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Original Article

Causal association between 473 types of gut microbiota and neonatal bacterial sepsis: a bidirectional two-sample Mendelian randomization study

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Abstract

Background: Neonatal bacterial sepsis represents a major health threat to newborns, leading to high mortality rates globally. However, the correlation between the gut microbiome and bacterial sepsis in neonates remains unclear.

Methods: This study utilized publicly available Genome-Wide Association Study data on 473 gut microbiota taxa as exposures. Instrumental variables were rigorously selected, and bidirectional two-sample Mendelian randomization (MR) analyses were performed. The MR and reverse MR analyses results were validated using Bayesian weighted MR (BWMR) analysis. Positive results from MR analysis will be validated through heterogeneity testing, evaluation of horizontal pleiotropy, and univariate sensitivity analysis.

Results: The findings revealed a significant genetic causal association between 18 gut microbial species and neonatal bacterial sepsis, including *Acetobacterales* (odds ratio [OR]: 159.844; $p = 0.04$), *Campylobacter D* (OR: 16.225; $p = 0.029$), and *Firmicutes A* (OR: 75.643; $p = 0.025$). Additionally, both MR and inverse MR analyses confirmed the absence of reverse causation ($p < 1e\text{-}5$), supporting the robustness of the findings ($p < 0.05$) across five statistical methods. Sensitivity analyses indicated high reliability without significant heterogeneity or pleiotropy ($p > 0.05$). Furthermore, BWMR analysis highlighted the complex roles of probiotic taxa, including *Bacteroides A plebeius* (OR: 0.526) and pathogenic bacteria, such as *Acetobacterales* (OR: 192.449), in neonatal sepsis.

Conclusions: A causal genetic association exists between gut microbiota and bacterial sepsis in neonates. These results underscore the potential of gut microbiota as biomarkers and therapeutic targets for the prevention and management of neonatal bacterial sepsis.

Key words: Neonatal bacterial sepsis; gut microbiota; Mendelian randomization; causal association.

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Background

Neonatal bacterial sepsis is a critical health concern, representing a leading cause of morbidity and mortality among newborns worldwide [1]. The complexity of this condition stems from its multifactorial etiology, involving both host and microbial factors [2]. Despite advances in medicine, the early diagnosis and effective treatment of neonatal sepsis remain challenging, often resulting in severe complications and long-term sequelae in affected infants [3]. Current therapeutic strategies rely predominantly on empirical antibiotic therapy. However, the emergence of antibiotic resistance complicates management and underscores the need for novel therapeutic approaches and preventive strategies [4].

Recent studies have highlighted the key role of gut microbiota in shaping host immunity and overall health [5]. The composition and diversity of the gut microbiome are crucial in maintaining homeostasis and preventing dysbiosis, which has been implicated in various pathological conditions, including infections [6]. Dysbiosis, characterized by an imbalance between beneficial and pathogenic microorganisms, may predispose neonates to septic conditions [7]. Understanding the interactions between gut microbiota and neonatal health is essential to developing targeted interventions that could potentially mitigate the risk of sepsis [8].

Recent studies exploring the association between gut microbiota and neonatal sepsis have revealed promising insights [9]. Specific microbial profiles are associated with increased susceptibility and resistance to infections in neonates [10]. This indicates that the gut microbiota may serve as a modifiable risk factor for sepsis, presenting an opportunity for therapeutic intervention through dietary modulation, probiotics, or fecal microbiota transplantation [11]. Furthermore, the observation that certain microbial species can enhance immune responses or protect against pathogenic colonization emphasizes the potential role of the microbiome in preventing neonatal infections [12].

