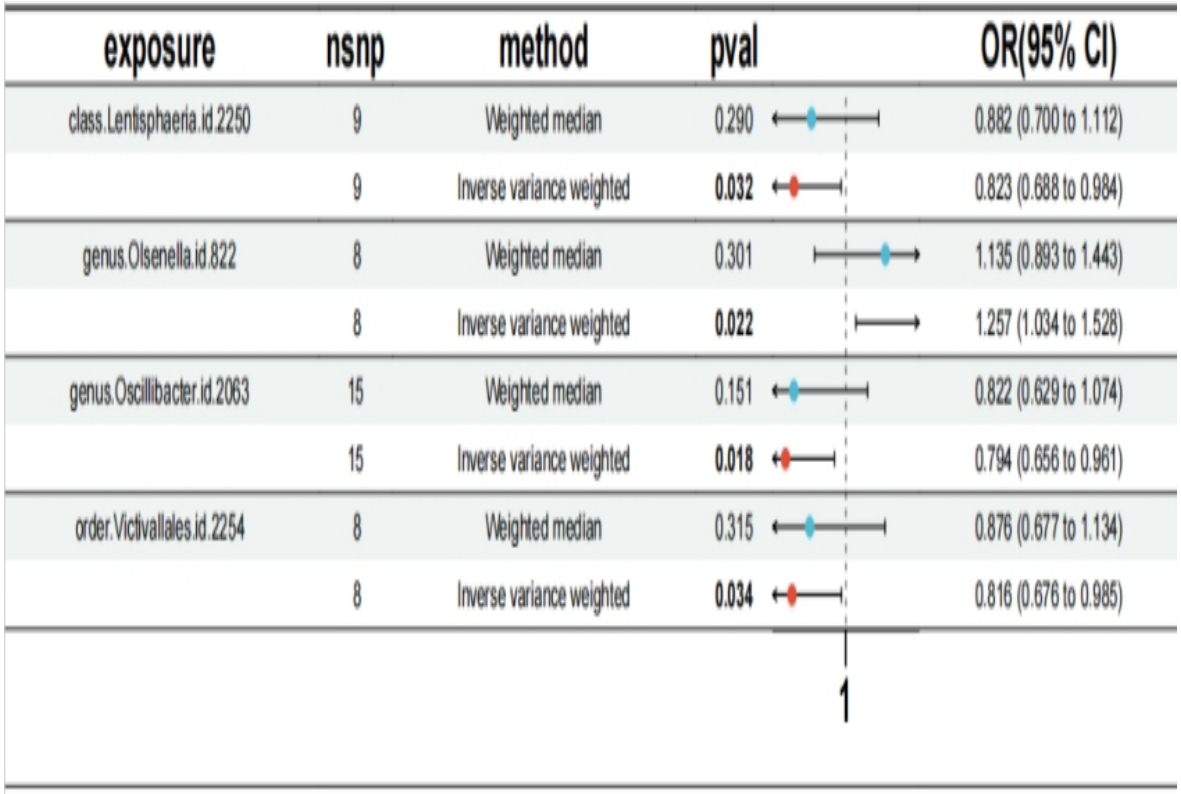

Figure 3. Forest plot of the associations between 4 genetically determined bacterial traits and the risk of KSD.

an influence on the structure and composition of the gut microbiota.[22] Various pathological metabolic changes, such as diabetes, obesity, chronic kidney disease, cardiovascular disease, metabolic syndrome, and hypertension, are thought to be associated with stone formation.[23,24] Oxalate formation has attracted medical attention because the human body mainly depends on the gut microbiota to maintain oxalate homeostasis. Siener and co-workers indicated that, by increasing intestinal oxalate degradation, O. formigenes decreases the oxalate concentration available for absorption at constant rates in the intestine.[25] Therefore, it reduces oxalate excretion in urine and protects against the formation of calcium oxalate kidney stones.

Little is known about the general role of gut microbiota in the pathophysiology of kidney stones. Stern et al published the first evidence that patients who form kidney stones have a unique gut microbiota compared with controls.[26] Using next-generation sequencing, they observed that Bacteroides spp were more abundant in kidney stone formers, whereas Prevotella spp were more abundant in controls. Currently, the available data suggest that manipulation of gut bacteria, such as colonization with O. formigenes, may represent a novel therapeutic application in patients who form kidney stones. Liu and co-workers indicated that no causal relationship was found between Oxalobacteriaceae and kidney stones. The relationship between gut microbiota and kidney stones is not entirely dependent on the presence or absence of Oxalobacter/Oxalobacter formigenes.[11]

