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Submitted to Journal:
Frontiers in Immunology

Specialty Section:
Microbial Immunology

ISSN:
1664-3224

Article type:
Original Research Article

Received on:
30 Sep 2023

Accepted on:
26 Feb 2024

Provisional PDF published on:
26 Feb 2024

Frontiers website link:
www.frontiersin.org

Citation:
Wang S, Yin F, Sun W, Li R, Guo Z, Wang Y, Zhang Y, Sun C and Sun D (2023) The causal relationship between gut microbiota and nine infectious diseases: A two-sample Mendelian randomization analysis. *Front. Immunol.* 15:1304973.
doi:10.3389/fimmu.2024.1304973

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Provisional

The causal relationship between gut microbiota and nine infectious diseases: A two-sample Mendelian randomization analysis

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Keywords: gut microbiota, infectious diseases, causality, GWAS, Mendelian randomization

Abstract

Background: Evidence from observational studies and clinical trials has associated gut microbiota with infectious diseases. However, the causal relationship between gut microbiota and infectious diseases remains unclear.

Methods: We identified gut microbiota based on phylum, class, order, family, and genus classifications, and obtained infectious disease datasets from the IEU OpenGWAS database. The two-sample Mendelian Randomization (MR) analysis was then performed to determine whether the gut microbiota were causally associated with different infectious diseases. In addition, we performed reverse MR analysis to test for causality.

Results: Herein, we characterized causal relationships between genetic predispositions in the gut microbiota and nine infectious diseases. 8 strong associations were found between genetic predisposition in the gut microbiota and infectious diseases. Specifically, the abundance of *class Coriobacteriia*, *order Coriobacteriales* and *family Coriobacteriaceae* was found to be positively associated with the risk of Lower Respiratory Tract Infections (LRTI). On the other hand, *family Acidaminococcaceae*, *genus Clostridium sensu stricto 1* and *class Bacilli* were positively associated with the risk of endocarditis, cellulitis, and osteomyelitis, respectively. We also discovered that the abundance of *class Lentisphaeria* and *order Victivallales* lowered the risk of sepsis.

Conclusion: Through MR analysis, we found that gut microbiota were causally associated with infectious diseases. This finding offers new insights into the microbe-mediated infection mechanisms for further clinical research.

1 INTRODUCTION

Infections such as pneumonia, gastrointestinal are the most common infections in hospitalized patients (1). Statistically, these infections account for more than 20% of deaths globally, with 245,000 sepsis cases occurring in the United Kingdom (UK) alone annually (2, 3). Due to antibiotic resistance, an aging population, and emerging pathogens, the infection-induced disease burden is expected to rise, making the identification of the factors that can modify these illnesses essential (4-6). Generally, severe bacterial infections are believed to be caused by the invasion of the blood and tissues by pathogenic microorganisms, resulting in tissue necrosis and even host death (7). Furthermore, with advancements in sepsis research in recent years, it has been found that uncontrolled infection may lead to dysregulation of the host's immune response. At the same time, excessive immune response results in the secretion of a multitude of cytokines, leading to organ dysfunction and, ultimately, host death (8-10). Therefore, effective prevention and treatment of serious infectious diseases has become critical.

In a healthy host, the gut microbiota regulate various homeostasis mechanisms, including immune function and gut barrier protection (11, 12). Mechanisms of gut microbiota leading to infectious diseases including allowing the expansion of pathogenic gut bacteria, primes the immune system to produce a robust pro-inflammatory response, and reducing the production of beneficial microbial products, such as short-chain fatty acids. ~~Previous research evidence has demonstrated a close relationship between intestinal microbial disorders and the emergence and progression of infectious diseases~~ (13-15). Furthermore, gut microbiota interact with infectious diseases. On the one hand, susceptibility to infectious diseases may be aggravated by intestinal micro-ecological disorders. Under certain conditions, intestinal bacteria can directly invade peripheral blood through intestinal mucosa. They could also enter distant organs via the "gut-organ" axis, causing bacterial translocation and eliciting systemic inflammatory responses. Further illness progression can lead to organ dysfunction ~~and even life-threatening septic shock~~ (16). On the other hand, severe infection could also cause alterations in the human intestinal microenvironment, resulting in the imbalance of intestinal flora and the release of inflammatory factors, damaging the intestinal mucosal barrier and further aggravating the disease (17). Although an increasing number of studies has associated gut microbiota with infectious diseases, the causal relationship between the two remains unclear.

In recent years, Mendelian Randomization (MR) analysis, a statistical approach for investigating causal relationships, has been mainly applied to the causal inference of epidemiological diseases. Since alleles follow the random allocation principle, this impact is not affected by confounding factors and reverse causation in traditional epidemiological research (18). The publication of large-scale gene-wide association (GWAS) data has resulted in the availability of a substantial number of reliable genetic variants for MR studies (19). As a result, this study analyzed the causal relationship between gut microbiota and infectious diseases through the MR analysis, providing useful insights into the clinical treatment of infectious diseases.

2 MATERIALS AND METHODS

2.1 Study Population

As shown in Figure 1, we used a two-sample MR (TSMR) approach to characterize the causal relationship between the intestinal microbiome and infectious diseases and finally conducted quality control tests, including the heterogeneity and gene pleiotropy tests, to verify the reliability of the results.

The gut microbiota, which is investigated in the context of human genetics by MiBioGen, an international consortium, was the primary exposure factor for our study (20). Herein, the human gut microbiota GWAS data, encompassing 18,340 individuals from 24 population cohorts, was used. A total of 196 bacterial groups (including 9 phyla, 16 classes, 20 orders, 32 families, and 119 genera) were included after excluding 15 genera with no specific species names.

Our primary outcomes were various infectious diseases with GWAS datasets from the UK Biobank project (21), a prospective cohort study that collected deep genetic and phenotypic data on approximately 500,000 individuals across the UK. Each participant had a wealth of phenotypic and health-related information. Genome-wide genotype data were collected from all participants by linking health and medical records to provide follow-up information. Pneumonia, upper respiratory tract infections (URTI), lower respiratory tract infections (LRTI), endocarditis, urinary tract infections (UTI), appendicitis, cellulitis, osteomyelitis, and sepsis were among the infectious diseases evaluated. [Information on exposure and outcome factors data is presented in Supplementary Table 1.](#)

2.2 Single Nucleotide Polymorphisms (SNPs) selection

Here, SNPs significantly associated with the relative abundance of 196 gut microbiota were selected as available Instrumental Variables (IVs). According to previous research, including multiple IVs can enhance the interpretation of exposure variation and improve the accuracy and reliability of analysis results. As a result, to ensure the independence of the included SNPs, this study selected IVs based on the results of association analysis (with $P < 1 \times 10^{-5}$ as the significance threshold), set the linkage disequilibrium criteria (with $R^2 < 0.001$) and genetic distance (with 10000 kb), and excluded highly correlated SNPs (22). Finally, SNPs associated with the relative abundance of gut microbiota were projected into the GWAS data on infectious diseases and the corresponding statistical parameters were retrieved. To align the effect exposure and outcome values with the same effect allele, the data were unified based on the statistical parameters of the same site in the relative abundance of gut microbiota and GWAS results of infectious diseases.

2.3 Research design

When using SNPs as IVs in MR analysis, three key assumptions should be met to better estimate the causal effects: (1) The IVs must be closely related to exposure factors; (2) The IVs should not be related to confounding factors; and (3) The IVs should only affect the results through exposure and not by any other means.

2.4 Statistical Analysis

In this study, Inverse variance weighted (IVW), MR-Egger, Weighted Median (WME) and Simple Mode (SM) and Weighted Mode (WM) were used to estimate the causal effect. The IVW method presumes that all genetic variants are valid. The IVW approach employs the ratio method to calculate the causal effect size of individual IVs and obtains the total effect size by aggregating each estimate for weighted linear regression (23). The primary distinction between the MR-Egger and the IVW methods is that the former considers the existence of the intercept term in regression analysis (24). The WME approach takes advantage of all available genetic variants' intermediate effects. An estimate (25) was obtained by weighting the inverse variance of each SNP's correlation with the outcome. The SM and WM methods are modality-based approaches, and modality-based estimation models aggregate SNPs with similar causal effects and return the estimates of causal effects for most cluster SNPs. The influence of each SNP on the cluster was weighted by WM per the inverse variance of its resulting effect.

Given that the IVW approach is more efficient than the other four MR Methods, it was used herein as the preferred causal effect estimation method. Additionally, the Beta values obtained in the results were converted into Odds Ratios (OR), and the 95% Confidence Interval (CI) was calculated to better explain the results. To verify whether the results were ‘false positives’ due to multiple tests, we used the Benjamini-Hochberg (BH) method under the False Discovery Rate (FDR) standard to correct the MR results for different classifications of gut microbiome (phyla, class, order, family and genus), the calculation formula is $FDR(i) = P(i) * m / i$, specifically, all p-values are arranged in ascending order, where p-values are denoted as P, the serial number of p-values is denoted as i, and the total number of p-values is denoted as m (26). Using the F statistic to test IV strength, the association of effect estimates that test causation may be affected by weak instrumental bias. The F statistic is calculated as follows: $F = R^2 (N - K - 1) / k (1 - R^2)$, where R^2 = variance (per gut microbiome) interpreted by IV, and n = sample size. The R^2 is estimated from the Minor Allele Frequency (MAF) and B-value using the following equation: $R^2 = 2 \times MAF \times (1 - MAF) \times b^2$ (27).