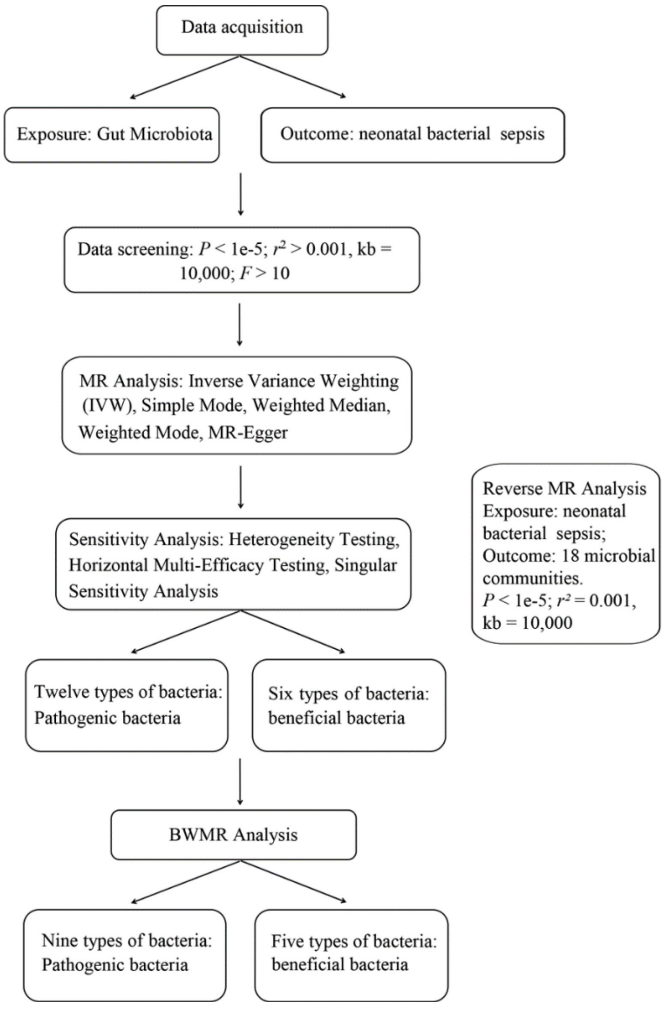
Bayesian weighted Mendelian randomization (BWMR) analysis, a supplementary method to two-sample Mendelian randomization (MR) analysis, can better account for the polygenic structure and pleiotropy of diseases or traits [13]. This approach improves the stability and reliability of MR analysis results. MR analysis has emerged as a robust approach

for investigating the causal associations between exposures, such as gut microbiota composition, and health outcomes [14]. This technique leverages genetic variants as instrumental variables (IVs) to infer causality while minimizing the confounding factors that often plague observational studies [15]. Recent application of MR in the context of neonatal sepsis research have provided evidence supporting a causal link between specific gut microbiota and the incidence of sepsis in newborns, suggesting that manipulation of the microbiome could yield beneficial effects in clinical practice.

Despite these advancements, the precise mechanisms by which the gut microbiota influences neonatal health and the development of sepsis remain poorly understood. Future investigations should focus on elucidating these mechanisms and identifying the specific microbial taxa that confer protective effects against sepsis. Additionally, integrating microbiome profiling with clinical data may enhance our understanding of the role of the gut microbiota in neonatal infections and inform the development of personalized therapeutic strategies.

Neonatal bacterial sepsis is a complex and multifaceted condition that poses significant challenges for clinical management. The gut microbiota plays a pivotal role in modulating neonatal immunity and health, presenting a promising avenue for intervention [16]. Employing advanced methodologies such as Mendelian randomization to explore the causal relationships between gut microbiota and sepsis can pave the way for innovative preventive and therapeutic strategies aimed at improving neonatal outcomes. As research progresses, the goal remains to translate these findings into clinical practices that effectively reduce the incidence and impact of neonatal sepsis.

Figure 1. Flowchart.



MR: Mendelian randomization; BWMR: Bayesian weighted Mendelian randomization.

