

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

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Background: Recently, numerous studies have explored the potential impact of gut microbiota on Chronic Obstructive Pulmonary Disease (COPD). However, the causal relationship between skin microbiota and COPD, as well as the differences and similarities between the relationships of gut microbiota and COPD, has not been thoroughly studied.

Methods: We conducted a comprehensive two-sample Mendelian randomization (MR) analysis to investigate the relationships between gut and skin microbiota and COPD. The inverse variance weighted (IVW) method was used as the primary approach. MR-Egger, weighted median, and MR-PRESSO methods were used as supplementary approaches. Various sensitivity and stability analyses were conducted to validate the results. Genetic variations of gut microbiota were obtained from the FR02 cohort study. Genetic variations of skin microbiota were derived from the KORA FF4 and PopGen cohorts, with a total of 1,656 skin samples. GWAS data for COPD were obtained from the FinnGen consortium, including 18,266 COPD cases and 311,286 controls from European cohorts.

Results: The results of IVW method of MR analysis showed that 10 gut microbiotas and 4 skin microbiotas were negatively associated with COPD [$p < 0.05$, odds ratio (OR) < 1]; 3 gut microbiotas and 6 skin microbiotas were positively associated with COPD ($p < 0.05$, OR > 1). None of them were heterogeneous or horizontally pleiotropic ($p > 0.05$) or reverse causality.

Conclusion: This study revealed the causal relationships between gut and skin microbiota and COPD, offering fresh perspectives for the prevention, diagnosis, and management of COPD.

Keywords: chronic obstructive pulmonary disease, gut microbiota, skin microbiota, Mendelian randomization

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a chronic lung disease characterized by partially irreversible airflow limitation¹ affecting over 250 million people worldwide.² It is the fourth primary cause of mortality around the world, posing a significant public health challenge.³ The onset of COPD is influenced by a multifaceted interplay between genetic predispositions (eg susceptibility) and environmental contributors, including smoking and air pollution. Although COPD has a multifactorial etiology, current diagnostic and therapeutic methods remain inadequate.⁴ Despite extensive efforts in COPD prevention and management, mortality rates have not shown a decreasing trend, indicating that prevention and treatment strategies for COPD still face significant challenges.⁵

In recent years, increasing evidence has indicated a potential connection between gut microbiota dysbiosis and the development of COPD.^{6,7} Both clinical and animal studies have highlighted the involvement of gut microbiota in the advancement of COPD.^{8,9} Mendelian randomization studies have been utilized to provide genetic support for the proposed causal relationship between gut microbiota and respiratory disorders.^{10,11} Cheng ZX et al employ MR methods to investigate the causal links between gut microbiota, lung function, and COPD, underscoring the significant role of gut microbiota imbalances in influencing lung function and contributing to the onset of COPD.¹² However, among the human-associated microbial communities, the gut microbiota is the largest and most heterogeneous, with its composition varying between individuals.¹³ Therefore, characterizing this human ecosystem is particularly challenging. The diversity and complexity of the human gut microbiota add to the difficulty in using it to guide the diagnosis and treatment of COPD.

Dysbiosis of the skin microbiota has been found to potentially lead to systemic inflammation, contributing to the development of various diseases. The most recent study by Belkaid Y et al emphasizes the intimate relationship between the skin microbiota and the immune system.¹⁴ This lays the groundwork for the development of microbiota-driven immunotherapies for chronic inflammatory diseases. Research has indicated that skin barrier dysfunction due to microbiota imbalances may increase the risk of systemic allergic inflammation, which includes inflammation of the airways.¹⁵ Furthermore, Charlson et al perform 16S rDNA sequencing on lower respiratory tract bronchoalveolar lavage (BAL) samples and identify the main bacterial genera as *Staphylococcus*, *Streptococcus*, *Veillonella* and so on, which are skin commensals. They also find soil- and water-related genera like *Burkholderia* and *Ralstonia*, suggesting that the lung microbiome acquires species from the skin, nasopharynx, and external environment. Therefore, exploring the possibility of skin microbiota interventions may provide new insights for the prevention and treatment of COPD. However, research on the causal relationship between skin microbiota and COPD, as well as the comparative effects of skin and gut microbiota on COPD, is limited.

Typically, the primary standard for establishing causality is the randomized controlled trial (RCT), which serves to examine direct effects but may have implementation limitations, including sample size requirements, implementation conditions, ethical considerations, and so forth. Additionally, reverse causality (ie, exposure is affected by disease) in observational studies may result in biased findings. A Mendelian randomization (MR) study is one of the effective alternative methods. Mendelian Randomization is a groundbreaking and reliable analytical technique that employs genetic variations as instrumental variables (IVs) to explore the causal links between exposures and outcomes. By exploiting genetic variations that occur naturally and are unaffected by confounding factors, MR analysis addresses the constraints of traditional observational research, such as confounding and reverse causation, thus providing more robust evidence for causal inference.¹⁶ With the emergence of large-scale genome-wide association studies (GWAS) and the release of extensive genetic variation data, MR study has rapidly advanced in the era of GWAS.¹⁷ This investigation utilized the most recent extensive summaries from large-scale GWAS for MR analysis, aiming to uncover the possible causal links between microbiota (gut and skin) and COPD. This research provides valuable perspectives on the diagnosis and prevention of COPD.