Additionally, we included sensitivity analysis, heterogeneity level test, and gene pleiotropy test in quality control to further test the stability and reliability of the results. For sensitivity analysis, the residual one method was used, and the combined effect value of the remaining SNPs was determined by sequentially deleting single SNPs to evaluate the impact of each SNP on the results. The heterogeneity test was performed to assess the heterogeneity of SNPs. The SNP measurement error caused by experimental conditions and population analysis, among other factors, could lead to bias in estimating causal effects (28). Using the intercept term of the MR-Egger regression, the horizontal gene pleiotropy test assesses whether IVs affect outcomes by other means apart from exposure (29). Potentially abnormal SNPs were identified through the Mendelian Randomization Multi-Effect Residual and Outlier (MR-PRESSO) (30) and leave-one-out methods (31). Finally, we performed reverse MR to analyze whether there was a reverse causality between infectious diseases and meaningful gut microbiota. The MR Analysis and quality control for this study were analyzed using version 4.0.3 R and version 0.5.6 TwoSampleMR packages.

3 RESULTS

3.1 TSMR analysis

The results of the 196 gut microbiota examined in relation to infectious disease are presented in Supplementary Table S4. The F-statistics for the gut flora ranged between 14.58 and 88.42 (all meeting the >10 threshold), implying that they are unlikely to be impacted by weak instrumental bias (Supplementary Table S23). Briefly, we identified 72 genera associated with infectious disease risk (Figure 2). However, after rigorous BH correction, only 8 gut microbiota showed stability in their association with infectious diseases (Table 1).

3.2 Gut microbiota and pneumonia

Overall, 9 gut microbiota were associated with the risk of respiratory infections in the primary MR analysis, suggesting that these gut microbiota may have an impact on the development of pneumonia. Among them, genus *Holdemanella* [odds ratio (OR): 1.10, 95% confidence interval (CI): 1.03- 1.19, P=0.006] and genus *Oxalobacter* (OR: 1.09, 95% CI: 1.02-1.15, P=0.005) were positively correlated with the risk of developing pneumonia. And class *Verrucomicrobiae* (OR: 0.88, 95% CI: 0.80- 0.97, P=0.009), order *Verrucomicrobiales* (OR: 0.88, 95% CI: 0.80- 0.97, P=0.009), family *Verrucomicrobiaceae* (OR: 0.88, 95% CI: 0.80- 0.97, P=0.009), genus *Akkermansi* (OR: 0.88, 95% CI: 0.80- 0.97, P=0.009), genus *Christensenellaceae* R.7group (OR: 0.83, 95% CI: 0.73-0.94,

P=0.005), *genus Coprococcus1* (OR: 0.89, 95% CI: 0.81-0.98, P=0.020) and *genus RuminococcaceaeUCG002* (OR: 0.90, 95% CI: 0.83-0.98, P=0.020) were negatively correlated with pneumonia (Figure 2). However, after BH correction these genera were not associated with pneumonia.

3.3 Gut microbiota and URTI

In the primary MR analysis, 7 gut microbiota were found to be associated with the risk of URTI. Among them *family Defluviitaleaceae* (OR: 1.41, 95% CI: 1.07- 1.85, P=0.014), *genus DefluviitaleaceaeUCG011* (OR: 1.44, 95% CI: 1.04-2.00, P=0.027), *genus Erysipelatoclostridium* (OR: 1.28, 95% CI: 1.02 -1.59, P=0.030) and *genus Veillonella* (OR: 1.51, 95% CI: 1.03-2.23, P=0.036) were positively associated with the risk of URTI. While *class Clostridia* (OR: 0.62, 95% CI: 0.44- 0.86, P=0.004), *genus Alistipes* (OR: 0.69, 95% CI: 0.51-0.93, P=0.015) and *genus Streptococcus* (OR: 0.75, 95% CI: 0.57-0.98, P=0.038) were negatively associated with the risk of URTI (Figure 2). None of these 7 gut microbiota were associated with significance in URTI after BH correction.

3.4 Gut microbiota and LRTI

9 gut microbiota were associated with the risk of LRTI (Figure 2). However, only 3 gut microbiota were associated with significance in LRTI after strict BH correction (Table 1). Specifically, we observed that the abundance of *class Coriobacteriia* (OR: 1.29, 95% CI: 1.12- 1.48 , $P_{FDR}=0.005$), *order Coriobacteriales* (OR: 1.29 , 95% CI: 1.12-1.48, $P_{FDR}=0.007$) and *family Coriobacteriaceae* (OR: 1.29 , 95% CI=1.12-1.48, $P_{FDR}=0.011$) were associated with a higher risk of LRTI.

In sensitivity analyses, the WME results were comparable to those of the IVW approach (OR: 1.28, 95% CI: 1.05- 1.55, P=0.012 for *class Coriobacteriia*; OR: 1.28, 95% CI: 1.06- 1.54, P=0.010 for *order Coriobacteriales* and OR: 1.28 , 95% CI=1.07- 1.53, P=0.007 for *family Coriobacteriaceae*), but with wider confidence intervals (Figure 3). Furthermore, the MR-Egger regression intercepts showed no evidence of pleiotropy of these gut microbiota with LRTI (intercept P=0.977 for *class Coriobacteriia*; intercept P=0.977 for *order Coriobacteriales* and intercept P=0.977 for *family Coriobacteriaceae*). (Table 2 and Supplementary Table S34) No outliers were detected in the MRPRESSO regression. Heterogeneity analysis confirmed the accuracy of the results (Table 3 and Supplementary Table S45). Data robustness was further validated by the leave-one-out results, showing a consistent positive association between gut flora and LRTI risk (Supplementary Table S56).

3.5 Gut microbiota and endocarditis

In the primary MR analysis, 9 gut microbiota were associated with the risk of endocarditis (Figure 2). After BH correction, it was found that *family Acidaminococcaceae* abundance was positively associated with the risk of endocarditis (OR: 2.70, 95% CI: 1.47- 4.97, $P_{FDR}=0.045$) (Table 1).

In the sensitivity analysis, the WME method did not show statistical significance (OR: 1.67 , 95% CI: 0.82- 3.42, P=0.159) (Figure 3). However, the MR-Egger regression intercept did not show evidence of multiplicity of *family Acidaminococcaceae* with endocarditis (Intercept P=0.159). (Table 2 and Supplementary Table S34) MRPRESSO regression did not detect outliers, too. The results of heterogeneity analysis confirmed the accuracy of the results (Table 3 and Supplementary Table S45). The leave-one-out method further validated the data robustness (Supplementary Table S56).

3.6 Gut microbiota and UTI

7 gut microbiota were confirmed to be associated with the risk of UTI after primary MR analysis. Among them, *phylum Euryarchaeota* (OR: 1.07, 95% CI:1.02- 1.13, P=0.011), *class Bacteroidia* (OR:1.11, 95% CI:1.00-1.22, P=0.044), *order Bacteroidales* (OR:1.11, 95% CI:1.00-1.22, P=0.044), *genus Intestinibacter* (OR: 1.10, 95% CI: 1.00-1.20, P=0.047) and *genus RuminococcaceaeUCG005* (OR: 1.12, 95% CI: 1.01-1.24, P=0.025) were positively associated with the risk of UTI. While *family defluviitaleaceae* (OR:0.92, 95% CI:0.84- 1.00, P=0.038) and *genus Defluviitaleaceae UCG011* (OR:0.90, 95% CI:0.82-0.99, P=0.022) were negatively associated with the risk of UTI (Figure 2). No gut microbiota was causally associated with UTI after BH correction.

3.7 Gut microbiota and appendicitis

Primary MR analysis identified 4 gut microbiota associated with the risk of appendicitis. Among them, *genus LachnospiraceaeFCS020group* (OR:1.32, 95% CI:1.09- 1.61, P=0.005) and *genus Turicibacteria* (OR:1.23, 95% CI:1.01-1.50, P=0.043) were positively associated with the risk of developing appendicitis. While *family Acidaminococcaceae* (OR:0.73, 95% CI:0.57- 0.95, P=0.017) and *genus Eisenbergiella* (OR: 0.86, 95% CI:0.74-1.00, P=0.045) were negatively associated with the risk of developing appendicitis (Figure 2). No gut microbiota was causally associated with appendicitis after BH correction.

3.8 Gut microbiota and cellulitis

Although 10 gut microbiota were associated with the risk of cellulitis (Figure 2), only *genus Clostridiumsensustricto1* was positively associated with cellulitis after BH correction (OR: 1.30, 95% CI: 1.13-1.55, $P_{FDR}=0.046$) (Table 1).