Materials and methods

Data acquisition

Genome-Wide Association Studies (GWAS) are a research method aimed at identifying genetic variations linked to specific diseases. This method analyzes genomic data across individuals, comparing genotypes and phenotypes to detect single nucleotide polymorphisms (SNPs) in their genomes. The OpenGWAS database (https: //gwas.mrcieu.ac.uk/) aggregates GWAS data from various diseases and genes. In this study, the gut microbiome data of exposed individuals is from previous research and encompasses 473 types of gut microbes. This represents a significant advancement in sample size and subject numbers compared to earlier microbiome studies [17]. Data on bacterial sepsis in neonates were sourced from the Finnish database (FinnGen consortium) available at the following link: https: //storage.googleapis.com/finngen-public-data-r10/summary_stats/finngen_R10_P16_BACTERIAL_SEPSIS_NEWBO.gz. Utilize the TwoSampleMR package to extract data on the exposure (gut microbiome) and the outcome (neonatal bacteremia). Figure 1 shows the flow chart.

Data screening

To obtain precise IVs and improve the reliability of our results, we adopted strict screening criteria. First, the IVs were required to be associated with the exposure factor (p < 1e-5). Consequently, we excluded SNPs with weak or no correlation with the gut microbiome (p > 1e-5). Second, linkage disequilibrium (LD) was eliminated (selection criteria: $r^2 < 0.001$, kb = 10,000).

Third, we ensured that the IVs for MR analysis had sufficient strength ($F > 10$). Finally, we used the OpenGWAS database to remove confounding factors. We screened and excluded SNPs that could potentially affect the results by using genotype and phenotype analysis databases. For reverse MR, with neonatal sepsis as exposure and gut microbiota as outcome, IVs were required to meet the same four selection criteria.

Use R software (version 4.2.1) and the TwoSample MR package (version 0.5.6) to match the alleles of exposure and outcome effects.

MR analysis and Reverse MR Analysis

This study employed five statistical methods to evaluate the genetic causality between gut microbiota and neonatal bacterial sepsis. These methods included Inverse Variance Weighting (IVW), Simple Mode, Weighted Median, Weighted Mode, and MR-Egger. Among these methods, the IVW is identified as the primary approach. A p of less than 0.05 indicated a significant genetic causal association between specific gut microbiota and neonatal bacterial sepsis. Subsequently, positive gut microbiota were identified via MR analysis, using neonatal bacterial sepsis as the exposure to perform reverse MR analysis. This approach further validated the stability of the results.

BWMR analysis

BWMR analysis is an efficient causal inference statistical method based on summary statistics that account for uncertainties arising from polygenicity, resulting in weak effects. Outlier detection using BWMR mitigates violations of IV assumptions caused by pleiotropy. This study conducted a BWMR analysis based on MR and reverse MR analyses to enhance the robustness and reliability of the final results.

Sensitivity analysis

This study employed three effective validation methods: heterogeneity testing, horizontal pleiotropy testing, and single sensitivity testing, to verify the positive results derived from MR analysis. This approach assessed the robustness and reliability of the findings and identified potential sources of bias. First, conduct a heterogeneity test to assess whether there is significant heterogeneity among the IVs. When significant heterogeneity was observed ($p < 0.05$), a random-effects IVW model was applied; otherwise, a fixed-effects IVW model was used [18]. Second, a leave-one-out analysis was performed to examine the impact of IVs on the overall results of the MR analysis to identify influential SNPs [19]. Finally, the study utilized intercept-based MR-Egger regression and outliers (MR-PRESSO) to assess pleiotropy. If each IV adhered to the assumptions of MR (no horizontal pleiotropy), the results obtained using the IVW method were deemed reliable. Otherwise, the MR-Egger method was used for the corroborative analysis [20,21].

Results

Samples and data

Gut microbiome samples were collected from 5,959 participants. The GWAS identifier for neonatal bacterial sepsis is Finngen_R10 P16_BACTERIAL_SEPSIS_NEWBO. The study population originated from Finland and encompassed 7,967,866 SNPs.

MR analysis and Reverse MR Analysis

An analysis of genetic causality linked to bacterial

Table 1. IVW and BWMR analysis.