In this study, genus Olsenella was the only bacterial taxon identified as being positively associated with KSD after pleiotropic SNPs were excluded. Genus Escherichia-Shigella was a risk factor for KSD, but the relationship was unstable when polymorphic SNPs were excluded. However, no studies have reported changes in genus Olsenella in patients with KSD. A recent paper by Colombo et al investigated subgingival biofilms in patients with periodontal disease and reported that a large number of opportunistic species, such as gut bacteria, Olsenella, Neisseria, and even Clostridioides difficile, in addition to yeasts such as Candida, are associated with periodontitis.[27] Previous studies have shown that the relative abundance of Escherichia-Shigella in patients with kidney stones is higher than that in healthy individuals, and the overall effect size is moderate and significant ($Z = 3.23$; $P = .001$). The proportion of KSD was 2.47 times higher than that in controls. Escherichia-Shigella was negatively correlated with urinary citrate ($r = -0.56$; $P < .08$). Citrate can bind free calcium and produce soluble calcium citrate, which reduces the supersaturation of calcium salts and makes citrate a urinary stone inhibitor. The risk of kidney stones increases with a decrease in citrate concentration.[28]

Lentisphaeria has the ability to produce acid and gas and has been found to be involved in the metabolism of polysaccharides and proteins in the gut. One study found that Lentisphaeria was more abundant in the gut of healthy people and less abundant in patients with inflammatory bowel disease and nonalcoholic fatty liver disease.[29] Oscillibacter, an understudied group of anaerobic bacteria in the Clostridium group, belongs to Firmicutes and the family Ruminococcaceae and is widely found in the gut of animals and humans. It is associated with obesity, emaciation, gallstones, and chronic constipation and has been shown to be associated with positive or negative changes during the course of disease. Oscillibacter is a short-chain fatty ac-

id-producing bacterium that produces butyrate, which is considered a candidate for next-generation probiotics because butyrate is an important parameter for screening next-generation probiotics.[30] Order Victivallales is a naturally occurring gut microbiota that plays an important role in ecosystems and interacts with other microorganisms. Current studies have shown that gut microbiota mainly affect the development of kidney stones through metabolites. Victivallales, which has been identified as a producer of short-chain fatty acids, produces acetic acid, propionic acid, and butyric acid, among others, which play an important role in oxalic acid metabolism and may shed light on its protective mechanism.[31]

Many previous studies have suggested that patients with KSD are often accompanied by dysbiosis of the gut microbiota, but these were observational studies.[32] This study reinforces the causal effect of gut microbiota on KSD by using genetic epidemiological methods. In addition, the F statistics of the IVs used in our study all satisfied the threshold of >10, suggesting that our analyses were less likely to suffer from weak instrument bias. We further performed reverse MR analysis, which excluded reverse causality. The study of causality will be the direction of future research on the role of intestinal flora in disease development. Today, many studies have focused on the role of certain gut bacteria in disease development using animal models. Our results may provide guidance for the selection of individual gut bacteria to study the role of gut microbiota in the pathogenesis of KSD.

However, our study has some limitations. First, bacterial taxa were analyzed only at the genus level, not at a more specific level, such as the species or strain level. Second, although most participants in the GWASs were of European descent, participants of other ethnicities might have influenced the results. Therefore, generalizing our findings to other ethnic groups may be limited. Furthermore, the effects of the bacterial traits we reported were relatively weak, and no other independent KSD GWASs had sufficient sample sizes to validate our findings. Finally, the study was not able to stratify disease severity in different age groups and populations. Therefore, more extensive and detailed studies are needed to confirm our results in the future. To translate these genetic findings into clinical insights, a multistage research pathway is recommended. First, in vivo animal models are needed to confirm that manipulating these specific bacterial taxa alters calcium oxalate crystal formation. Second, prospective cohort studies can assess whether changes in these microbiotas over time predict KSD incidence in humans. Finally, understanding the underlying mechanisms, such as the roles of bacterial-derived metabolites including oxalate, short-chain fatty acids, or immune-modulatory molecules, will be crucial for developing targeted therapies.

CONCLUSIONS

In conclusion, our MR analysis provides novel genetic evidence supporting a causal relationship between specific gut microbiota and KSD. Lentisphaeria, genus Oscillibacter, and order Victivallales are effective protective factors against this disorder, whereas genus Olsenella may act as a prominent risk factor for KSD. These findings are primarily hypothesis-generating and highlight the need for future experimental and mechanistic studies to validate these microbiota as potential therapeutic targets for the prevention of kidney stones.

SUMMARY

This study suggests that some gut bacteria may influence kidney stone risk: Lentisphaeria, Oscillibacter, and Victivallales may be protective, whereas Olsenella may increase risk.

AVAILABILITY OF DATA AND MATERIALS

The original contributions presented in the study are included in the article material. Further inquiries can be directed to the corresponding authors.

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AUTHORS' CONTRIBUTIONS

Conceptualization, SW; data curation, YC and SW; formal analysis, SW and YC; investigation, BF and TS; methodology, SW and SX; project administration, SW and JG; software, SW and ZW; validation, SW; visualization, YC; writing – original draft, SW; writing – review and editing, YC and SZ. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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