In sensitivity analyses, the WME method showed similar results to IVW (OR: 1.25 , 95% CI: 1.01- 1.54, P=0.036)(Figure 3). The MR-Egger regression intercept did not show evidence of multiplicity of *genus.Clostridiumsensustricto1* with cellulitis (Intercept P= 0.856) (Table 2 and Supplementary Table S3). MRPRESSO regression did not detect outliers. The results of heterogeneity analysis confirmed the accuracy of the results (Table 2 and Supplementary Table S45). Meanwhile, leave-one-out results further validated the data robustness (Supplementary Table S56).

3.9 Gut microbiota and osteomyelitis

7 gut microbiota were associated with the risk of osteomyelitis (Figure 2). However, only *class Bacilliidae* was positively causally associated with osteomyelitis after BH correction (OR: 1.36, 95% CI: 1.13- 1.64, $P_{FDR}=0.022$) (Table 1).

In sensitivity analyses, the WME method showed similar results to IVW (OR: 1.22 , 95% CI: 0.93- 1.61, P=0.151)(Figure 3).The MR-Egger regression intercept did not show evidence of multiplicity of *class Bacilliidae* with cellulitis (Intercept P=0.125) (Table 2 and Supplementary Table S3).The MRPRESSO regression did not detect outliers. The results of heterogeneity analysis confirmed the accuracy of the results (Table 2 and Supplementary Table S45). Meanwhile, leave-one-out results further validated the data robustness (Supplementary Table S56).

3.10 Gut microbiota and sepsis

We identified a total of 10 gut microbiota associated with sepsis (Figure 2), only 2 gut microbiota were associated with sepsis after BH correction (Table 1). Notably, *class Lentisphaeria* (OR: 0.86,

95% CI: 0.78- 0.94, $P_{FDR}=0.026$) and order *Victivallales* (OR: 0.86, 95% CI= 0.78-0.94, $P_{FDR}=0.033$) abundance were negatively correlated with the risk of developing sepsis.

In the sensitivity analysis, the WME method showed similar results to IVW (OR: 0.85, 95% CI: 0.75- 0.97, $P=0.016$ for class *Lentisphaeria* and OR: 0.85, 95% CI: 0.75- 0.97, $P=0.015$ for order *Victivallales*) (Figure 3), the MR-Egger regression intercept showed no evidence of pleiotropy (intercept $P=0.125$ for class *Lentisphaeria* and intercept $P=0.944$ for order *Victivallales*) (Supplementary Table S3). Heterogeneity analysis confirmed the accuracy of the results (Table 2 and Supplementary Table S45). Leave-one-out results verified data robustness (Supplementary Table S56).

3.11 Inverse MR analysis

In the reverse MR, infectious disease was used as an exposure factor, and gut microbiota, which has been associated with infectious disease, was the outcome factor. The IVW results did not support a causal relationship between infectious disease and altered gut microbiota (Supplementary Table 67).

4 DISCUSSION

In this study, TSMR was used to investigate the causal relationship between the relative abundance of gut microbiota and infectious diseases. It is currently believed that ~~gut microbiota alterations may increase susceptibility to infectious diseases through the gut-organ axis~~ gut microbiota influences host metabolic health by producing a range of metabolites and molecules, including SCFA, bile acids, TMAO, LPS, etc. For instance, enterogenic SCFAs can affect the pulmonary immune environment in the respiratory system. Bacterial transmission, inflammation, and mortality increased when mice whose gut microbiota was disrupted by antibiotics developed pulmonary streptococcal infections. Furthermore, in mice with disrupted gut microbes, the alveolar macrophage metabolic pathway was upregulated, and the cellular response was altered, resulting in a reduced ability to phagocytize *S. pneumoniae*, causing a less pronounced immunomodulatory response (38). An imbalance of gut microbes can lead to damage to the intestinal wall, or "leaky gut." A large number of toxins and bacteria enter the bloodstream through intestinal leakage to specific organs and tissues, thus triggering a series of inflammatory immune responses. Acute appendicitis is an intestinal infectious illness. ~~Intestinal microecological imbalance crucially influences appendicitis onset and progression.~~ Pathogenic bacteria multiply and secrete endotoxins and exotoxins, damaging the mucosal epithelium, forming ulcers, and allowing bacterial entry into the muscle layer of the appendix via the ulcerative surface. Increased interstitial pressure in the appendix wall affects arterial blood flow, resulting in appendicular ischemia, and in severe cases, infarction and gangrene (39). Infective endocarditis refers to the inflammation of the inner lining of the heart valve or ventricle caused by direct infection by bacteria, fungi and other microorganisms. Studies have shown that intestinal flora destroys the intestinal mucosal barrier, and enterococcus faecalis are released into the blood to attach to the normal valve and cause endocarditis(40). The main pathogen of cellulitis is hemolytic streptococcus, which is caused by external invasion of subcutaneous tissue or caused by lymphatic and hematologic infection(41). The interaction between intestinal flora and susceptibility to recurrent Urinary Tract Infections (rUTI) may promote intestinal colonization of Uropathogenic *Escherichia Coli* (UPEC) through intestinal flora dysregulation and increase the risk of bladder infection. Furthermore, intestinal flora has been reported as an instigator, and its imbalance may cause systemic inflammation, further worsening the inflammation and symptoms after bladder infection (4042). Gut microbiota can release pro-inflammatory or anti-inflammatory mediators and

cytokines to regulate systemic bone metabolism through blood circulation. Studies have shown that gut microbiota disturbances that up-regulate pro-IL1 β levels indirectly affect osteomyelitis(43). The occurrence and development of sepsis are closely related to the imbalance of gut microbiota. The disturbance of gut microbiota can induce sepsis through the destruction of intestinal mucosal barrier function, mucosal immune function and bacterial translocation. At the same time, sepsis can also aggravate the imbalance of intestinal flora, resulting in multiple organ dysfunction(44). ~~Deshmukh et al. (41) demonstrated that the microbiome regulates neutrophil homeostasis by establishing an E. coli sepsis model in neonatal mice. Through a TLR4-induced signaling cascade, Lipopolysaccharides (LPS) expression on the surface of gram-negative bacteria activates IL-17A production by innate lymphoid cells, resulting in increased plasma granulocyte colonies, potentially stimulating the recruitment of neutrophils from the bone marrow into the bloodstream to fight invasive pathogens such as E. coli.~~

~~Several large observational studies have provided indirect evidence that disruption of the gut microbiota predisposes individuals to bacterial infections. Metagenomic sequencing of stool from COVID-19 patients found that baseline abundations of *Coelobacterium*, *Clostridium reticulum*, and *Clostridium* were associated with COVID-19 severity (42). There are a large number of fusobacterium groups in patients with acute appendicitis. However, these clostridium groups are usually absent in stool samples from healthy adults and children (39). Metagenomic and transcriptomic analyses of fecal samples from 31 women found that women with a history of rUTI had significantly lower gut flora richness, as did butyricogenes, and that rUTI were associated with intestinal flora dysbiosis comparable to the inflammatory bowel disease (43). Agudelo et al. (44) found that the intestinal microbiota of sepsis patients was characterized by increased inflammatory microorganisms such as *Paracelobacter*, *Clostridium*, and *Haemophilus*. This could predict sepsis development, especially the richness of enterococcus species, which may be a potential prognostic sepsis biomarker.~~

Our study identify a causal link between gut microbiota and infectious diseases, particularly that the abundance of *class Coriobacteriia*, *order Coriobacteriales* and *family Coriobacteriaceae* are positively associated with the risk of LRTI. *Coriobacteriia* can be found in the mouth, respiratory tract, gastrointestinal tract and reproductive tract. In the gut, *class Coriobacteriia* performs important functions such as the conversion of bile salts and steroids and the activation of dietary polyphenols. However, they can also be regarded as pathological diseases. According to previous research, the abundance of *class Coriobacteriia* can increase the incidence of diseases such as allergic rhinitis and endometriosis(45,46). *Family Acidaminococcaceae*, *genus Clostridium sensu stricto 1*, *class Bacilli* were positively related to the risk of endocarditis, cellulitis, osteomyelitis, **respectively**. *Family Acidaminococcaceae* belongs to strictly anaerobic gram-negative coccus. Amino acids, especially glutamate, are a major source of energy (47). *Genus Clostridium sensu stricto 1* belongs to gram-positive bacterium fusobacterium, in the case of hypoxia, fusobacterium cause serious infections **including tetanus and gas gangrene**. ~~Often, the deeper the wound, the more serious it is, especially when there is foreign body or contamination, the more likely it is to be infected with *Clostridium*, and tetanus and gas gangrene are serious infectious diseases caused by *Clostridium*~~ (48). *Class Bacilli* can bind lipopolysaccharide (LPS) and neutralize endotoxin. Therefore, the microecological preparation prepared by *Bacilli* has played an important role in the treatment of intestinal flora disorders and candida infection (49). However, *Bacillus cereus* strains usually cause local wound and eye infection and systemic diseases (50). At the same time, the increased abundance of *class Lentisphaeria* and *order Victivallales* decreased the risk of sepsis. Surprisingly, *Lentisphaerae* has been reported to be more abundant in cases of inflammatory bowel disease (51) and less abundant in patients with sepsis, which is consistent with our conclusions (52). *Order*

Victivallales has important effects on human infection and immune development. Specifically, it was found to be positively associated with clinical response to anti-programmed cell death protein-1 (PD-1) immunotherapy in patients with advanced cancer (53). In this regard, we believe that these gut microbiota may play a role in the occurrence and development of infectious diseases by regulating immunity. Interestingly, the findings of the reverse MR Study do not support a causal relationship between infectious diseases and changes in gut microbiota.