Exposure (Gut Microbiota)	No. SNP	IVW		BWMR analysis	
		OR (95%CI)	*p*	OR (95%CI)	*p*
Acetobacterales	17	159.844 (1.235-2.068E+04)	0.040	192.449 (0.951-3.892E+04)	0.052
Atopobiaceae	22	8.327 (1.485-46.666)	0.015	8.769 (1.423-54.023)	0.019
Aureimonas	18	16.518 (1.078-253.098)	0.044	19.753 (1.099-355.027)	0.042
Bacillus velezensis	13	13.905 (1.207-160.114)	0.034	15.538 (1.194-202.133)	0.036
Bacteroides A plebeius	21	0.519 (0.275-0.981)	0.043	0.526 (0.254-1.092)	0.084
Brevibacillaceae	17	31.546 (1.444-689.121)	0.028	32.525 (1.208-875.229)	0.038
CAG-390 sp003523225	22	0.235 (0.055-0.993)	0.048	0.182 (0.041-0.793)	0.023
CAG-488	30	2.974 (1.020-8.667)	0.045	3.093 (0.997-9.592)	0.050
Campylobacter D	20	16.225 (1.315-200.063)	0.029	21.485 (1.556-296.548)	0.021
Citrobacter A	22	0.214 (0.046-0.999)	0.049	0.191 (0.038-0.941)	0.041
Elusimicrobiota	79	68.498 (4.487-1.046E+03)	0.002	60.441 (3.169-1.152E+03)	0.006
Firmicutes A	17	75.643 (1.718-3.329E+03)	0.025	81.807 (1.387-4.823E+03)	0.034
Halomonadaceae	18	0.002 (3.020E-05-0.172)	0.005	0.001 (1.580E-05-0.192)	0.008
Herbidospora	24	15.842 (1.969-127.415)	0.009	17.673 (1.948-160.282)	0.010
Lachnoanaerobaculum saburreum	14	11.224 (1.379-91.350)	0.023	12.258 (1.313-114.386)	0.027
Mycoplasmatales	16	21.588 (1.014-459.216)	0.048	20.527 (0.884-476.222)	0.059
Spirillospora	19	0.035 (0.001-0.669)	0.025	0.029 (0.001-0.655)	0.026
UCG-010 sp003150215	15	0.320 (0.120-0.851)	0.022	0.307 (0.109-0.861)	0.024

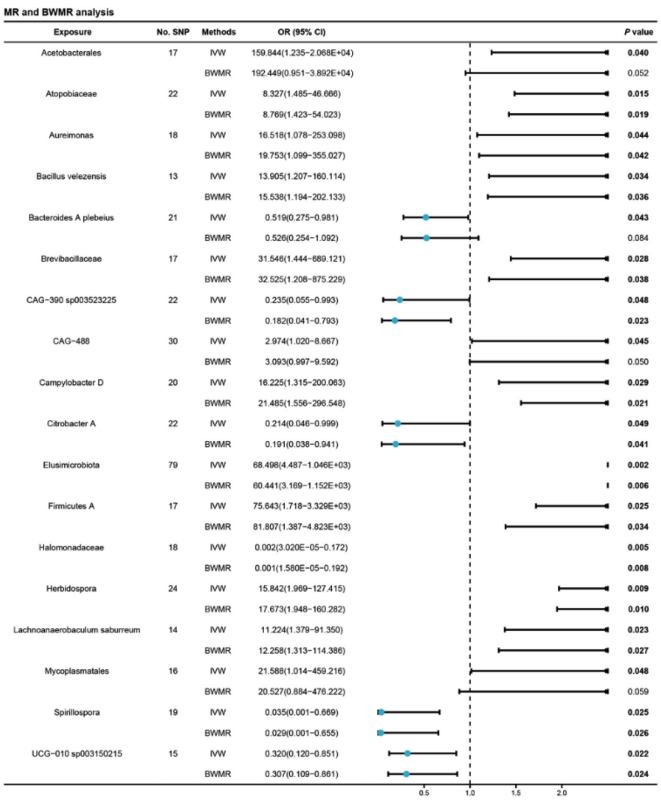
IVW: Inverse Variance Weighting; BWMR: Bayesian weighted Mendelian randomization.

