International Journal of Chronic Obstructive Pulmonary Disease Dovepress
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ORIGINAL RESEARCH

Causal Relationship Between Gut Microbiota and Chronic Obstructive Pulmonary Disease: A Bidirectional Two-Sample Mendelian Randomization Study

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Background: The associations between gut microbiota and chronic obstructive pulmonary disease (COPD) have gained increasing attention and research interest among scholars. However, it remains unclear whether gut microbiota serves as a causal factor for COPD or if it is a consequence of the disease. Therefore, we investigated the causal relationship between COPD and gut microbiota, with intention of providing novel insights and references for clinical diagnosis and treatment.

Methods: Based on the genome-wide association study (GWAS) data, we employed MR-Egger regression, random-effects inverse variance-weighted (IVW) method, and weighted median method for bidirectional Mendelian randomization (MR) analysis. We conducted Cochran's Q test for heterogeneity assessment and performed multivariable analysis, sensitivity analysis, and heterogeneity testing to validate the reliability and stability of results.

Results: Utilizing MR analysis, mainly employing the IVW method, we detected a collective of 11 gut microbiota species that exhibited associations with COPD. Among them, Bacteroidia, family XIII, Clostridium innocuum group, Barnesiella, Collinsella, Lachnospiraceae NK4A136 group, Lachnospiraceae UCG004, Lachnospiraceae UCG010, and Bacteroidales were found to be protective factors for COPD. On the other hand, Holdemanella and Marvinbryantia were identified as risk factors for COPD. Individuals with elevated levels of Holdemanella exhibited a 1.141-fold higher risk of developing COPD compared to their healthy counterparts, and those with increased levels of Marvinbryantia had a 1.154-fold higher risk. Reverse MR analysis yielded no evidence indicating a causal relationship between gut microbiota and COPD occurrence.

Conclusion: Our study established a causal link between 11 specific gut microbiota species and COPD, offering novel insights and valuable references for targeted therapies in the clinical management of COPD. However, our results were mainly based on the analysis of database, and further clinical studies are needed to clarify the effects of gut microbiota on COPD and its specific protective mechanism.

Keywords: gut microbiota, COPD, bidirectional MR, causal, association

Introduction

Chronic obstructive pulmonary disease (COPD), commonly known as 'chronic bronchitis' or "emphysema", is a heterogeneous pulmonary disorder characterized by persistent and progressive airflow limitation.[1–3] Clinical manifestations of COPD include chronic cough, sputum production, and dyspnea, primarily associated with abnormalities in the airways and alveoli. The etiology of COPD is multifactorial and complex, encompassing individual and environmental

Received: 20 February 2024
Accepted: 20 July 2024
Published: 2 September 2024

factors.[4,5] Individual factors include genetic predisposition, age, gender, and a low body mass index, while environmental factors mainly consist of smoking, biomass smoke, air pollution, and occupational dust exposure.[4,5] The pathogenesis of COPD is intricate and not yet fully elucidated.

The gut microbiota is a vast collection of microorganisms, estimated to consist of approximately 10^14 microbial species, comprising ten times the quantity of human cells and commonly known as 'second genome of humans'.[6,7] It primarily comprises phyla such as Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Verrucomicrobia, and Fusobacteria.[8] Gut microbiota plays a role in preserving immunity of intestinal mucosa and regulates normal immune responses through interactions with lymphocytes.[9–11] In recent years, research has begun to focus on connection between COPD and gut microbiota. Studies examining fecal microbiota of COPD patients and healthy controls have identified several members of Streptococcus, Veillonella, and Moraxellaceae that are associated with decreased lung function. COPD patients have shown a significantly lower abundance of gut microbial communities compared to healthy individuals, with an enrichment of Streptococcus in COPD patients.[12] Although an association between COPD and gut microbiota has been noted, the causal relationship remains unclear.

Mendelian randomization (MR) analysis is an approach that employs genetic variation as instrumental variables to deduce causal associations between exposures and outcomes.[13–15] As genetic variations are acquired congenitally and are not influenced by confounding factors, MR analysis can effectively reduce interference from confounders on the exposure and outcome, making it advantageous compared to other study methods.[16] Hence, in this study, we utilized bidirectional MR analysis to investigate causal link between COPD and gut microbiota, aiming to offer novel perspectives for clinical treatment of COPD.

Methods

Study Design

We first considered gut microbiota as the exposure factor and COPD as the outcome variable. We employed single nucleotide polymorphisms (SNPs) highly correlated with both exposure factor and the outcome variable, ensuring their independence, as instrumental variables. Employing the MR package in R software, we performed an analysis to investigate causal association between COPD and gut microbiota. Furthermore, we employed Cochran Q test to assess heterogeneity and performed tests for pleiotropy and sensitivity analysis to validate reliability of causal association results. We then carried out a reverse MR analysis, utilizing COPD as the exposure factor and gut microbiota as outcome variable, to explore possible existence of a reverse causal relationship between the two.

Data Sources

GWAS data for gut microbiota were acquired from the MiBioGen International Consortium, which consolidated information from 24 cohorts (https://mibiogen.gcc.rug.nl/). This dataset included details from 18,340 participants. Each cohort conducted 16S rRNA sequencing to explore gut microbiota, and participants underwent genotyping using a whole-genome SNP array.[17] Our study incorporated 196 gut microbiota samples, representing 9 phyla, 16 classes, 20 orders, 32 families, and 119 genera. Additional information can be found in references,[17,18] providing details on 122,110 SNPs. The GWAS data for COPD were retrieved from version R9 of FinnGen database (https://www.finngen.fi/en/access_results) and encompassed information from 18,266 patients and 311,286 controls, covering a total of 20,169,090 SNPs.

Instrument Variables (IVs) Selection

In the context of MR analysis, IVs are employed to investigate the causal relationship between the exposure factor and the outcome variable. These IVs usually incorporate genetic variations, with SNPs being the most frequently utilized. Following the reference of whole-genome information from the 1000 Genomes Project, we compiled SNPs from the gut microbiota dataset that were genome-wide significant ($P < 1\times10\text{-}5$) while considering linkage disequilibrium. We set the parameter (r2) to 0.01 with genetic distance between genes to 10,000 kb. Ultimately, we obtained a set of independent SNPs that were most strongly associated with the outcome variable to serve as the final instrumental variables.