Materials and Methods

Study Design

Based on GWAS summary statistics, a two-sample Mendelian randomization (2SMR) analysis was conducted to investigate the associations between gut and skin microbiota and COPD. The overall study details were illustrated in [Figure 1](#). To obtain robust results, two-sample MR analysis must satisfy three core assumptions: strong relevance, independence, and the exclusion restriction assumption.¹⁸ The IVs used for two-sample MR analysis must also satisfy these three core assumptions. Additionally, reverse 2SMR analysis was conducted to rule out reverse causation that could affect causal inference, as illustrated in [Figure 1](#). Our study report followed the STROBE-MR guidelines.¹⁹

Data Sources for the Exposure

Genetic variations of gut microbiota were sourced from a large-scale GWAS study led by the Cambridge University-Baker Systems Genomics Initiative. This study included 5,959 European individuals from the FINRISK population

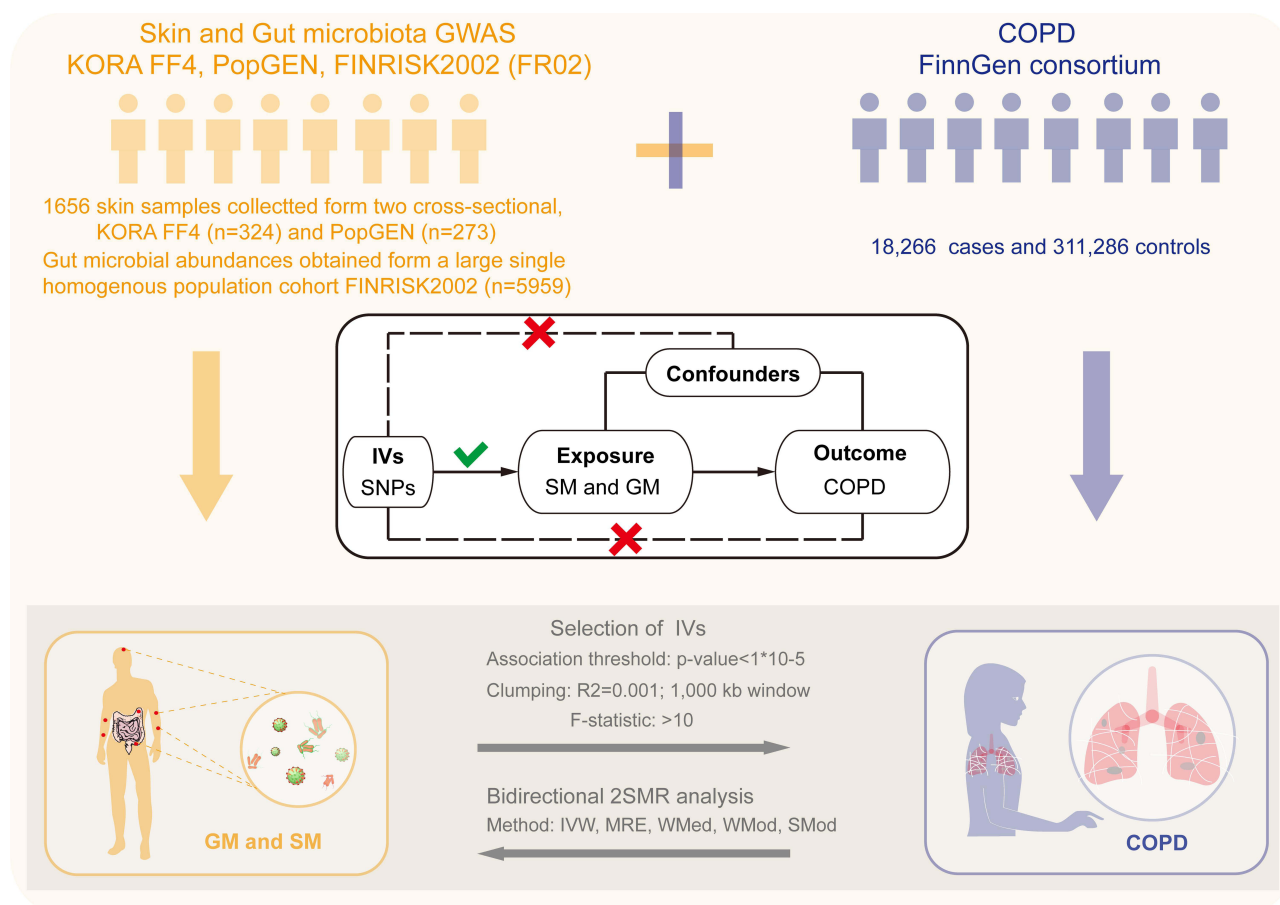


Figure 1 The study design and overall workflow of MR analysis. MR analysis include 3 assumptions. Relevance hypothesis: IVs are robustly related to exposure; Independence hypothesis: IVs are not related to known or unknown confounders; Exclusionary hypothesis: IVs influenced outcome only through exposure.

Abbreviation: IVs, instrumental variables; SM, Skin microbiota; GM, Gut microbiota; SNPs, single-nucleotide polymorphisms; IVW, inverse variance weighted; MRE, MR-Egger; WMed, weighted median; WMod, weighted mode; SMod, simple mode; MR, Mendelian randomization; 2SMR, two-sample Mendelian randomization.

cohort mapping the microbial composition of a total of 2,801 microbial taxa. Detailed clinical characteristics of all participants can be found in a previous study.²⁰

We obtained genetic variants of skin microbiota from 1,656 skin samples of participants in two population-based cross-sectional German cohorts: KORA FF4 (n = 324) and PopGEN (n = 273). Detailed clinical characteristics of all participants were available in previous studies.^{21,22} This extensive study outlined the microbial composition of 79 microbial taxa from phylum to genus level.