One of the strengths of this study is that it established a causal relationship between alterations in gut microbiota and infectious diseases, offering candidate gut microbiota for subsequent functional studies. However, the study also has limitations. First, it only used European population GWAS data for TSMR analysis, ~~excluding key studies in other populations.~~ ~~Second,~~ and the abundance of gut microbiota included herein is limited, ~~and~~ GWAS data of other gut microbiota need to be obtained in the future, to explore the causal relationship between gut microbiota and infectious diseases more comprehensively. Second, ~~we did not further validate these results with public or our own datasets.~~ Third, although TSMR is an efficient method of causality analysis, animal tests should be conducted in the future to further verify whether there is a potential causal relationship between gut microbiota and infectious diseases. Fourth, ~~there are few studies on these gut flora that have causal relationship with infectious diseases, and more extensive studies are needed to support our conclusions in the future.~~ Fifth, the causal relationship between gut microbiota and infectious diseases is multifaceted, necessitating the exploration of the etiology and pathogenesis of infectious diseases from multiple perspectives.

In conclusion, we used TSMR to explore the causal relationship between gut microbiota and infectious diseases. The results showed that the abundance of *class Coriobacteriia*, *order. Coriobacteriales* and *family Coriobacteriaceae* was associated with LRTI risk, *family Acidaminococcaceae*, *genus Clostridium sensu stricto 1*, *class Bacilli* were found to be positively related to the risk of and endocarditis, cellulitis, osteomyelitis, *respectively*. At the same time, the increased abundance of *class Lentisphaeria* and *order Victivallales* lowered the risk of sepsis. These findings elucidate the involvement of gut microbiota in the development of infectious diseases and offer a reference value for the treatment of infectious diseases.

5 Ethics approval and consent to participate

Since the data used are publicly available in the database, no additional ethical approval was needed in this case.

6 Consent for publication

Not applicable.

7 Competing interests

The authors declare that they have no competing interests.

8 Funding

This work was supported by the General Program of the National Natural Science Foundation of China (82070554 and 81770537); the Major Scientific and Technological Special Project for Public Health in Tianjin (21ZXGWSY00080); the Tianjin Medical University General Hospital Clinical

Research Program (22ZYYLCCG06) to Daqing Sun. The funding bodies played no role in the study design, data collection, analysis, interpretation, or manuscript writing.

9 Authors' contributions

DS and SW: conception and design. SW and FY: development of methodology. SW and RL: acquisition of data. WS and ZG: analysis and interpretation of data. WS, ZG, and YW: writing, review, and/or revision of the manuscript. YZ and WS: administrative, technical, or material support. DS and CS: study supervision. All authors participated in the writing of the final manuscript and approved the final submission.

10 Acknowledgments

None.

11 Availability of data and material

The data of infectious diseases can be downloaded from <http://www.nealelab.is/uk-biobank/>. And the gut microbiota data can be downloaded from https://www.fnngen.f/en/access_results. [The code required during data processing in Supplementary Table 8.](#)

Reference passage

1. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. (2018) 392: 1736-1788.doi: 10.1016/s0140-6736(18)32203-7
2. Singer M , Deutschman C S , Seymour C W , Shankar-Hari M , Annane D , Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *Jama*. (2016) 315: 801-10.doi: 10.1001/jama.2016.0287
3. Rhee C , Dantes R , Epstein L , Murphy D J , Seymour C W , Iwashyna T J, et al. Incidence and Trends of Sepsis in US Hospitals Using Clinical vs Claims Data, 2009-2014. *Jama*. (2017) 318: 1241-1249.doi: 10.1001/jama.2017.13836
4. Evans L , Rhodes A , Alhazzani W , Antonelli M , Coopersmith C M , French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Intensive Care Med*. (2021) 47: 1181-1247.doi: 10.1007/s00134-021-06506-y
5. Kollef M H , Torres A , Shorr A F , Martin-Loeches I , Micek S T. Nosocomial Infection. *Crit Care Med*. (2021) 49: 169-187.doi: 10.1097/ccm.0000000000004783
6. Bollen C , Louwagie E , Verstraeten N , Michiels J , Ruelens P. Environmental, mechanistic and evolutionary landscape of antibiotic persistence. *EMBO Rep*. (2023) 24: e57309.doi: 10.15252/embr.202357309
7. Kumar V. Sepsis roadmap: What we know, what we learned, and where we are going. *Clin Immunol*. (2020) 210: 108264.doi: 10.1016/j.clim.2019.108264

-
8. Zhang Y Y ,Ning B T. Signaling pathways and intervention therapies in sepsis. *Signal Transduct Target Ther.* (2021) 6: 407.doi: 10.1038/s41392-021-00816-9
 9. van der Poll T , Shankar-Hari M ,Wiersinga W J. The immunology of sepsis. *Immunity.* (2021) 54: 2450-2464.doi: 10.1016/j.immuni.2021.10.012
 10. Conti F , Marzollo A , Moratti M , Lodi L ,Ricci S. Inborn errors of immunity underlying a susceptibility to pyogenic infections: from innate immune system deficiency to complex phenotypes. *Clin Microbiol Infect.* (2022) 28: 1422-1428.doi: 10.1016/j.cmi.2022.05.022
 11. de Vos W M , Tilg H , Van Hul M ,Cani P D. Gut microbiome and health: mechanistic insights. *Gut.* (2022) 71: 1020-1032.doi: 10.1136/gutjnl-2021-326789
 12. Simpson R C , Shanahan E R , Scolyer R A ,Long G V. Towards modulating the gut microbiota to enhance the efficacy of immune-checkpoint inhibitors. *Nat Rev Clin Oncol.* (2023) 20: 697-715.doi: 10.1038/s41571-023-00803-9
 13. Alcazar C G , Paes V M , Shao Y , Oesser C , Miltz A , Lawley T D, et al. The association between early-life gut microbiota and childhood respiratory diseases: a systematic review. *Lancet Microbe.* (2022) 3: e867-e880.doi: 10.1016/s2666-5247(22)00184-7
 14. Ghani R , Mullish B H , Roberts L A , Davies F J ,Marchesi J R. The potential utility of fecal (or intestinal) microbiota transplantation in controlling infectious diseases. *Gut Microbes.* (2022) 14: 2038856.doi: 10.1080/19490976.2022.2038856
 15. Fang J , Wang H , Zhou Y , Zhang H , Zhou H ,Zhang X. Slimy partners: the mucus barrier and gut microbiome in ulcerative colitis. *Exp Mol Med.* (2021) 53: 772-787.doi: 10.1038/s12276-021-00617-8
 16. Haak B W ,Wiersinga W J. The role of the gut microbiota in sepsis. *Lancet Gastroenterol Hepatol.* (2017) 2: 135-143.doi: 10.1016/s2468-1253(16)30119-4
 17. Thursby E ,Juge N. Introduction to the human gut microbiota. *Biochem J.* (2017) 474: 1823-1836.doi: 10.1042/bcj20160510
 18. Skrivankova V W , Richmond R C , Woolf B A R , Yarmolinsky J , Davies N M , Swanson S A, et al. Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization: The STROBE-MR Statement. *Jama.* (2021) 326: 1614-1621.doi: 10.1001/jama.2021.18236
 19. Davies N M , Holmes M V ,Davey Smith G. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. *Bmj.* (2018) 362: k601.doi: 10.1136/bmj.k601
 20. Kurilshikov A , Medina-Gomez C , Bacigalupe R , Radjabzadeh D , Wang J , Demirkan A, et al. Large-scale association analyses identify host factors influencing human gut microbiome composition. *Nat Genet.* (2021) 53: 156-165.doi: 10.1038/s41588-020-00763-1
 21. Bycroft C , Freeman C , Petkova D , Band G , Elliott L T , Sharp K, et al. The UK Biobank resource with deep phenotyping and genomic data. *Nature.* (2018) 562: 203-209.doi: 10.1038/s41586-018-0579-z