MR Analysis

We mainly utilized the inverse variance weighted (IVW) method, MR-Egger regression, and the weighted median estimator (WME) for MR analysis. We established a statistical strength threshold of F > 10, determined by formula F = (R2/1-R2) (N-K-1/K), where N denotes the sample size, K represents the number of instrumental variables, and R^2 indicates the proportion of exposure variance explained by the instrumental variables.

Heterogeneity Testing

\To assess heterogeneity among the individual IVs, we employed the Cochran Q test. If $p < 0.05$, it indicates presence of heterogeneity. Conversely, if $p > 0.05$, it suggests no heterogeneity, allowing us to disregard its impact on the assessment of causal effects.

Multivariable Analysis

Multivariableity refers to the influence of genetic variations on outcome through pathways other than specific "genetic variation-exposure-outcome" pathway.[19,20] In this study, we utilized the intercept term in MR Egger regression to assess multivariablity. If $p < 0.05$, it indicates presence of multivariablity. Conversely, if the $p > 0.05$, it suggests no multivariableity.

Sensitivity Analysis

We performed a leave-one-out sensitivity test to assess how each SNP individually influenced the outcomes. Specifically, we iteratively excluded each SNP and recalculated the MR results with the remaining SNPs. If the exclusion of a specific SNP leads to a substantial difference in the results compared to the overall results, it indicates that MR results are sensitive to that of the SNP.

Results

IVs

After excluding SNPs in linkage disequilibrium and ensuring an F value greater than 10, we included 119 SNPs related to the gut microbiota as instrumental variables. Please refer to Supplementary Table 1 for specific information.

MR results

Using the IVW method, we identified 11 gut microbiota groups associated with COPD. The results are as follows: Bacteroidia: OR (95% CI) = 0.856(0.742–0.988), p = 0.033; FamilyXIII: OR (95% CI) = 0.797(0.675–0.941), p = 0.007; Clostridium innocuum group: OR (95% CI) = 0.923 (0.858–0.992), p = 0.030; Barnesiella: OR (95% CI) = 0.889 (0.793–0.996), p = 0.043; Collinsella: OR (95% CI) = 0.828(0.718–0.955), p = 0.001; LachnospiraceaeNK4A136 group: OR (95% CI) = 0.900(0.819–0.988), p = 0.028; LachnospiraceaeUCG010: OR (95% CI) = 0.870(0.769–0.985), p = 0.028; LachnospiraceaeUCG004: OR (95% CI) = 0.886(0.790–0.993), p = 0.038; Bacteroidales: OR (95% CI) = 0.856(0.742–0.988), p = 0.033. The p-values for all the gut microbiota groups using the IVW method were less than 0.05, indicating statistically significant differences. OR for these groups were less than 1, suggesting that class Bacteroidia, family FamilyXIII, genus Clostridium innocuum group, genus Barnesiella, genus Collinsella, genus LachnospiraceaeNK4A136group, genus LachnospiraceaeUCG004, genus LachnospiraceaeUCG010, and order Bacteroidales may be protective factors for COPD.

Moreover, employing the IVW method yielded the subsequent outcomes: Holdemanella: OR (95% CI) = 1.141 (1.055–1.235), p = 0.001; Marvinbryantia: OR (95% CI) = 1.154(0.026–1.298), p = 0.017. Both Holdemanella and Marvinbryantia exhibited $p < 0.05$ using the IVW method, indicating statistically significant distinctions. The OR values for both groups were above 1, suggesting that the genera Holdemanella and Marvinbryantia might be detrimental factors for COPD. MR-Egger regression and WME analyses were also conducted, as illustrated in Table 1. The scatter plots demonstrated that consistent causal effects were observed across the IVW, MR-Egger, and WME methods, as depicted in Figures 1 and 2. To validate the robustness of the findings, a horizontal pleiotropy test was conducted on the included SNPs, revealing non-significant horizontal pleiotropy ($p > 0.05$). A funnel plot, like those in the meta-analysis literature,