Data Sources for the Outcome

The GWAS data for COPD were obtained from the latest FinnGen consortium R9 version (<https://r9.finnngen.fi/>).²³ The GWAS dataset comprised 18,266 COPD cases and 311,286 controls, derived from a prospective cohort study of the European population. The detailed information on the exposures and outcomes used in the 2SMR analysis, was listed in Table 1.

Selection of Instrumental Variables

The selection of optimal instrumental variables (IVs) was conducted in accordance with stringent screening protocols to guarantee the reliability and precision of our results. In summary, the GWAS statistics pertaining to gut and skin microbiota were meticulously examined, and single nucleotide polymorphisms (SNPs) were chosen based on a significance level of $P < 1 \times 10^{-5}$. Following the independence assumption of MR, a coefficient R^2 of 0.001 and clump distance of 10,000 kb maximized their efforts to avoid any potential linkage disequilibrium IVs. Additionally, palindromic SNPs were excluded from consideration

Table 1 Details of the Exposure and Outcome

Trait	Consortium	Samples	Case	Control
Exposure				
Gut microbiota	FR02	5,959	/	/
Skin microbiota	KORA FF4 and PopGen cohorts	1,656	/	/
Outcome				
COPD	FinnGen (R9)	329, 552	18,266	311,286

to ensure that alleles for each SNP were consistent across both the gut and skin microbiota groups as well as the COPD group. All instrumental variables underwent filtration based on F-statistics calculations to mitigate bias stemming from weak instruments, ensuring that the F-statistic for each chosen instrument surpassed the minimum threshold of 10. The process of selecting IVs was depicted in [Figure 1](#).

MR Analyses

The principal method employed for causal inference in this investigation was the inverse variance weighted (IVW) approach, which integrates the ratio estimates from each genetic instrument within a meta-analysis framework.²⁴ To further substantiate the reliability of our results, we utilized several supplementary analytical techniques, including MR-Egger, weighted median, simple mode, weighted mode, and MR-PRESSO. MR-Egger helps identify potential violations of MR assumptions, such as horizontal pleiotropy, and yields effect estimates that remain robust in the presence of such violations.²⁵ The weighted median method aggregates the ratio estimates from genetic instruments via a median-based method, offering reliable estimates even when as many as 50% of the instruments may be invalid. Both the simple mode and weighted mode methods concentrate on evaluating the majority or the weighted majority of genetic instrument estimates, respectively, to assess the direction and intensity of the causal relationship.²⁴ The MR-PRESSO method was employed to identify and exclude outliers that contribute to heterogeneity, using a simulation-based approach.²⁶ By integrating these additional methods, we are able to assess the consistency of our findings and attain a more nuanced comprehension of the causal associations, while accounting for potential violations of MR assumptions. Additionally, a reverse causality analysis was performed to explore any reverse causal links. All statistical analyses were conducted using R version 4.1.3.

Sensitivity Analyses

To assess the robustness of our primary causal estimates, we conducted several sensitivity analyses. Cochran’s Q statistic was applied using both the IVW and MR-Egger methods to evaluate the heterogeneity of effects. Furthermore, the MR-Egger intercept and MR-PRESSO were utilized to investigate the existence of horizontal pleiotropy. Any results showing pleiotropy at a significance level of $p < 0.05$ were excluded from the analysis.^{25,26} Moreover, a leave-one-out analysis was performed to detect outliers and evaluate the stability of the results. These sensitivity tests were essential for establishing the reliability and robustness of our findings.

Results

Gut Microbiota

The results of MR analysis showed that 13 gut microbiotas were causally associated with COPD, excluded 1 microbiota (*Halomonadaceae*) to be reverse causality, and 13 unnamed gut microbiotas. IVW test estimates showed that species *Bacteroides faecis* (OR: 1.12), species *Copro bacter secundus* (OR: 1.16), species *Faecalicatena glycyrrhizinilyticum* (OR: 1.19), all of which belong to the order *Bacteroidales*, were negatively associated with COPD (all $p < 0.05$). Additionally, the family *Francisellaceae* (OR: 1.56), order *Francisellales* (OR: 1.53),family *Thioalkalivibrionaceae* (OR: 1.53), genus *Collinsella* (OR: 1.08), and three other genera revealed a causal association with increased risk of COPD (all $p < 0.05$). Moreover, the genus *Bacillus* (OR: 0.62), genus *Citrobacter* (OR: 0.84) and genus *Magnetospirillum* (OR: 0.67) were positively associated with COPD (all $p < 0.05$) ([Figure 2](#)). MR-Egger, simple mode, weighted median, and weighted mode were employed to evaluate the causality

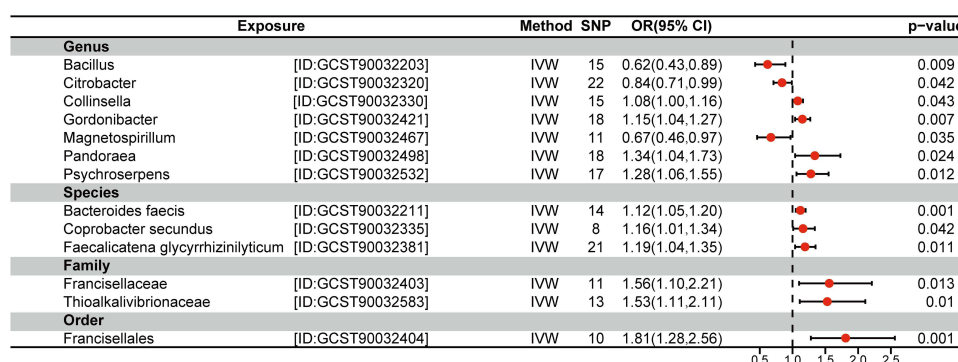


Figure 2 Forest plot of the causality between GM taxa with the risk of COPD. The horizontal bars correspond to the estimated OR with 95% CI using the IVW method for GM on COPD.