-
22. Purcell S , Neale B , Todd-Brown K , Thomas L , Ferreira M A , Bender D, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet.* (2007) 81: 559-75.doi: 10.1086/519795
 23. Burgess S , Dudbridge F ,Thompson S G. Combining information on multiple instrumental variables in Mendelian randomization: comparison of allele score and summarized data methods. *Stat Med.* (2016) 35: 1880-906.doi: 10.1002/sim.6835
 24. Bowden J , Davey Smith G ,Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Epidemiol.* (2015) 44: 512-25.doi: 10.1093/ije/dyv080
 25. Bowden J , Davey Smith G , Haycock P C ,Burgess S. Consistent Estimation in Mendelian Randomization with Some Invalid Instruments Using a Weighted Median Estimator. *Genet Epidemiol.* (2016) 40: 304-14.doi: 10.1002/gepi.21965
 26. Glickman M E , Rao S R ,Schultz M R. False discovery rate control is a recommended alternative to Bonferroni-type adjustments in health studies. *J Clin Epidemiol.* (2014) 67: 850-7.doi: 10.1016/j.jclinepi.2014.03.012
 27. Palmer T M , Lawlor D A , Harbord R M , Sheehan N A , Tobias J H , Timpson N J, et al. Using multiple genetic variants as instrumental variables for modifiable risk factors. *Stat Methods Med Res.* (2012) 21: 223-42.doi: 10.1177/0962280210394459
 28. Bowden J , Spiller W , Del Greco M F , Sheehan N , Thompson J , Minelli C, et al. Improving the visualization, interpretation and analysis of two-sample summary data Mendelian randomization via the Radial plot and Radial regression. *Int J Epidemiol.* (2018) 47: 2100.doi: 10.1093/ije/dyy265
 29. Burgess S ,Thompson S G. Interpreting findings from Mendelian randomization using the MR-Egger method. *Eur J Epidemiol.* (2017) 32: 377-389.doi: 10.1007/s10654-017-0255-x
 30. Verbanck M , Chen C Y , Neale B ,Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nat Genet.* (2018) 50: 693-698.doi: 10.1038/s41588-018-0099-7
 31. Stock M , Pahikkala T , Airola A , Waegeman W ,De Baets B. Algebraic shortcuts for leave-one-out cross-validation in supervised network inference. *Brief Bioinform.* (2020) 21: 262-271.doi: 10.1093/bib/bby095
 32. Fan Y ,Pedersen O. Gut microbiota in human metabolic health and disease. *Nat Rev Microbiol.* (2021) 19: 55-71.doi: 10.1038/s41579-020-0433-9
 33. Park S Y , Rao C , Coyte K Z , Kuziel G A , Zhang Y , Huang W, et al. Strain-level fitness in the gut microbiome is an emergent property of glycans and a single metabolite. *Cell.* (2022) 185: 513-529.e21.doi: 10.1016/j.cell.2022.01.002
 34. Woo V ,Alenghat T. Epigenetic regulation by gut microbiota. *Gut Microbes.* (2022) 14: 2022407.doi: 10.1080/19490976.2021.2022407

-
35. Birchenough G M , Nyström E E , Johansson M E ,Hansson G C. A sentinel goblet cell guards the colonic crypt by triggering Nlrp6-dependent Muc2 secretion. *Science*. (2016) 352: 1535-42.doi: 10.1126/science.aaf7419
36. Knoop K A , Gustafsson J K , McDonald K G , Kulkarni D H , Kassel R ,Newberry R D. Antibiotics promote the sampling of luminal antigens and bacteria via colonic goblet cell associated antigen passages. *Gut Microbes*. (2017) 8: 400-411.doi: 10.1080/19490976.2017.1299846
37. Singh N , Gurav A , Sivaprakasam S , Brady E , Padia R , Shi H, et al. Activation of Gpr109a, receptor for niacin and the commensal metabolite butyrate, suppresses colonic inflammation and carcinogenesis. *Immunity*. (2014) 40: 128-39.doi: 10.1016/j.immuni.2013.12.007
38. Wypych T P , Wickramasinghe L C ,Marsland B J. The influence of the microbiome on respiratory health. *Nat Immunol*. (2019) 20: 1279-1290.doi: 10.1038/s41590-019-0451-9
39. Rogers M B , Brower-Sinning R , Firek B , Zhong D ,Morowitz M J. Acute Appendicitis in Children Is Associated With a Local Expansion of Fusobacteria. *Clin Infect Dis*. (2016) 63: 71-78.doi: 10.1093/cid/ciw208
40. Silva E C F , Montalvão C R ,Bonafé S. Infectious Endocarditis from *Enterococcus faecalis* Associated with Tubular Adenoma of the Sigmoid Colon. *Case Rep Infect Dis*. (2017) 2017: 3095031.doi: 10.1155/2017/3095031
41. Raff A B ,Kroshinsky D. Cellulitis: A Review. *Jama*. (2016) 316: 325-37.doi: 10.1001/jama.2016.8825
402. Worby C J , Olson B S , Dodson K W , Earl A M ,Hultgren S J. Establishing the role of the gut microbiota in susceptibility to recurrent urinary tract infections. *J Clin Invest*. (2022) 132.doi: 10.1172/jci158497
- ~~41. Deshmukh H S , Liu Y , Menkiti O R , Mei J , Dai N , O'Leary C E, et al. The microbiota regulates neutrophil homeostasis and host resistance to Escherichia coli K1 sepsis in neonatal mice. *Nat Med*. (2014) 20: 524-30.doi: 10.1038/nm.3542~~
- ~~42. Zuo T , Zhang F , Lui G C Y , Yeoh Y K , Li A Y L , Zhan H, et al. Alterations in Gut Microbiota of Patients With COVID-19 During Time of Hospitalization. *Gastroenterology*. (2020) 159: 944-955.e8.doi: 10.1053/j.gastro.2020.05.048~~
- ~~43. Worby C J , Schreiber H L t , Straub T J , van Dijk L R , Bronson R A , Olson B S, et al. Longitudinal multi-omics analyses link gut microbiome dysbiosis with recurrent urinary tract infections in women. *Nat Microbiol*. (2022) 7: 630-639.doi: 10.1038/s41564-022-01107-x~~
- ~~44. Agudelo-Ochoa G M , Valdés-Duque B E , Giraldo-Giraldo N A , Jaillier-Ramírez A M , Giraldo-Villa A , Acevedo-Castaño I, et al. Gut microbiota profiles in critically ill patients, potential biomarkers and risk variables for sepsis. *Gut Microbes*. (2020) 12: 1707610.doi: 10.1080/19490976.2019.1707610~~
43. Chen J , Xiong A , Ma Y , Qin C ,Ho C L. Impact of the Host-Microbiome on Osteomyelitis Pathogenesis. *Front Mol Biosci*. (2021) 8: 702484.doi: 10.3389/fmolb.2021.702484

-
44. Haak B W , Prescott H C , Wiersinga W J. Therapeutic Potential of the Gut Microbiota in the Prevention and Treatment of Sepsis. *Front Immunol.* (2018) 9: 2042.doi: 10.3389/fimmu.2018.02042
45. Jin Q , Ren F , Dai D , Sun N , Qian Y , Song P. The causality between intestinal flora and allergic diseases: Insights from a bi-directional two-sample Mendelian randomization analysis. *Front Immunol.* (2023) 14: 1121273.doi: 10.3389/fimmu.2023.1121273
46. Svensson A , Brunkwall L , Roth B , Orho-Melander M , Ohlsson B. Associations Between Endometriosis and Gut Microbiota. *Reprod Sci.* (2021) 28: 2367-2377.doi: 10.1007/s43032-021-00506-5
47. Morotomi M , Nagai F , Sakon H. Genus Megamonas should be placed in the lineage of Firmicutes; Clostridia; Clostridiales; 'Acidaminococcaceae'; Megamonas. *Int J Syst Evol Microbiol.* (2007) 57: 1673-1674.doi: 10.1099/ijs.0.65150-0
48. Dürre P. Physiology and Sporulation in Clostridium. *Microbiol Spectr.* (2014) 2: Tbs-0010-2012.doi: 10.1128/microbiolspec.TBS-0010-2012
49. Mongkolthanaruk W. Classification of Bacillus beneficial substances related to plants, humans and animals. *J Microbiol Biotechnol.* (2012) 22: 1597-604.doi: 10.4014/jmb.1204.04013
50. Ehling-Schulz M , Lereclus D , Koehler T M. The Bacillus cereus Group: Bacillus Species with Pathogenic Potential. *Microbiol Spectr.* (2019) 7.doi: 10.1128/microbiolspec.GPP3-0032-2018
51. Fan H N , Zhu P , Lu Y M , Guo J H , Zhang J , Qu G Q, et al. Mild changes in the mucosal microbiome during terminal ileum inflammation. *Microb Pathog.* (2020) 142: 104104.doi: 10.1016/j.micpath.2020.104104
52. Zhang Z , Cheng L , Ning D. Gut microbiota and sepsis: bidirectional Mendelian study and mediation analysis. *Front Immunol.* (2023) 14: 1234924.doi: 10.3389/fimmu.2023.1234924
53. Cheng X , Wang J , Gong L , Dong Y , Shou J , Pan H, et al. Composition of the Gut Microbiota Associated with the Response to Immunotherapy in Advanced Cancer Patients: A Chinese Real-World Pilot Study. *J Clin Med.* (2022) 11.doi: 10.3390/jcm11185479

FIGURE 1 | The study design of the present MR study of the associations of gut microbiota and sepsis. Abbreviations: LD, linkage disequilibrium, which used to measure the correlations between SNPs; IVW, Inverse-variance-weighted, the main analyses to evaluate the relationship between exposure and outcome; MR-PRESSO, Mendelian Randomization Pleiotropy RESidual Sum and Outlier, a method test the pleiotropic biases in the SNPs and correct the pleiotropic effects; MR, Mendelian randomization; SNP, single nucleotide polymorphism, as instrumental variables for the exposures and outcomes.