sepsis in neonates examined 473 types of gut microbiota. This analysis revealed a positive MR (p < 1e-5, kb = 10,000, r^2 = 0.001) that identified 18 types of gut microbiota. The intestinal microbiota significantly influences the genetic causation of bacterial sepsis in neonates. The key findings included: *Acetobacterales* (Odds Ratio [OR]: 159.844; 95% Confidence Interval: 1.235-20680.19; p = 0.04), *Campylobacter D* (OR: 16.225; 95% CI: 1.315-200.063; p = 0.029), and *Firmicutes A* (OR: 75.643; 95% CI: 1.718-3328.863; p = 0.025). No heterogeneity was observed among the genetic IVs for these gut microbiota. The MR Egger regression intercepts did not significantly deviate from zero, indicating no evidence of horizontal pleiotropy (all intercepts had p > 0.05). Furthermore, a single sensitivity analysis demonstrated no significant differences in the causal assessment of each microbiome and other outcomes. This suggests that no definitive causal association was driven by any single instrumental variable. Additionally, to confirm that the impact of gut microbiota on neonatal sepsis was not due to reverse causation, we conducted a reverse MR analysis. The final results indicated the absence of reverse causal association between gut microbiota and neonatal sepsis, further enhancing the reliability of the findings (p < 1e-5, kb = 10,000, r^2 = 0.001).

BWMR analysis

This study validated the results of MR and reverse MR analyses through BWMR analysis. The findings indicate that the beneficial bacteria *Bacteroides A plebeius* (OR: 0.526; 95% CI: 0.254-1.092; p = 0.084) were observed. The harmful bacteria *Acetobacterales* (OR: 192.449; 95% CI: 0.951-38917.981; p = 0.052), *CAG-488* (OR: 3.093; 95% CI: 0.997-9.592; p = 0.0504), and *Mycoplasmatales* (OR: 20.527; 95% CI: 0.884-476.222; p = 0.059) (Table 1; Figure 2).

Figure 2. Forest plot.



MR analysis and BWMR analysis of the gut microbiome and neonatal sepsis. MR: Mendelian randomization; BWMR: Bayesian weighted Mendelian randomization.

Table 2. Sensitivity analysis.

Exposure (Gut Microbiota)	No. SNP	Heterogeneity		Pleiotropy	
		Q	*p*	Intercept	*p*
Acetobacterales	17	16	0.505	-0.220	0.173
Atopobiaceae	22	21	0.862	-0.010	0.897
Aureimonas	18	17	0.643	0.146	0.246
Bacillus velezensis	13	12	0.944	0.169	0.266
Bacteroides A plebeius	21	20	0.413	-0.068	0.568
Brevibacillaceae	17	16	0.710	-0.147	0.204
CAG-390 sp003523225	22	21	0.074	-0.028	0.797
CAG-488	30	29	0.860	0.091	0.298
Campylobacter D	20	19	0.396	0.176	0.070
Citrobacter A	22	21	0.355	-0.025	0.810
Elusimicrobiota	79	78	0.134	-0.073	0.333
Firmicutes A	17	16	0.629	-0.083	0.489
Halomonadaceae	18	17	0.397	0.235	0.052
Herbidospora	24	23	0.861	0.0007	0.994
Lachnoanaerobaculum saburreum	14	13	0.694	0.055	0.705
Mycoplasmatales	16	15	0.440	-0.118	0.378
Spirillospora	19	18	0.316	0.022	0.850
UCG-010 sp003150215	15	14	0.918	0.007	0.944

Sensitivity analysis

The heterogeneity and horizontal pleiotropy test results indicated that *p* values were greater than 0.05. This confirmed the absence of heterogeneity or horizontal pleiotropy among the instrumental variables. This study presented the results of the IVW analysis as MR findings, utilizing a fixed-effects model to illustrate the final results (Table 2).