Table 1 MR Results of Gut Microorganisms That Have Been Correlated with COPD

Gut Microbiota	MR Results						Heterogeneity	
	Methods	SNPs	Beta	SE	P-value	OR (95% CI)	Cochran's Q	P-value
COPD								
Bacteroidia	IVW	12	−0.156	0.073	3.3E-02	0.856(0.742–0.988)	13.676	0.251
	MR Egger	12	−0.429	0.154	1.9E-02	0.651(0.482–0.880)	9.812	0.457
	Weighted median	12	−0.221	0.088	1.2E-02	0.802(0.666–0.965)		
Family XIII	IVW	7	−0.227	0.085	0.7E-02	0.797(0.675–0.941)	4.477	0.612
	MR Egger	7	−0.351	0.315	31.6E-02	0.704(0.380–1.305)	4.309	0.506
	Weighted median	7	−0.155	0.112	16.4E-02	0.856(0.682–1.075)		
Clostridium innocuum group	IVW	8	−0.080	0.037	3.0E-02	0.923(0.858–0.992)	6.440	0.490
	MR Egger	8	−0.116	0.192	56.8E-02	0.891(0.611–1.298)	6.402	0.380
	Weighted median	8	−0.098	0.051	5.4E-02	0.907(0.826–0.996)		
Barnesiella	IVW	12	−0.118	0.058	4.3E-02	0.889(0.793–0.996)	8.930	0.628
	MR Egger	12	−0.286	0.239	26.0E-02	0.751(0.470–1.200)	8.403	0.589
	Weighted median	12	−0.051	0.080	52.2E-02	0.950(0.812–1.112)		
Collinsella	IVW	9	−0.188	0.073	0.1E-02	0.828(0.718–0.955)	4.670	0.792
	MR Egger	9	−0.111	0.271	69.5E-02	0.895(0.526–1.524)	4.583	0.711
	Weighted median	9	−0.160	0.094	8.8E-02	0.852(0.708–1.026)		
Holdemanella	IVW	11	0.132	0.040	0.1E-02	1.141(1.055–1.235)	4.806	0.904
	MR Egger	11	0.134	0.115	27.3E-02	1.143(0.913–1.432)	4.806	0.851
	Weighted median	11	0.125	0.054	2.1E-02	1.134(1.017–1.263)		
Lachnospiraceae NK4A136 group	IVW	15	−0.106	0.048	2.8E-02	0.900(0.819–0.988)	12.143	0.595
	MR Egger	15	−0.049	0.096	61.8E-02	0.952(0.789–1.149)	11.677	0.554
	Weighted median	15	−0.075	0.072	29.9E-02	0.928(0.812–1.060)		
LachnospiraceaeUCG004.	IVW	13	−0.121	0.058	3.8E-02	0.886(0.790–0.993)	10.892	0.538
	MR Egger	13	−0.030	0.250	90.6E-02	0.970(0.595–1.583)	10.751	0.464
	Weighted median	13	−0.119	0.080	13.8E-02	0.888(0.752–1.048)		
LachnospiraceaeUCG010	IVW	10	−0.139	0.063	2.8E-02	0.870(0.769–0.985)	5.920	0.748
	MR Egger	10	−0.426	0.192	5.8E-02	0.653(0.448–0.953)	3.43	0.904
	Weighted median	10	−0.095	0.085	26.4E-02	0.910(0.776–1.065)		
Marvinbryantia	IVW	10	0.143	0.060	1.7E-02	1.154(0.026–1.298)	6.246	0.715
	MR Egger	10	0.090	0.238	71.2E-02	1.094(0.690–1.737)	6.191	0.626
	Weighted median	10	0.077	0.079	32.8E-02	1.080(0.919–1.270)		
Bacteroidales	IVW	12	−0.156	0.073	3.3E-02	0.856(0.742–0.988)	13.676	0.251
	MR Egger	12	−0.429	0.154	1.9E-02	0.651(0.482–0.880)	9.812	0.457
	Weighted median	12	−0.220	0.092	1.6E-02	0.802(0.668–0.963)		

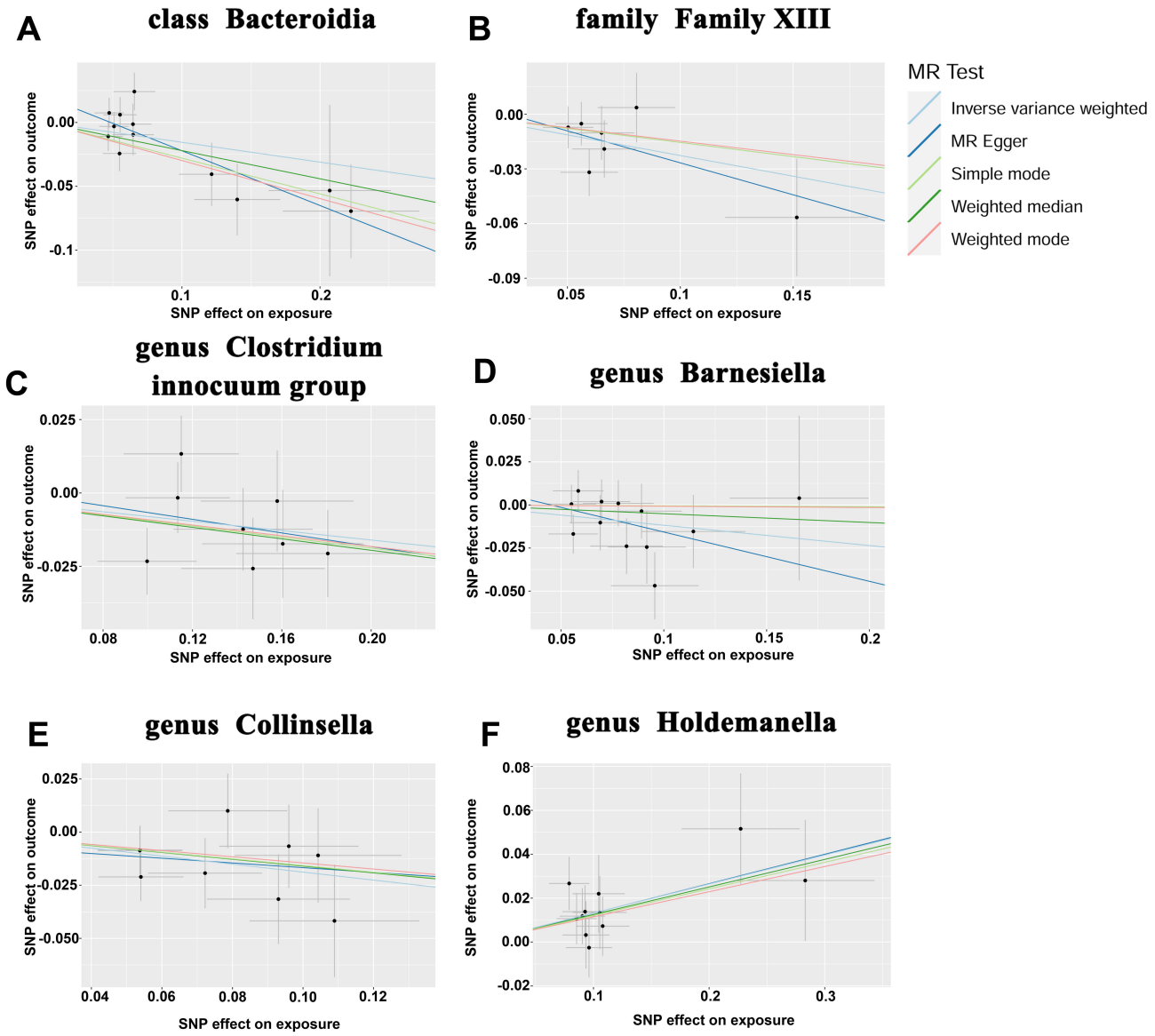

Figure 1 Scatter plots of MR results of gut microbiota on including (**A**) class Bacteroidia, (**B**) family Family XIII, (**C**) genus Clostridium innocuum group, (**D**) genus Barnesiella, (**E**) genus Collinsella and (**F**) genus Holdemanella COPD.

has also been employed to visualize possible evidence of directional pleiotropy in our study.[21] The MR result funnel plot displayed no bias, as depicted in Figures 3 and 4.