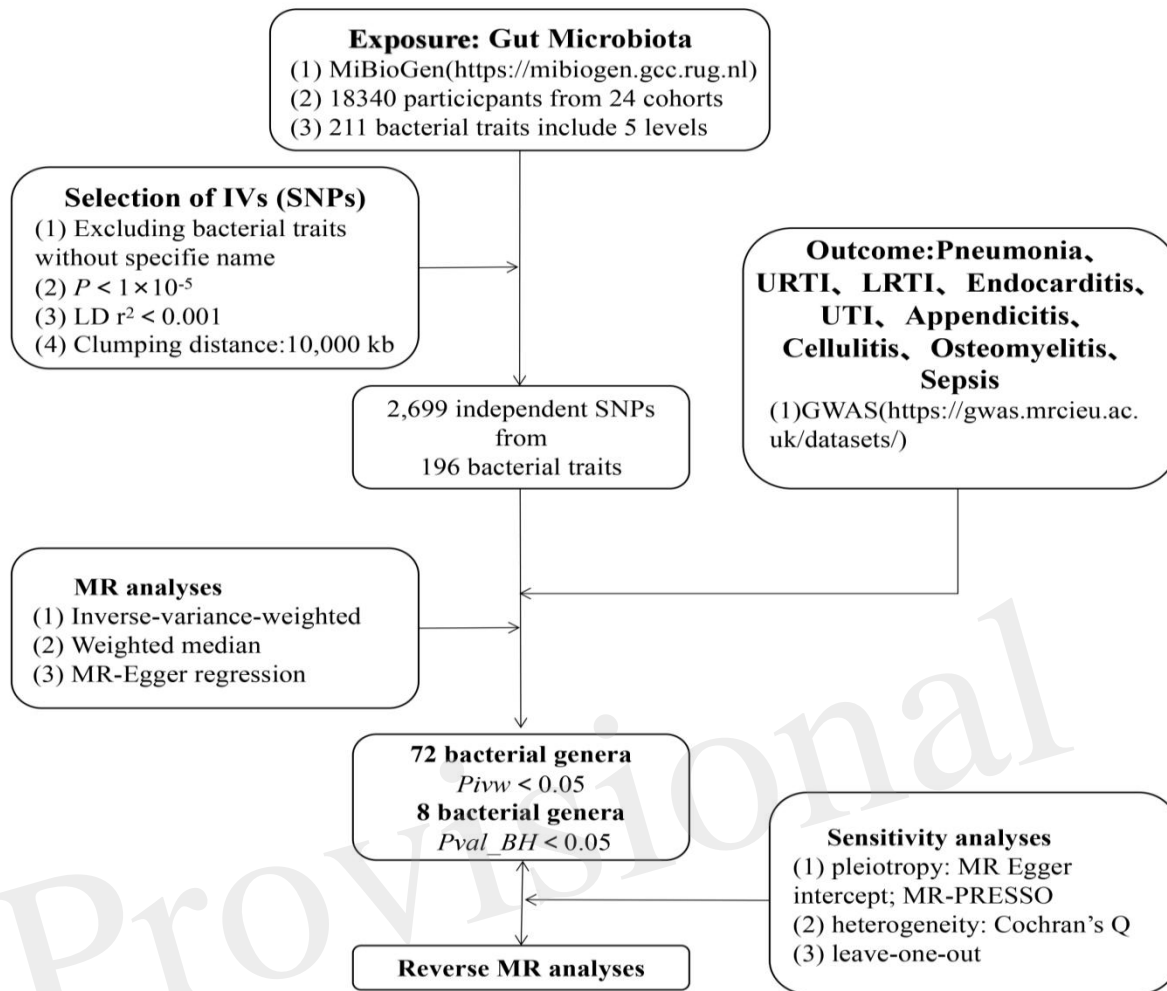


FIGURE 2 | Effect estimates of the association between meaningful gut microbiota and infectious disease risk in IVW analysis. Abbreviations: SNPs, single nucleotide polymorphisms, as instrumental variables for the exposures and outcomes; OR, odds ratio; CI, confidence interval; URTI, Upper respiratory tract infection; LRTI, Lower respiratory tract infection; UTI, Urinary tract infection.

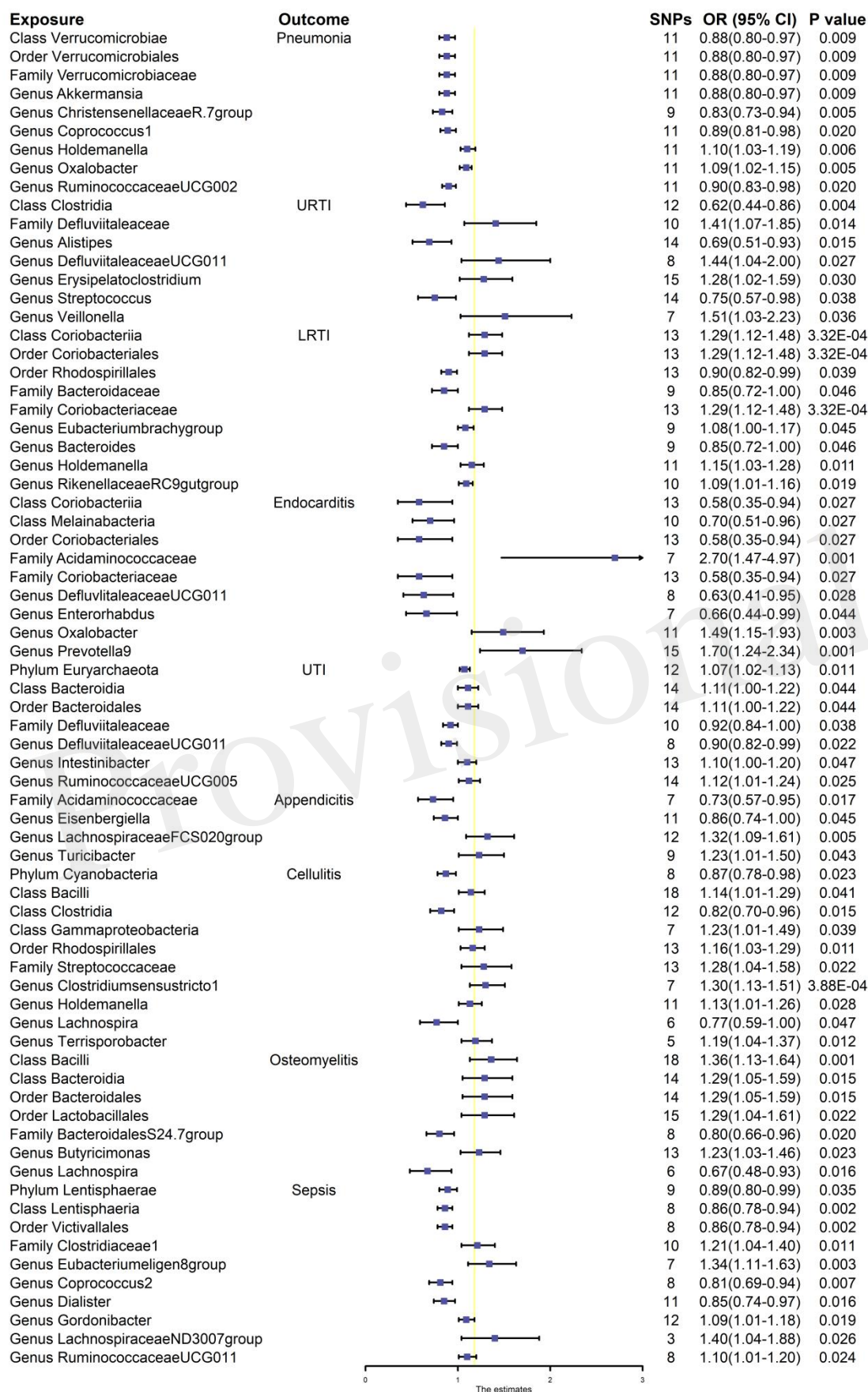


FIGURE 3 | Scatter plots for the causal association between gut microbiota and infectious diseases. A. Class *Coriobacteriia* and LRTI; B. Order *Coriobacteriales* and LRTI; C. Family *Coriobacteriaceae* and LRTI; D. Family *Acidaminococcaceae* and Endocarditis; E. Genus *Clostridium sensu stricto 1* and Cellulitis; F. Class *Bacilli* and Osteomyelitis; G. Class *Lentisphaeria* and Sepsis; H. Order *Victivallales* and Sepsis. Abbreviations: LRTI, Lower respiratory tract infection.