Discussion

Neonatal bacterial sepsis is a significant contributor to infant mortality and morbidity rates. An imbalance in the gut microbiota correlates with various microbial-related diseases, including neonatal sepsis and necrotizing enterocolitis in infants, as well as multiple conditions in children and adults [22]. Therefore, the association between gut flora and bacterial sepsis in neonates is drawing increasing attention [23,24]. The study utilized MR and reverse MR analyses to examine the association between neonatal bacterial sepsis and gut microbiome from a genetic perspective. This approach mitigates the influence of confounding variables and reverse causality typically associated with traditional epidemiological statistical methods. At the same time, the results of MR and reverse MR analyses were validated through BWMR analysis, further enhancing the depth of the research and improving the reliability of the findings. Through the aforementioned research methodology, we have analyzed the genetic causal association between neonatal bacterial sepsis and the gut microbiome, revealing both beneficial and harmful microbes.

This study identified both beneficial microbiota and harmful bacteria from a total of 473 types of gut flora, with the latter being capable of causing neonatal bacterial sepsis. Several bacteria, including *Brevibacillaceae*, *Aureimonas,* and *Bacillus velezensis*, were identified as pathogenic. Other harmful bacteria included *Campylobacter D*, *Elusimicrobiota*, *Firmicutes A*, *Herbidospora*, and *Lachnoanaerobaculum saburreum*. *CAG-390 sp003523225*, *Citrobacter A*, *Halomonadaceae*, *Spirillospora*, and *UCG-010 sp003150215* are beneficial bacteria that serve as protective factors against bacterial sepsis in neonatal. The *genus Acetobacter* falls under the category of acetic acid bacteria. These microorganisms partially oxidize alcohols or sugars, resulting in the buildup of acetic acid [25]. Recent research discovered an unknown bacterium, potentially belonging to the *Acetobacter genus*, which has been named *Ranulobacter bethesdensis*; this bacterium was found in a patient with lymphadenitis. This bacterium exhibits notable pathogenicity [26]. *Aureimonas altamirensis* can cause invasive infections in humans and has been isolated from blood, thoracic, and abdominal fluid samples. Cases of bacteremia caused by this organism have been reported in South Korea [27]. The *phylum Firmicutes* predominantly consists of Gram-positive bacteria and represents a major component of the human gut microbiota. It is commonly linked to metabolic disorders [28,29], such as obesity and diabetes [30]. This study demonstrated that *phylum Firmicutes*, specifically *Bacillus velezensis*, were pathogenic and exhibited a significant causal association with neonatal bacteremia. The occurrence of sepsis is closely linked to abnormal gut microbiome development, low microbial diversity characterized by higher levels of *Proteobacteria* and *Firmicutes*, and delayed colonization by strict anaerobes [31]. *Campylobacter jejuni* is a Gram-negative, spiral-shaped bacterium that can lead to invasive infections, sepsis, and pericarditis [32,33]. Immunocompromised individuals face a higher risk of *Campylobacter* infections [34]. The research findings indicated that *Campylobacter* is a pathogenic bacterium. Research on *Elusimicrobiota*, *Herbidospora*, and *Lachnoanaerobaculum saburreum* as pathogens in neonatal bacterial sepsis is limited. This topic warrants increased scholarly attention.