Abbreviation: GM, Gut microbiota; IVW, inverse variance weighted; SNP, single-nucleotide polymorphisms; OR, odds ratio; CI, confidence interval; COPD, Chronic Obstructive Pulmonary Disease.

of these gut microbiotas on COPD. As anticipated, the outcomes estimated by these methods were consistent with the IVW results (Figure 3, [Supplementary Table 1](#)).

Skin Microbiota

MR analysis results demonstrated a causal association between 10 identified skin microbiotas and COPD, excluding 14 unnamed skin microbiotas. The IVW test results indicated that the class *gammaproteobacteria* (OR: 1.02), genus *Corynebacterium* (OR: 1.03), genus *Acinetobacter* (OR: 1.02) and order *actinomycetales* (OR: 1.02) were negatively associated with COPD (all $p < 0.05$), while the genus *micrococcus* (OR: 0.98) and genus *kocuria* (OR: 0.98), all of which belong to the order Actinomycetales, were positively associated with COPD (all $p < 0.05$). Meanwhile, the protective effects of order *burkholderiales* (OR: 0.97) and two other genera against COPD were detected (all $p < 0.05$) (Figure 4). MR-Egger, simple mode, weighted median, and weighted mode were also used to access the causality of these skin microbiota on COPD, and the outcomes from these methods closely mirrored the IVW results (Figure 5, [Supplementary Table 2](#)).

Validation Analysis

As shown in Figures 6–7, and [Supplementary Table 3](#), the results of Cochran's Q-test suggested the absence of heterogeneity ($p > 0.05$). In addition, MR-Egger, weighted median and MR-PRESSO tests for selected IVs did not have horizontal pleiotropy. MR-PRESSO test could not be performed due to insufficient SNPs in Bacillales (ID: GCST90133196), we utilized other methods to demonstrate the absence of horizontal pleiotropy.

Reverse 2SMR Analysis

We also conducted reverse MR analysis between COPD and identified gut and skin microbiota. No significant reverse causal estimates were observed, indicating the absence of causal relationship of COPD on the identified gut and skin microbiota ([Supplementary Tables 4 & 5](#)).

Discussion

Currently, comorbidities and medication side effects challenge the treatment of COPD. It is crucial to better understand the mechanisms behind COPD and develop corresponding diagnostic and therapeutic strategies. Based on comprehensive genetic data, we found genetic liability to 13 gut and 10 skin microbiota species is causally associated with COPD. These results could have implications for public health interventions aimed at reducing COPD risk.

Our study indicates that *Bacillus* in the gut microbiota and *Bacillales* in the skin microbiota serve as protective factors against COPD. This finding is consistent with recent research.²⁷ Most of the species of the genus *Bacillus* are Gram-positive, aerobic endospore-forming and rod-shaped bacteria, which are found in diverse environments and in the gastrointestinal tracts of various insects and animals. Studies have shown that *Bacillus* is able to influence the diversity