Sensitivity Analysis

In the Cochran's Q test, all p-values exceeded 0.05, suggesting an absence of heterogeneity among the SNPs. Specific details can be found in Table 1. The intercept term in MR-Egger regression yielded p-values greater than 0.05, indicating a lack of statistically significant differences. Consequently, no horizontal pleiotropy exists among the SNPs. Additional information is available in Supplementary Table 2. Through the leave-one-out sensitivity analysis, we investigated the influence of each SNP on the results. Results of "Leave-one-out" sensitivity analysis showed that no significant variations in MR analysis when each SNP was individually excluded and no SNP exhibited a substantial impact on the causal relationship (Figures 5 and 6).

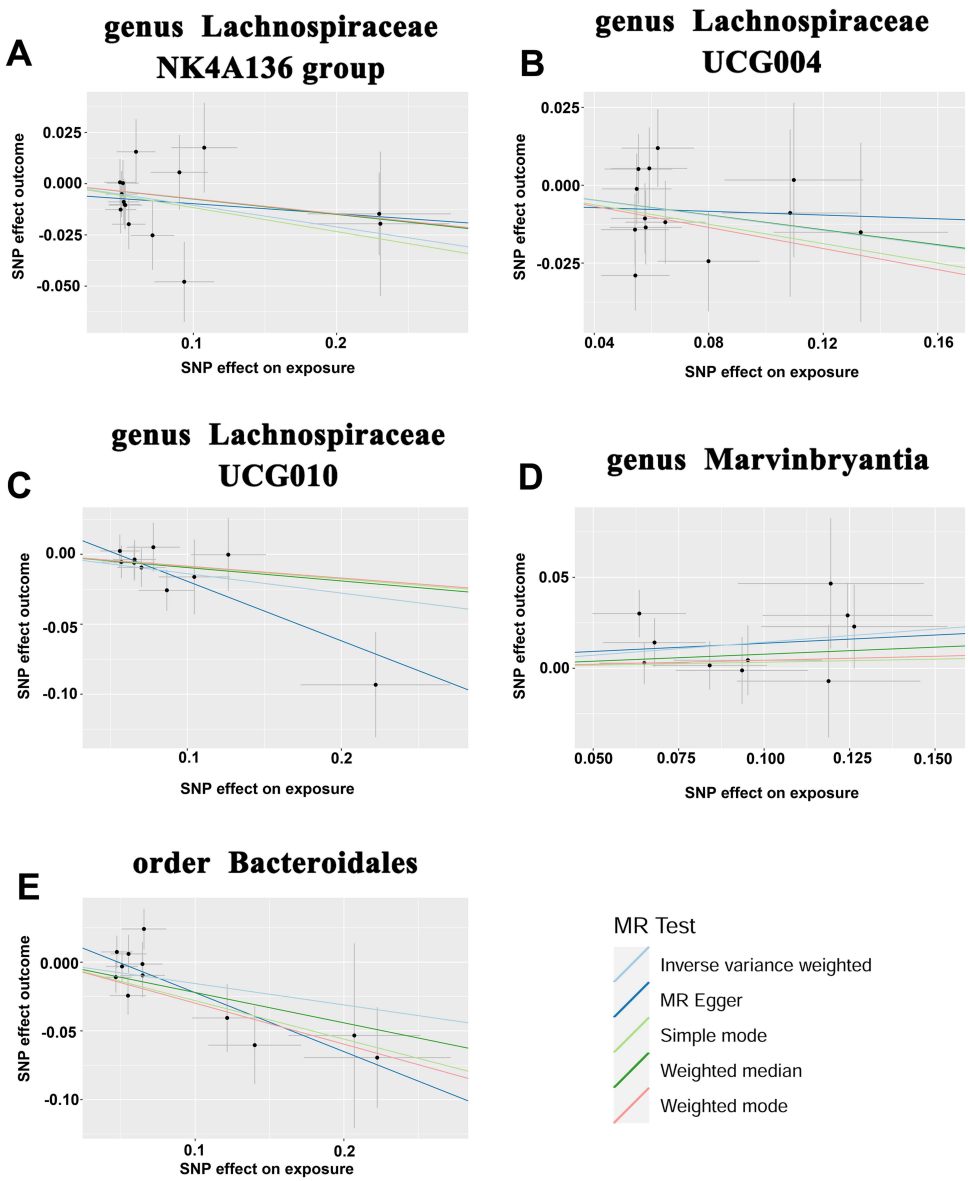

Figure 2 Scatter plots of MR results of gut microbiota including (**A**) genus Lachnospiraceae NK4A136 group, (**B**) genus Lachnospiraceae UCCG004, (**C**) genus Lachnospiraceae UCG010, (**D**) genus Marvinbryantia and (**E**) order Bacteroidales on COPD.

Reverse MR Results

By employing the IVW method, we conducted a reverse MR analysis to investigate the potential existence of a causal relationship in the opposite direction between 11 gut microbiota groups and COPD. The results are as follows: Bacteroidia: p = 0.951; FamilyXIII: p = 0.141; Clostridium innocuum group: p = 0.245; Barnesiella: p = 0.702; Collinsella: p = 0.826; Lachnospiraceae NK4A136 group: p = 0.575; LachnospiraceaeUCG010: p = 0.333; LachnospiraceaeUCG004: p = 0.648; Bacteroidales: p = 0.951; Holdemanella: p = 0.440; Marvinbryantia: p = 0.254. The p-values obtained from the IVW analysis for these 11 specific gut microbiota groups were all greater than 0.05, indicating no statistically significant differences. The MR-Egger analysis and weighted median analysis similarly produced p-values exceeding 0.05. Specific details can be found in Supplementary Table 3. The outcomes of the reverse MR analysis suggest the absence of a causal relationship in the opposite direction between these 11 gut microbiota groups and COPD.