Despite BWMR results for *Bacteroides A plebeius* (OR: 0.526; 95% CI: 0.254-1.092; $p = 0.084$), *Bacteroides* may still confer protection in neonatal bacterial sepsis. *Bacteroides* is a genus of obligate anaerobic bacteria that are typically beneficial to human health, except for *Bacteroides fragilis*. It resides in the human gastrointestinal tract, forming bacterial biofilms and serving as a crucial cornerstone genus in the gut microbiome [35]. *Bacteroides* play a crucial role in maintaining the integrity of the intestinal mucosal barrier and the biological barrier. The *Bacteroides genus* can enhance intestinal homeostasis by secreting immune-regulatory factors [36]. Moreover, the lipopolysaccharides present in these bacteria are key participants in immune modulation [37]. *Firmicutes* can produce short-chain fatty acids (SCFA) in the gut, such as acetate and propionate, which are essential for maintaining intestinal epithelial integrity and biodiversity homeostasis [38]. A study reported that the *Firmicutes/Bacteroidetes* (F/B) ratio decreased during pediatric sepsis and septic shock [39]. Furthermore, the abundance of *Bacteroides* significantly drops on the third day compared to the first day of sepsis [24]. The MR analysis demonstrated that the *genus Bacteroides* plays a protective role against bacterial sepsis in

neonates. Increasing the abundance of Bacteroides in the gut benefits the defense against pathogen invasion. *CAG-390 sp003523225* and *UCG-010 sp003150215* play a significant role as beneficial microbiota in neonatal bacterial sepsis. Reports indicate that *Citrobacter A*, *Halomonadaceae*, and *Spirillospora* can cause infections, including meningitis [40]. The specific mechanisms remain unclear. This finding is not entirely consistent with the results of this study. It is possible that confounding factors and reverse causation influenced related research. Further clinical and fundamental studies are required to validate these findings.

Based on the above findings, the biological significance of key microbial taxa warrants discussion, particularly regarding the gut microbiota's role in neonatal immunity. Recent studies have revealed important functions of the gut microbiome in supporting the development of the immune system, host metabolism, and colonization resistance against enteric pathogens [41]. The interaction of gut microbiota plays a significant role in driving the development of the immune system. However, immune development disorders may occur when the gut microbiota is imbalanced. The delayed maturation of the intestinal microbiome in infants may hinder the development of immune cells, such as regulatory T cells (Tregs), as well as the maturation of the intestinal epithelium and the formation of the mucus layer. The development of intestinal immune cells is dependent on microbial signals derived from the gut microbiota of neonates. In an animal study, intestinal microbiome inhibited the accumulation of invariant natural killer T cells (iNKT) in the colon by inhibiting the expression of CXCL16 (an iNKT chemokine) in young mice, thereby limiting the possibility of iNKT cell-mediated intestinal inflammation [42]. Studies have shown that ecological imbalance in the intestinal microbiome of newborns can reduce the resistance of circulating neutrophils and intestinal pathogenic bacteria to colonization, thereby significantly increasing the risk of late-onset sepsis in newborns [43,44].

Halomonadaceae is one of the beneficial bacteria representatives in our research.

Studies have shown that the most abundant group associated with SCFAs, valeric acid, and butyric acid is *Halomonadaceae*, which exhibits a positive correlation [45]. SCFAs are produced by anaerobic intestinal microbiota fermentation and decomposition of dietary fiber, which can regulate inflammatory pathways and affect immune tolerance. They play important roles in maintaining gut barrier and modulation the immune system, by stimulating the secretion of antimicrobial factors and reducing the production of reactive oxygen species and proinflammatory cytokines. They support the development of Tregs, which are essential for maintaining immune tolerance. Notably, SCFAs have been shown to exert strong positive effects on B cells, promoting their activation and differentiation into plasma cells. Previous studies have shown that the harmful bacteria *Atopobiaceae,* identified in this study, can upregulate proinflammatory cytokines (IL-1α, IL-1β, IL-12, TNFα), immune checkpoint proteins (PD-L1, LAG3), and cancer biomarkers (CEA, MIF, TRAIL). And it is involved in lipid regulation, oxidative stress, inflammatory response, and immune evasion [46]. In addition, *Campylobacter D* mediates oxidative stress, promotes the goblet cells proliferation and mucus secretion, and correlates with increased intestinal permeability and systemic inflammation [47].