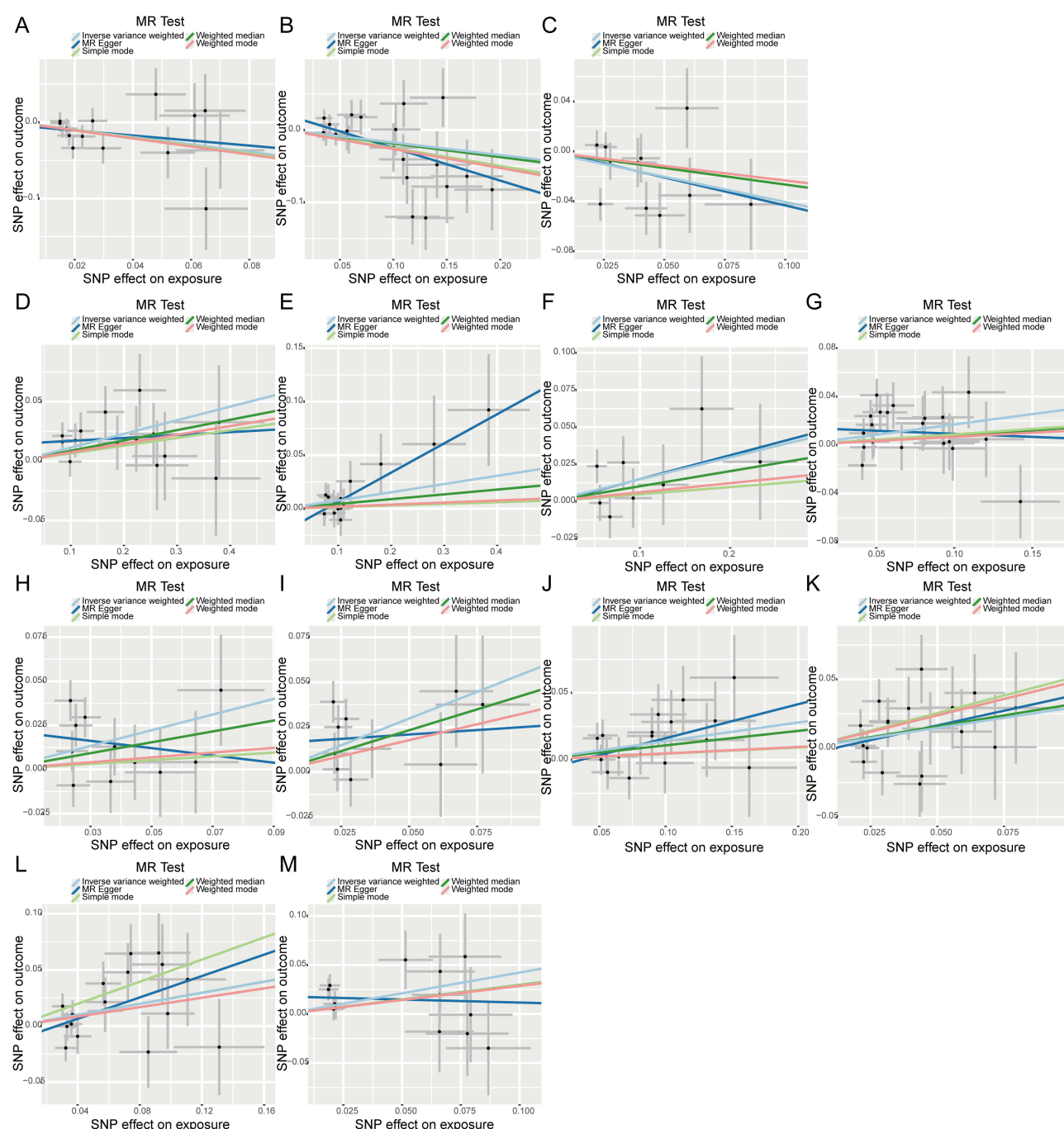


Figure 3 Scatter plots for MR analysis of GM on COPD for exploring causal effects. (A). *Bacillus*; (B). *Citrobacter*; (C). *Magnetospirillum*; (D). *Bacteroides faecis*; (E). *Collinsella*; (F). *Coprobacter secundus*; (G). *Faecalicatena glycyrrhizynilyticum*; (H). *Francisellaceae*; (I). *Francisellales*; (J). *Gordonibacter*; (K). *Pandoraea*; (L). *Psychroserpens*; (M). *Thioalkalivibrionaceae*. Each line's slope represents the causal estimates for the respective method, while the background illustrates the effect of each individual SNP on the outcome (vertical line) and its effect on the exposure (horizontal line).

Abbreviation: GM, Gut microbiota; SNPs, single-nucleotide polymorphisms; MR, Mendelian randomization; COPD, Chronic Obstructive Pulmonary Disease.

and stability of the respiratory microbiome through its antimicrobial properties and immunomodulatory effects. For example, strains such as *Bacillus subtilis* and *Bacillus amyloliquefaciens* have been found to have the ability to inhibit airborne pathogens, thus potentially reducing the risk of respiratory infections.²⁸ In addition, metabolites of *Bacillus* such as 2,3-butanediol and propylene glycol, which inhibit bacterial growth and promote a healthy microbiome balance, have also been implicated as key factors in its antimicrobial activity.²⁹ At the same time, studies have shown that *Bacillus* are capable of producing short-chain fatty acids (SCFAs),^{30,31} which are essential for maintaining health and modulating

	Exposure	Method	SNP	OR(95% CI)	p-value
Class					
gammaproteobacteria	[ID:GCST90133198]	IVW	7	1.02(1.00,1.05)	0.048
Genus					
corynebacterium	[ID:GCST90133202]	IVW	6	1.03(1.00,1.06)	0.037
haemophilus	[ID:GCST90133219]	IVW	11	0.98(0.97,0.99)	0.02
micrococcus	[ID:GCST90133232]	IVW	6	0.98(0.96,0.99)	0.042
acinetobacter	[ID:GCST90133237]	IVW	9	1.02(1.00,1.04)	0.028
kocuria	[ID:GCST90133241]	IVW	7	0.98(0.97,0.99)	0.038
streptococcus	[ID:GCST90133309]	IVW	6	0.98(0.96,0.99)	0.049
Order					
actinomycetales	[ID:GCST90133222]	IVW	12	1.02(1.00,1.04)	0.025
burkholderiales	[ID:GCST90133294]	IVW	8	0.97(0.95,0.99)	0.011
bacillales	[ID:GCST90133196]	IVW	3	0.97(0.94,0.99)	0.024

Figure 4 Forest plot of the causality between SM taxa with the risk of COPD. The horizontal bars correspond to the estimated OR with 95% CI using the IVW method for SM on COPD.

Abbreviation: SM, Skin microbiota; IVW, inverse variance weighted; SNP, single-nucleotide polymorphisms; OR, odds ratio; CI, confidence interval; COPD, Chronic Obstructive Pulmonary Disease.