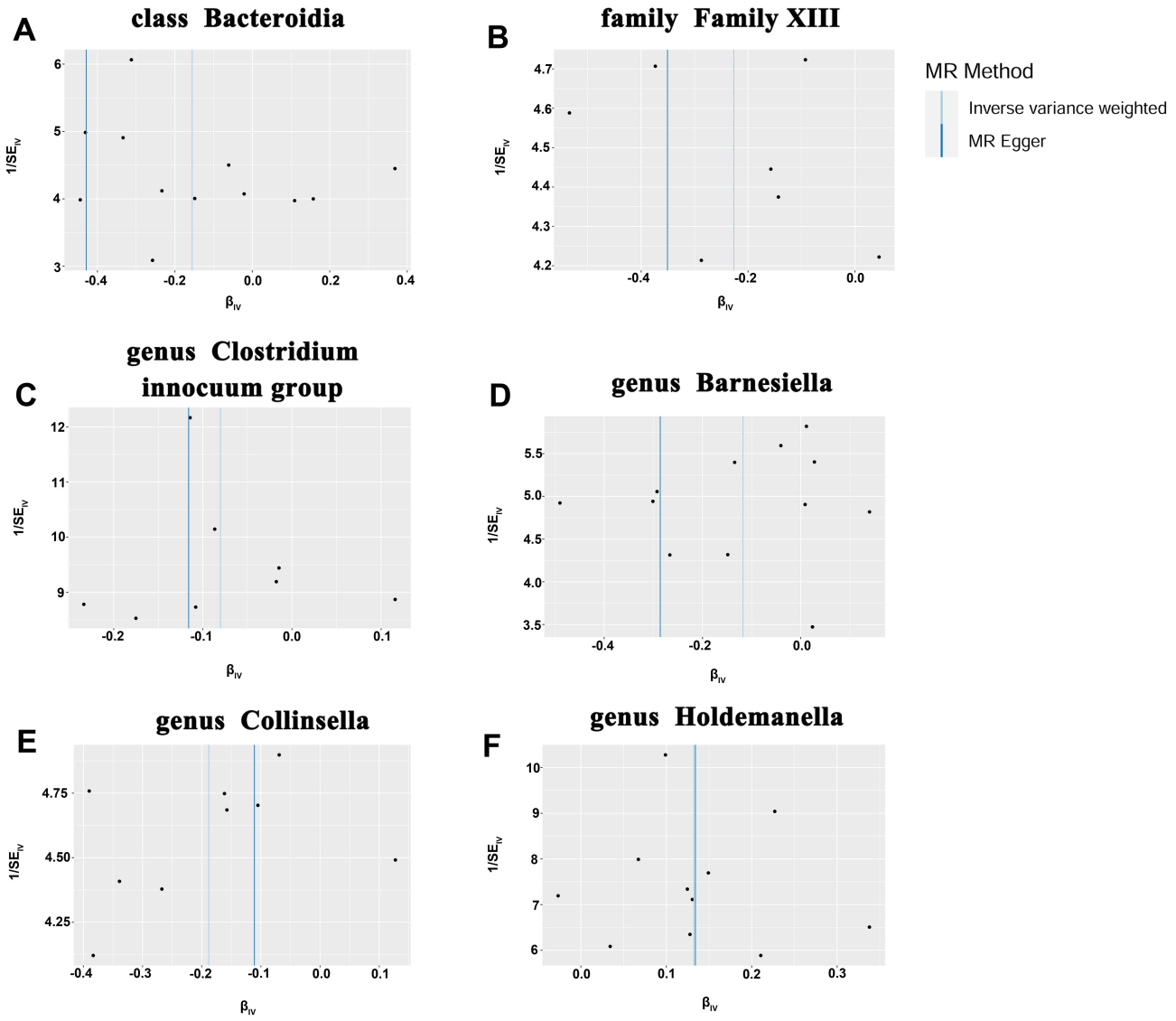

Figure 3 Funnel plots for MR results of gut microbiota (**A**) class Bacteroidia, (**B**) family Family XIII, (**C**) genus Clostridium innocuum group, (**D**) genus Barnesiella, (**E**) genus Collinsella and (**F**) genus Holdemanella on COPD.

Discussion

Approximately 98% of the gut microbiota is categorized into the phyla Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria. A symbiotic relationship exists between the gut microbiota and the human host, where the host provides a conducive environment for the flourishing of gut microbiota. In return, the gut microbiota contributes to enhanced digestion and immune capabilities for the host, while also mitigating the presence of pathogenic microorganisms. Numerous studies have highlighted the correlation between dysbiosis of gut microbiota and various diseases, including diabetes, bronchial asthma, lung cancer, multiple sclerosis, among others.[22–24] Recently, the association between gut microbiota and COPD has garnered increased attention and research.

In our study, utilizing extensive GWAS data, we primarily employed the random-effects inverse variance-weighted method, MR-Egger regression, and the weighted median method for MR analysis. We accounted for environmental and other confounding factors to investigate the potential causal relationship between gut microbiota and COPD. Our research findings suggest that Bacteroidia, FamilyXIII, Clostridium innocuum group, Barnesiella, Collinsella, Lachnospiraceae NK4A136 group, Lachnospiraceae UCG004, Lachnospiraceae UCG010, and Bacteroidales act as protective factors for COPD. Conversely, Holdemanella and Marvinbryantia emerge as risk factors for COPD. The