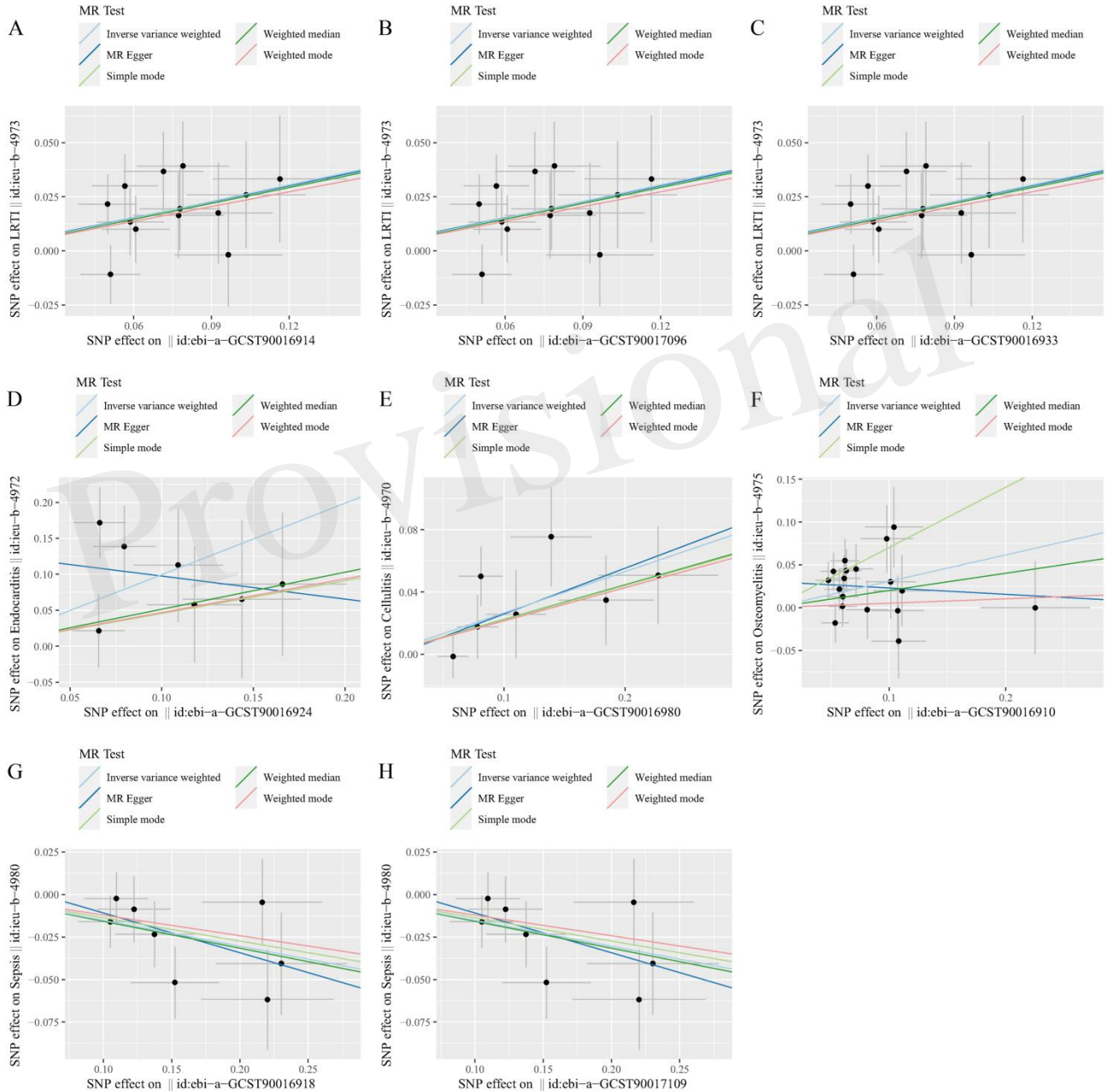


TABLE 1 | Effect estimates of the association between meaningful gut microbiota and infectious disease risk in MR analysis.

Gut microbiota	Outcome	SNPs	Methods	OR (95% CI)	P value	P _{FDR}
<i>Class Coriobacteriia</i>	LRTI	13	MR-Egger	1.28 (0.74- 2.22)	0.401	0.005
		13	Weighted Median	1.28 (1.05- 1.55)	0.012	
		13	IVW	1.29 (1.12- 1.48)	3.32E-04	
		13	Simple mode	1.26 (0.91- 1.73)	0.187	
		13	Weighted mode	1.26 (0.92- 1.71)	0.176	
<i>Order Coriobacteriales</i>	LRTI	13	MR-Egger	1.28 (0.74- 2.22)	0.401	0.007
		13	Weighted Median	1.28 (1.06- 1.54)	0.010	
		13	IVW	1.29 (1.12- 1.48)	3.32E-04	
		13	Simple mode	1.26 (0.94- 1.67)	0.147	
		13	Weighted mode	1.26 (0.92- 1.71)	0.177	
<i>Family Coriobacteriaceae</i>	LRTI	13	MR-Egger	1.28 (0.74- 2.22)	0.401	0.011
		13	Weighted Median	1.28 (1.07- 1.53)	0.007	
		13	IVW	1.29 (1.12- 1.48)	3.32E-04	
		13	Simple mode	1.26 (0.93- 1.69)	0.160	
		13	Weighted mode	1.26 (0.92- 1.72)	0.184	
<i>Family Acidaminococcaceae</i>	Endocarditis	7	MR-Egger	0.73 (0.14- 3.77)	0.719	0.045
		7	Weighted Median	1.67 (0.82- 3.42)	0.159	
		7	IVW	2.70 (1.47- 4.97)	0.001	
		7	Simple mode	1.58 (0.61- 4.05)	0.382	
		7	Weighted mode	1.60 (0.66- 3.88)	0.341	
<i>Genus Clostridium sensu stricto 1</i>	Cellulitis	7	MR-Egger	1.34 (0.96- 1.87)	0.145	0.046
		7	Weighted Median	1.25 (1.01- 1.54)	0.036	
		7	IVW	1.30 (1.13- 1.51)	3.88E-04	
		7	Simple mode	1.25 (0.94- 1.65)	0.173	
		7	Weighted mode	1.24 (0.97- 1.57)	0.132	
<i>Class Bacilli</i>	Osteomyelitis	18	MR-Egger	0.93 (0.57- 1.53)	0.775	0.022
		18	Weighted Median	1.22 (0.93- 1.61)	0.151	
		18	IVW	1.36 (1.13- 1.64)	0.001	
		18	Simple mode	2.02 (1.15- 3.55)	0.025	
		18	Weighted mode	1.05 (0.68- 1.64)	0.823	
<i>Class Lentisphaeria</i>	Sepsis	8	MR-Egger	0.79 (0.57- 1.10)	0.211	0.026
		8	Weighted Median	0.85 (0.75- 0.97)	0.016	
		8	IVW	0.86 (0.78- 0.94)	0.002	
		8	Simple mode	0.87 (0.71- 1.07)	0.235	
		8	Weighted mode	0.89 (0.73- 1.08)	0.273	
<i>Order Victivallales</i>	Sepsis					

TABLE 1 | Effect estimates of the association between meaningful gut microbiota and infectious disease risk in MR analysis.

Gut microbiota	Outcome	SNPs	Methods	OR (95% CI)	<i>P</i> value	<i>P_{FDR}</i>
		8	MR-Egger	0.79 (0.57- 1.10)	0.211	0.033
		8	Weighted Median	0.85 (0.75- 0.97)	0.015	
		8	IVW	0.86 (0.78- 0.94)	0.002	
		8	Simple mode	0.87 (0.71- 1.08)	0.243	
		8	Weighted mode	0.89 (0.73- 1.08)	0.266	

Abbreviations:MR, Mendelian randomization; SNPs, Number of single nucleotide polymorphism.CI, confidence interval; OR, odds ratio;*P_{FDR}*, *P* value was calculated by the Benjamini-Hochberg method;LRTI, Lower respiratory tract infection; IVW, Inverse variance weighted.

Provisional

TABLE 2 | Heterogeneity and sensitivity analysis between meaningful gut microbiota and infectious diseases.

Gut microbiota	Outcome	Methods	Q	P	Intercept	P	MR-PRESSO
Class Coriobacteriia	LRTI	IVW	7.998	0.785	0.001	0.977	0.927
		MR-Egger	7.997	0.714			
Order Coriobacteriales	LRTI	IVW	7.998	0.785	0.001	0.977	0.923
		MR-Egger	7.997	0.714			
Family Coriobacteriaceae	LRTI	IVW	7.998	0.785	0.001	0.977	0.929
		MR-Egger	7.997	0.714			
Family Acidaminococcaceae	Endocarditis	IVW	8.185	0.225	0.130	0.159	0.302
		MR-Egger	5.290	0.382			
Genus Clostridium sensu stricto 1	Cellulitis	IVW	5.574	0.473	-0.004	0.856	0.299
		MR-Egger	5.534	0.354			
Class Bacilli	Osteomyelitis	IVW	18.370	0.366	0.030	0.125	0.416
		MR-Egger	15.746	0.471			
Class Lentisphaeria	Sepsis	IVW	5.159	0.641	0.012	0.628	0.403
		MR-Egger	4.899	0.557			
Order Victivallales	Sepsis	IVW	5.159	0.641	0.012	0.628	0.394
		MR-Egger	4.899	0.557			

Abbreviations: MR-PRESSO, Mendelian Randomization Pleiotropy RESidual Sum and Outlier; IVW, Inverse variance weighted; LRTI, Lower respiratory tract infection.