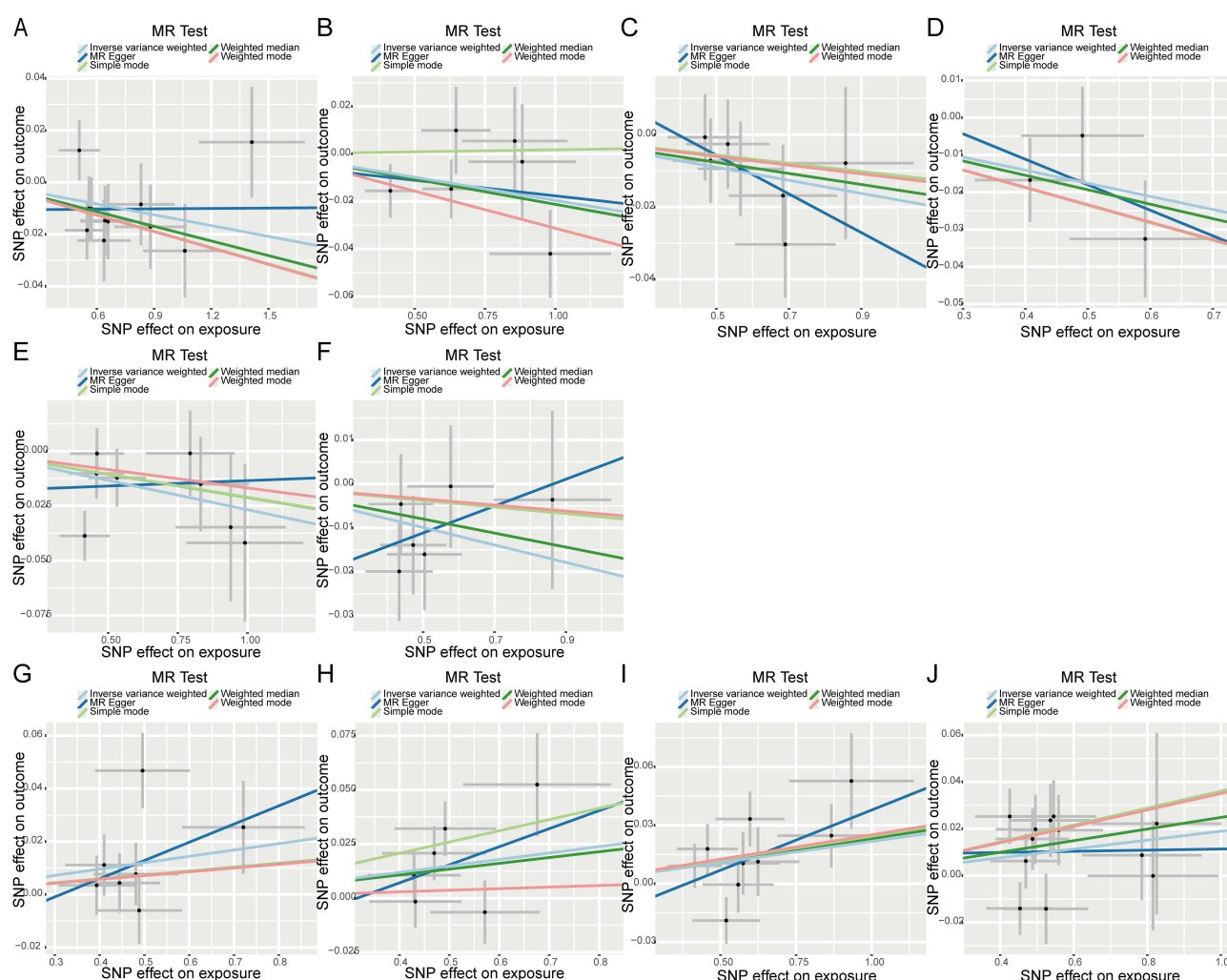


Figure 5 Scatter plots for MR analysis of SM on COPD for exploring causal effects. (A). Haemophilus; (B). Micrococcus; (C). Kocuria; (D). Bacillales; (E). Burkholderiales; (F). Streptococcus; (G). Gammaproteobacteria; (H). Corynebacterium; (I). Acinetobacter; (J). Actinomycetales. Each line's slope represents the causal estimates for the respective method, while the background illustrates the effect of each individual SNP on the outcome (vertical line) and its effect on the exposure (horizontal line).

Abbreviation: SM, Skin microbiota; SNPs, single-nucleotide polymorphisms; MR, Mendelian randomization; COPD, Chronic Obstructive Pulmonary Disease.