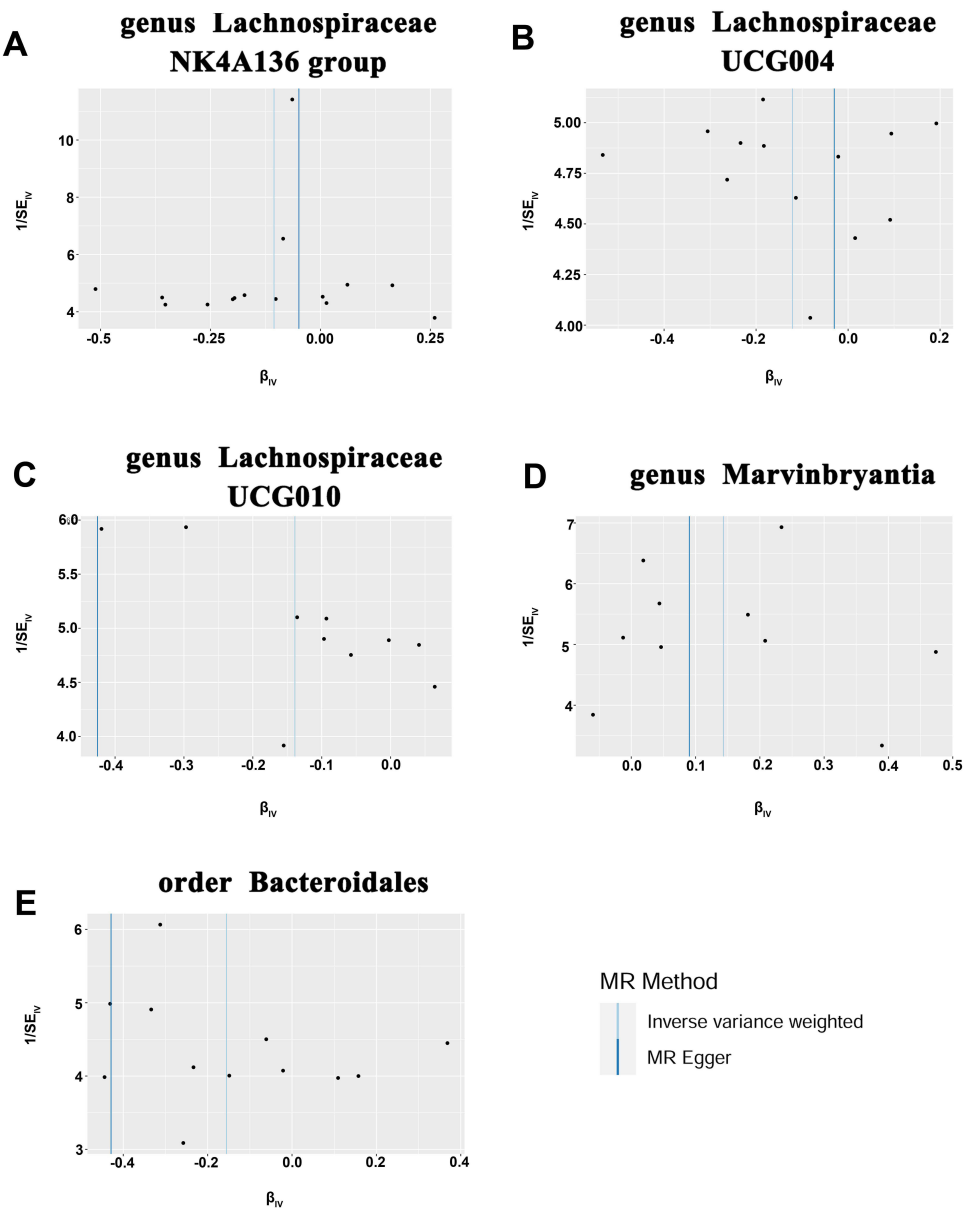

Figure 4 Funnel plots for MR results of gut microbiota including (**A**) genus Lachnospiraceae NK4A136 group, (**B**) genus Lachnospiraceae UCCG004, (**C**) genus Lachnospiraceae UCG010, (**D**) genus Marvinbryantia and (**E**) order Bacteroidales on COPD.

random-effects inverse variance-weighted method revealed that Holdemanella exhibited an odds ratio (OR) of 1.141 (95% CI: 1.055–1.235) with a p-value of 0.001, indicating that an increase in Holdemanella is associated with a 1.141-fold higher risk of COPD compared to the general population. Marvinbryantia, with an OR of 1.154 (95% CI: 0.026–1.298) and a p-value of 0.017, suggests that an increase in Marvinbryantia is linked to a 1.154-fold higher risk of COPD compared to the general population.

With the deepening research on microbiome and immunology, researchers have proposed the concept of the "lung-gut axis", which may play an important role in the pathogenesis of COPD. The respiratory tract and the gastrointestinal tract share a common embryonic origin, as both the mucous epithelium of the respiratory tract and the gastrointestinal tract differentiate from the endoderm. This determines the physiological similarities between the respiratory and gastrointestinal tracts, which may serve as the basis for their similar responses to stimuli. The bidirectional communication network between the lungs and the intestines is formed by the mutual interaction of bacteria and their metabolites, bacterial surface molecules, and the lymphatic, circulatory, and mucosal immune systems.[25,26] Metabolic byproducts of gut