This study used a bidirectional MR approach to identify the genetic causal association between the gut microbiome and neonatal bacterial sepsis for the first time, thereby avoiding the confounding effects common in traditional epidemiological methods. Additionally, reverse MR analysis was performed to determine whether a reverse causal association exists between the gut microbiota and neonatal sepsis. Although our primary MR analysis reveals the potential causal relationship between exposure and outcome, the inherent reverse causality in observational association, where the outcome influences the exposure, remains a possible explanation. Therefore, a reverse MR analysis was conducted to formally assess the possibility of this opposite causality. The results showed that the estimated causal effect of the outcome of the genetic prediction on exposure was not significant, indicating no reverse causal association between the gut microbiota and neonatal sepsis, which effectively alleviated the concerns about the reverse causal bias and greatly enhanced the credibility of our conclusion that the relationship is one-way, from exposure to results. This finding does not support that the outcome is the cause of exposure from a genetic perspective. Of course, it only shows that under the current genetic tools and statistical power, we have found no evidence to support reverse causality, and there may be weak, non-linear, or reverse effects through other unknown pathways, which are not detected by our current analysis. Nevertheless, the current research results have provided important genetic support for our main causal hypothesis. Moreover, based on the MR and reverse MR analyses, we utilized BWMR to enhance the reliability of our results. In BWMR, the uncertainty of

estimated weak effects in GWAS and the influence of horizontal pleiotropy have been addressed in a unified statistical framework for two-sample MR. A comprehensive simulation study showed that BWMR was computationally stable and statistically efficient. BWMR can account for uncertainty in estimated weak effects and low-level pleiotropy, while adaptively detecting outliers caused by a few strong pleiotropy effects. The BWMR exhibited satisfactory performance in terms of estimation accuracy, type I error control, and statistical power. The satisfactory performance of BWMR can be attributed to the following characteristics: (i) the adaptive use of variance components τ to explain the weak pleiotropic effect; (ii) Robustness of strong level pleiotropy guaranteed by the Bayesian weighting scheme, and (iii) Stable and efficient parameter estimation and inference algorithms [13]. Therefore, the findings of this study are more robust than those of previous studies. The real-time updated database and rigorous filtering criteria enhanced the robustness of the results. Ultimately, this study identified both beneficial and harmful bacteria associated with neonatal bacterial sepsis. However, it is crucial to acknowledge the limitations of this study, including potential biases from sample size and demographic factors. Potential biases in the results arose from factors such as the gut microbiome sample size and variation in participants' geography, age, and ethnicity. Future research can collect more data under favorable conditions to enhance result generalizability. In addition, the study's results included some extreme Odds Ratio (OR) values with wide confidence intervals, although rigorous and comprehensive MR analysis was performed and verified by BWMR, potential overfitting or weak instrument bias cannot be completely excluded.

Conclusions

In conclusion, this study elucidated a significant potential causal association between the gut microbiota and neonatal bacteremia, using MR analysis to provide robust evidence supporting this link. These findings underscore the importance of the gut microbiota in the pathogenesis of neonatal infections and highlight new avenues for targeted interventions. By establishing a foundation for future research, this study paves the way for the development of microbiota-based therapeutic strategies aimed at reducing the incidence and severity of neonatal bacteremia. Continued exploration in diverse populations alongside experimental approaches is crucial for validating these associations and translating them into clinical practice, ultimately enhancing neonatal health outcomes.

Data Availability

The datasets analyzed in this study are from: FinnGen consortium (https: //www.finngen.fi/en/access_results) (Accession nos. finngen_R10_P16_BACTERIAL_SEPSIS_NEWBO and PubMed (https://pubmed.ncbi.nlm.nih.gov/) (Accession nos. PMID：35115689). Supplementary datasets are available upon request.

Authors contributions

FS proposed and designed this article. SL conducted the entire research, including the drafting of the manuscript, and is the first author of this article. YD and FS revised and finalized the manuscript. All the authors have read and approved the manuscript.

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Conflict of interest

No conflict of interest is declared.

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