Table S1. Information on exposure and outcome factors.

Table S12. Effect estimates of the associations between 196 bacterial traits and risk of infectious diseases in MR analyses.

Table S23. The F number and R2 detect the intensity of the IVs between 196 bacterial traits and risk of infectious diseases in MR analyses.

Table S34. MR-Egger regression analysis between 196 bacterial traits and risk of infectious diseases in MR analyses.

Table S45. Testing for heterogeneity between 196 bacterial traits and risk of infectious diseases in MR analyses.

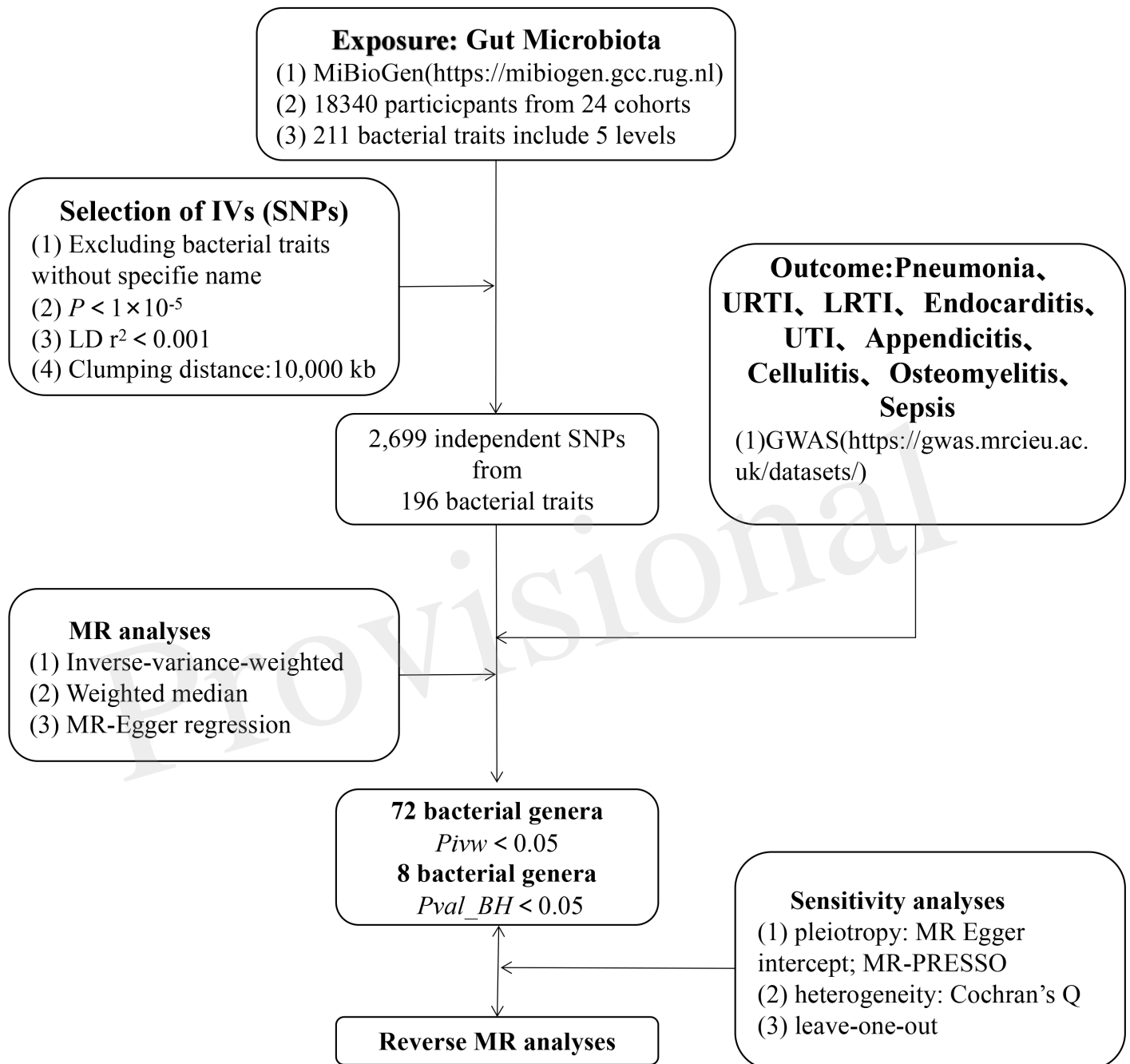
Table S56. Leave one out between 196 bacterial traits and risk of infectious diseases in MR analyses.

Table S67. Effect estimates of the associations between infectious diseases and risk of nine infectious diseases in the reverse MR analyses.

Table S8. Code required during data processing.

Provisional

Figure 01.TIF



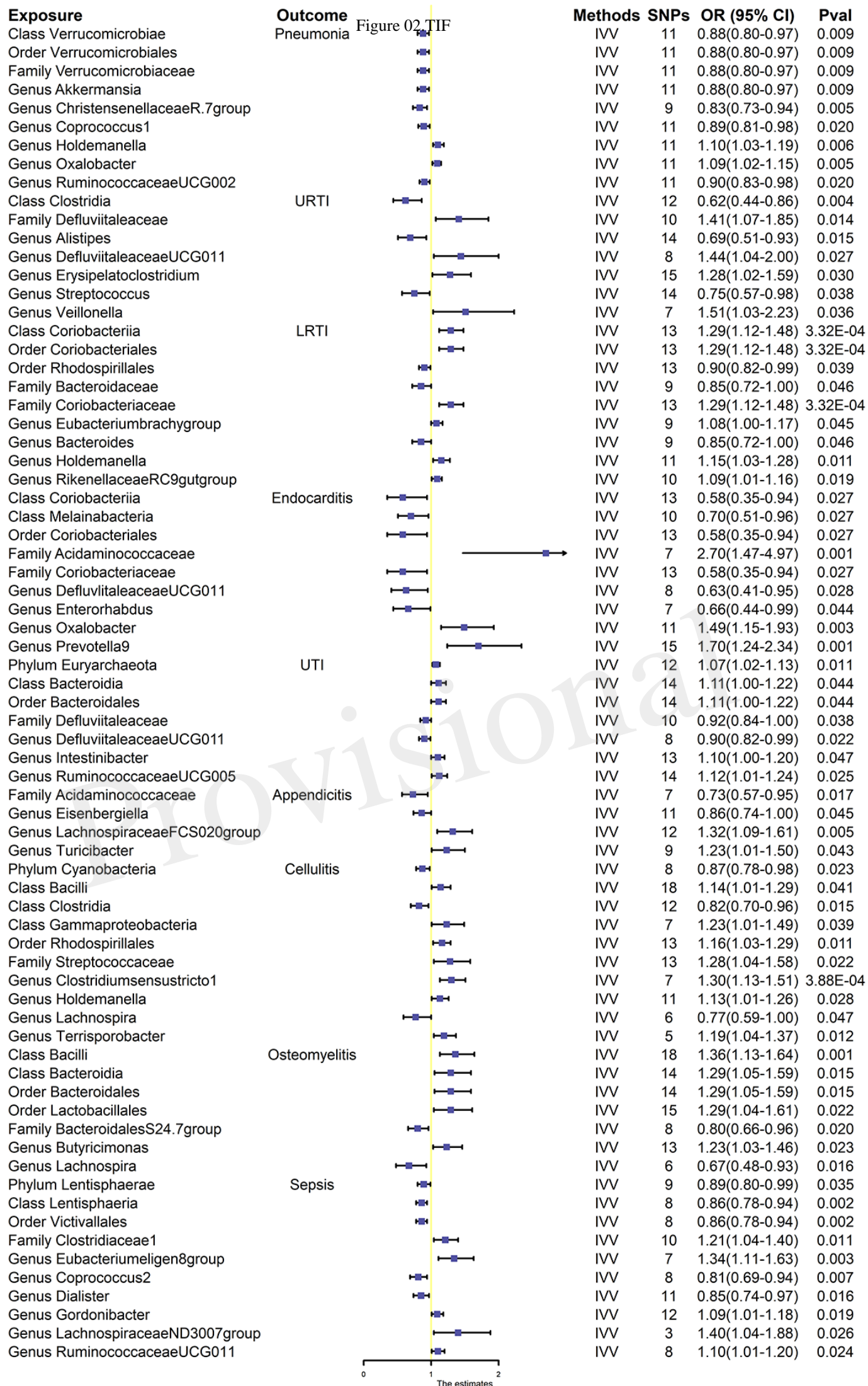


Figure 03.TIF