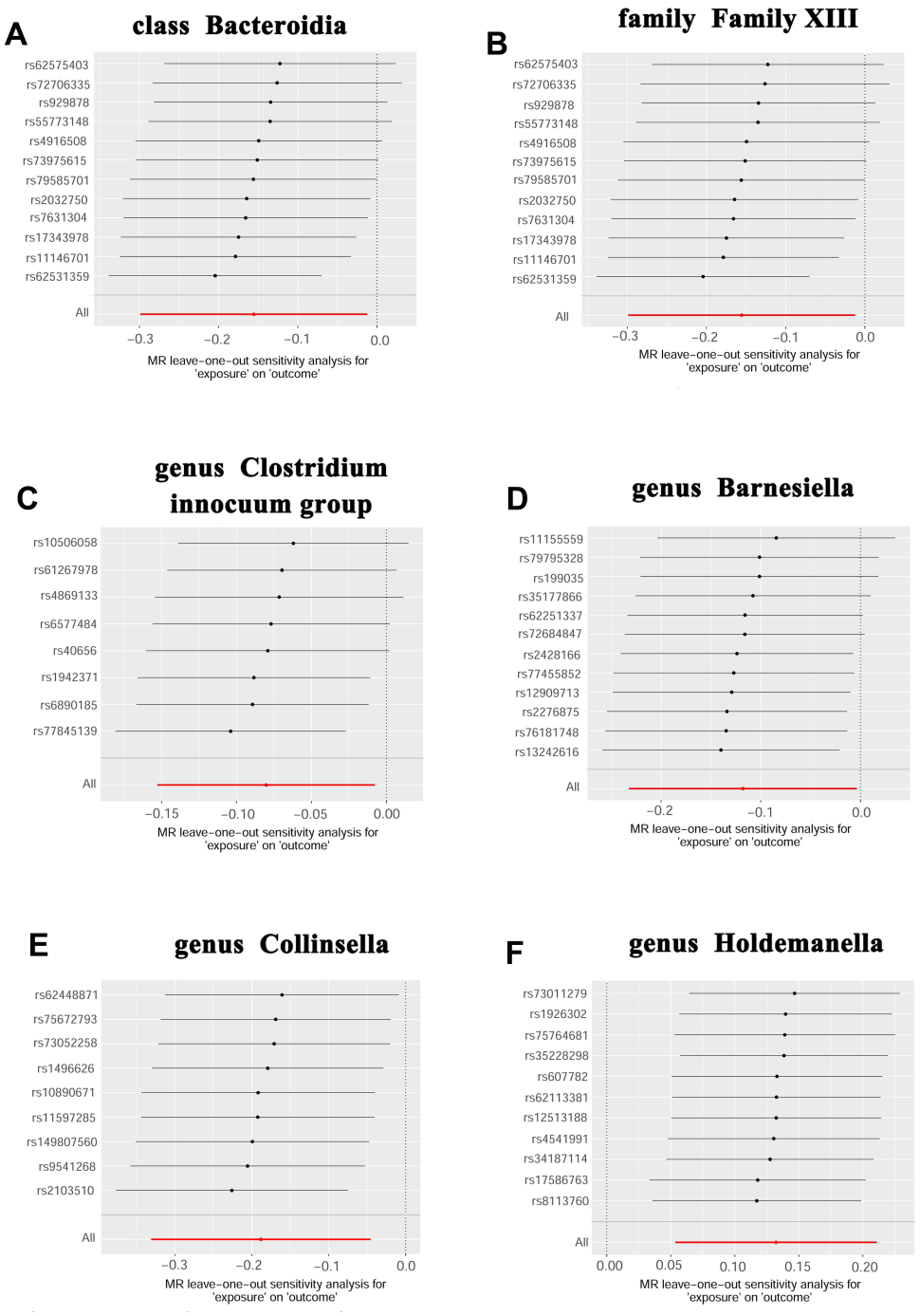

Figure 5 Results of "Leave-one-out" sensitivity analysis for (**A**) class Bacteroidia, (**B**) family Family XIII, (**C**) genus Clostridium innocuum group, (**D**) genus Barnesiella, (**E**) genus Collinsella and (**F**) genus Holdemanella.

microbiota fermentation, known as butyrate, propionate, and acetate, exhibiting immunoregulatory capabilities. These byproducts play a direct role in inhibiting histone deacetylases, thereby regulating dendritic cell signaling, facilitating dendritic cell migration to intestinal lymph nodes, initiating the differentiation of naïve CD4+ T cells, and inducing the development of regulatory T (Treg), Th17, and Th1 cells. These cells, in turn, exert effector functions in distant locations, including the lungs. Peripheral SCFAs traverse the bloodstream to reach the lungs, where they influence pulmonary immune mechanisms through direct signaling via G protein-coupled receptors (GPCRs) 41/43.[27] The acetate signal mediated by GPR43 is crucial for the phagocytosis and killing of Klebsiella pneumoniae by alveolar macrophages and