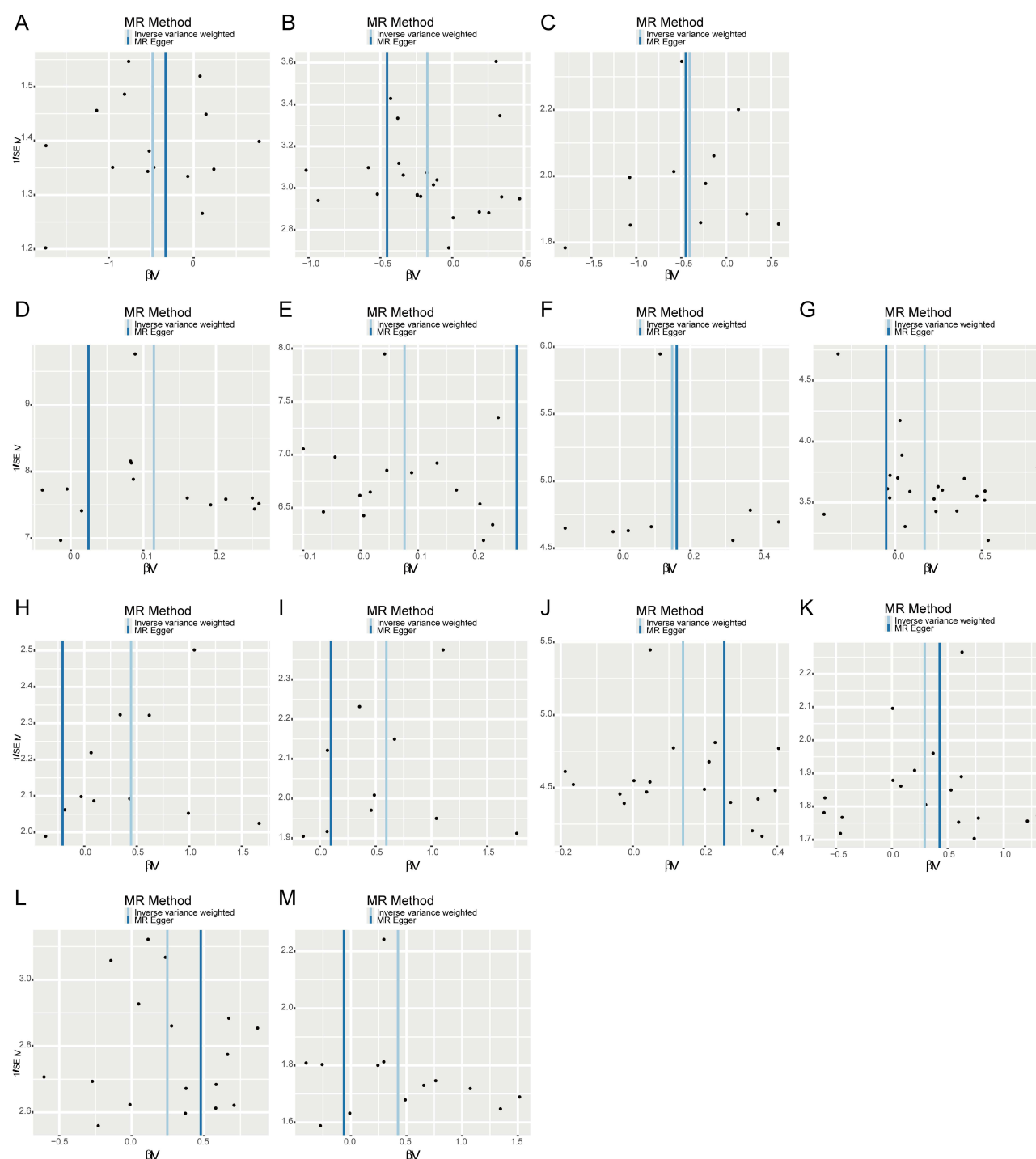


Figure 6 Funnel plots for MR analysis of GM on COPD for exploring casual effects. (A). *Bacillus*; (B). *Citrobacter*; (C). *Magnetospirillum*; (D). *Bacteroides faecis*; (E). *Collinsella*; (F). *Coprobacter secundus*; (G). *Faecalitena glycyrrhizinilyticum*; (H). *Francisellaceae*; (I). *Francisellales*; (J). *Gordonibacter*; (K). *Pandoraea*; (L). *Psychroserpens*; (M). *Thioalkalivibrionaceae*.

Abbreviation: GM, Gut microbiota; MR, Mendelian randomization; COPD, Chronic Obstructive Pulmonary Disease.

immune and inflammatory reactions.³² Research indicates that dietary supplementation with *Bacillus subtilis*, especially *Bacillus licheniformis*, elevates various SCFAs in cecal contents, particularly *butyrate*, which is recognized for its protective anti-inflammatory and anti-cancer effects.^{33,34} Butyrate has broad effects on immune cells in lung diseases such as allergic asthma, COPD, and pulmonary fibrosis,³⁵ this may correlated with the mechanism of activation of