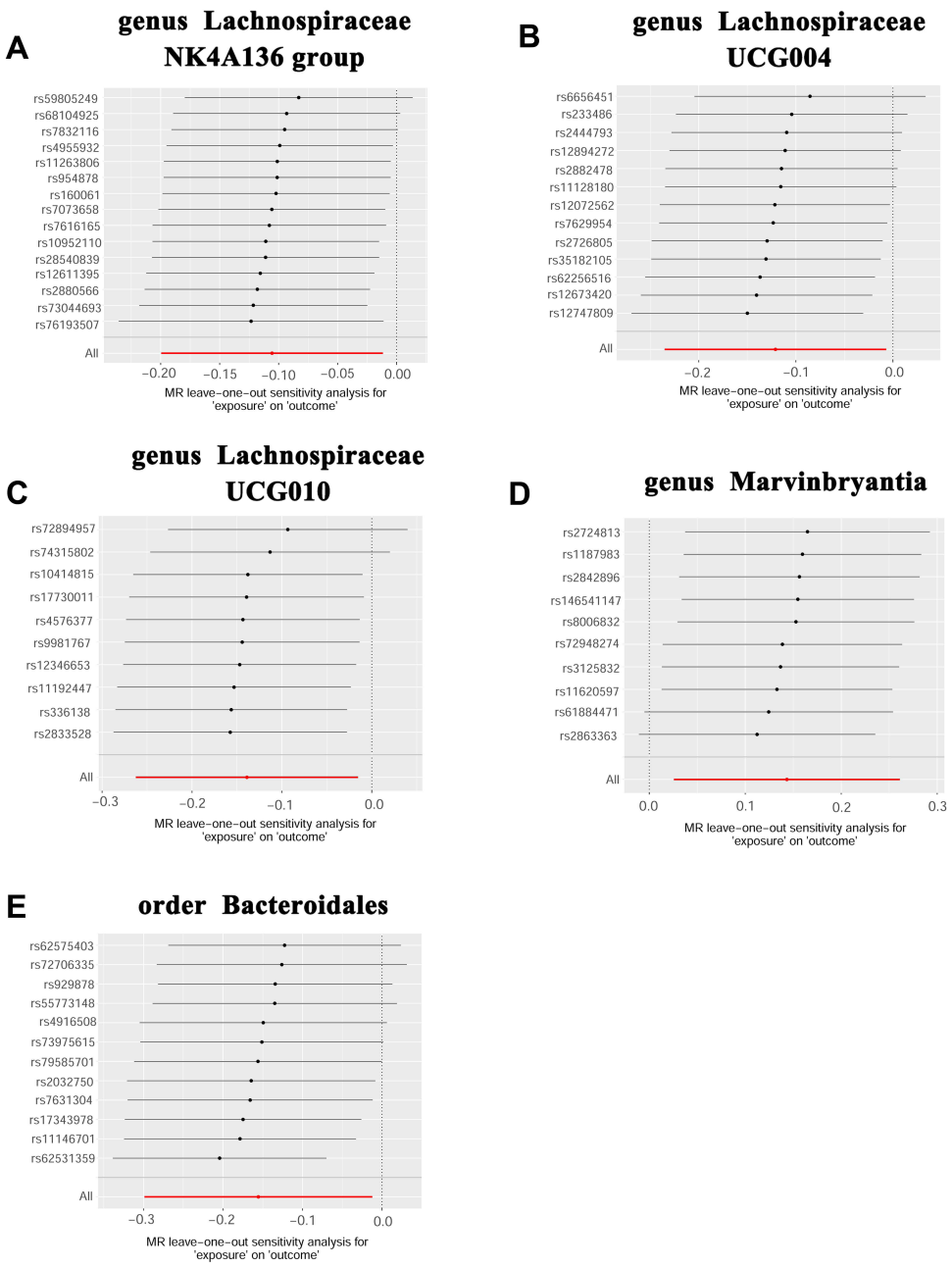

Figure 6 Results of "Leave-one-out" sensitivity analysis for (**A**) genus Lachnospiraceae NK4A136 group, (**B**) genus Lachnospiraceae UCCG004, (**C**) genus Lachnospiraceae UCG010, (**D**) genus Marvinbryantia and (**E**) order Bacteroidales.

neutrophils during pulmonary infection, reducing bacterial load in the airways and controlling pulmonary inflammation.[28] In a COPD model exposed to cigarette smoke, high-fiber supplementation (cellulose and pectin) was found to modulate the microbial community structure and effectively alter the composition of the gut microbiota. SCFAs with anti-inflammatory properties, such as acetate, propionate, and butyrate, were significantly enriched in the gut, and through anti-inflammatory mechanisms including the metabolism of arachidonic acid pathway, they prevented the development of COPD, inhibited local and systemic inflammatory responses, and reduced alveolar destruction.[29]

The abundances of the genera Holdemanella and Marvinbryantia are negatively correlated with propionate and isobutyrate, suggesting their potential role in inhibiting the anti-inflammatory mechanisms and promoting the development of COPD.[30] The class Bacteroidia and order Bacteroidales are both protective factors against COPD. Bacteroidia is an obligate

anaerobic Gram-negative bacteria associated with tryptophan hydroxylase-II serotonin pathway. Serotonin, as one of the neurotransmitters in the brain, has immunostimulatory and anti-inflammatory effects during mucosal infections.[31]

The bacterial genus Clostridium inoculum, classified as an obligate anaerobic Gram-positive organism within the phylum Firmicutes, primarily generates acetate and butyrate, both known for their inflammation-inhibiting properties.[32] The genus Collinsella is noteworthy for harboring a gene encoding NADPH-dependent 7β-hydroxysteroid dehydrogenase (7β-HSDH) and serves as a crucial intestinal bacterium for the synthesis of UDCA and other secondary bile acids.[33] UDCA exhibits inhibitory effects on pro-inflammatory cytokines, including TNF-α, IL-1β, IL-2, IL-4, and IL-6, operating at both mRNA and protein levels.[34,35] The family Lachnospiraceae encompasses the Lachnospiraceae NK4A136 group, along with the genera Lachnospiraceae UCG004 and Lachnospiraceae UCG010. These entities collectively produce short-chain fatty acids, such as acetate and butyrate, which display positive correlations with their respective levels. Through the "lung-gut axis" mechanism, they possess the ability to alleviate pulmonary inflammation.[36] Family XIII and the genus Barnesiella have been less extensively studied, necessitating further investigations to comprehend their mechanisms in the context of chronic obstructive pulmonary disease. Results from the reverse MR analysis indicated p-values greater than 0.05, signifying the absence of a statistically significant reverse causal relationship between the 11 specific gut microbiota and COPD.

There are several limitations in this MR study including: (1) inclusion of the European population, which limits the extrapolation of conclusions to other populations; (2) Difficulty in conducting stratified analysis based on gender, age, and past history according to GWAS summary data; (3) This study is a statistical result and cannot further explore the underlying mechanisms.

Conclusions

Our study indicated a causal relationship between 11 specific gut microbiota and COPD, while no reverse causality was observed. These findings offer novel insights and valuable implications for targeted therapeutic strategies in the clinical management of COPD such as probiotics to modulate the gut microbiota and alleviate COPD progression. However, our results were mainly based on the analysis of database, and further clinical studies are needed to clarify the effects of gut microbiota on COPD and its specific protective mechanism.

Data Sharing Statement

All data generated during this study are included in this published article. The datasets analysed during the current study are available in the FinnGen biobank R9 (https://www.finngen.fi/en/access_results) and MiBioGen International Consortium (https://mibiogen.gcc.rug.nl/).

Ethics Approval and Consent to Participate

This study utilizes aggregated data rather than individual-level data. The data involved all originate from publicly published GWAS summary databases, which complies with the conditions for exemption from review as stated in the "Ethical Review Measures for Life Sciences and Medical Research Involving Humans".

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by Science, Technology and Innovation Commission of Shenzhen Municipality (JCYJ20210324131204012).

Disclosure

The authors report no conflicts of interest in this work.

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