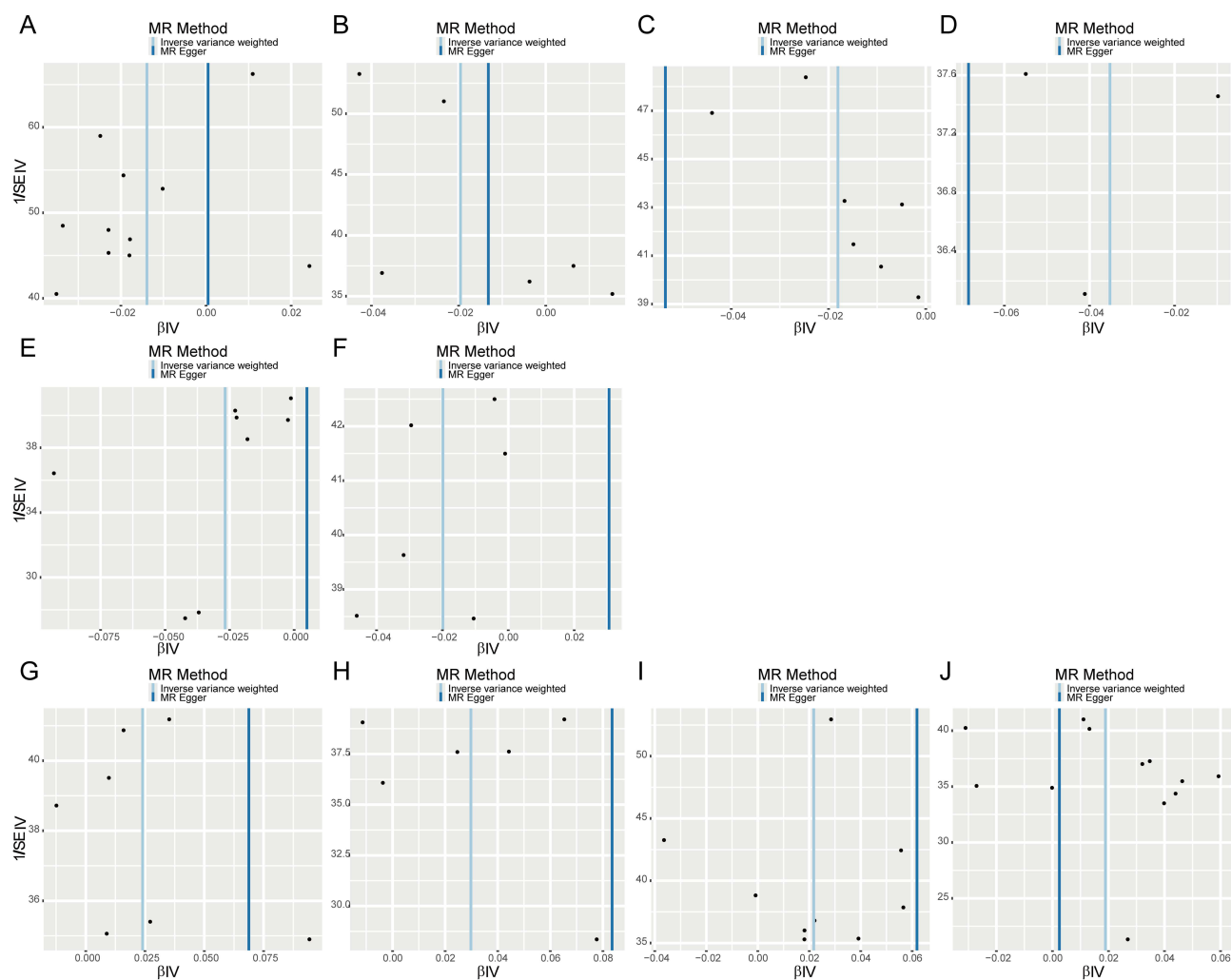


Figure 7 Funnel plots for MR analysis of SM on COPD for exploring casual effects. (A). Haemophilus; (B). Micrococcus; (C). Kocuria; (D). Bacillales; (E). Burkholderiales; (F). Streptococcus; (G). Gammaproteobacteria; (H). Corynebacterium; (I). Acinetobacter; (J). Actinomycetales.

Abbreviation: SM, Skin microbiota; MR, Mendelian randomization; COPD, Chronic Obstructive Pulmonary Disease.

PPAR γ , and promotes epithelial barrier integrity to improve the anti-inflammation effects.³⁶ Members of the order *Bacillales*, especially genus *Bacillus* are well known as probiotic organisms, however, it is important to note that they may affect host health by producing toxins or other pathogenic factors under specific environmental conditions.³⁷ Therefore, further research on the pathogenicity under specific conditions is necessary for the development of new therapeutics.

Our MR results also indicate that *Micrococcus* and *Kocuria* in the skin microbiota (SM) were protective factors against COPD, while *Corynebacterium* in the SM was a risk factor for COPD. These microbial groups all belong to the order *Actinomycetales*, which belong to *Actinobacteria*. Studies have shown that the airway microbiome undergoes significant changes during acute exacerbations of COPD, particularly in the case of bacterial infections, where the abundance of Actinomycetales bacteria may increase.³⁸ Generally, the clinical presentation and disease progression in COPD patients are closely related to infections, with potential mechanisms involving changes in bacterial diversity and abundance, which can lead to inflammation and a decline in lung function.³⁹ Studies showed that the abundance of *Corynebacterium* is significantly increased in the nasal and oral cavity of COPD subjects.^{40,41} The pathogenic mechanisms of *Corynebacterium* are complex. Studies have found that *Corynebacterium* can evade host immune surveillance through various mechanisms, including inhibiting macrophage maturation and inducing cell death. Additionally, this may also be related to the ability of certain *Corynebacterium* species to survive within host cells, enhancing their pathogenicity.^{42,43} Notably, an investigation employing

the neutral theory of community ecology indicated that the lung tissue microbiota closely mirrors that found in the bronchial, oral, and nasal regions, as evidenced by immigration parameter estimates of 0.69, 0.62, and 0.74, respectively,⁴⁰ with some evidence of ecologic drift occurring in the lung tissue, this is in line with the view that the upper respiratory tract microbiome might predict the lung tissue microbiome⁴⁰ both suggesting the significant impact of the skin microbiota on lung diseases. *Micrococcus* and *Kocuria* are common taxa in the human skin microbiota. Recent studies have found that *Micrococcus* and *Kocuria* are closely related to the immune function of the body.^{44–46} The immune system of COPD patients typically exhibits a chronic inflammatory state, such as impaired Treg cell function, which leads to a reduced tolerance to self-antigens and exacerbates the inflammatory response in lung tissue.⁴⁷ Furthermore, immune cell infiltration, such as the proportion of CD8+ T cells, M2 macrophages, and monocytes, varies at different stages of COPD, contributing to different immune regulatory functions,⁴⁸ the specific mechanisms underlying these interactions require further investigation.

Bacteroidales is an important bacterial order that includes several genera, belonging to *Firmicutes* and *Proteobacteria*. Previous studies have shown that *Bacteroidales* can break down complex polysaccharides and cellulose, releasing various SCFAs, which play a significant role in the host's immune regulation and energy metabolism.^{49,50} It is important to note that the impact of gut microbiota on the host's immune system suggests that gut microbiota may participate in the pathogenesis of COPD by influencing systemic inflammatory responses. Our MR results indicate that *Bacteroides*, *Faecalibacterium*, and *Coprobacter* in the gut microbiota are risk factors for COPD. These microbial groups belong to the order *Bacteroidales*. This may be related to the activation of immune responses and inflammatory infiltration by *Bacteroidales*. It has been reported that the proportion of *Bacteroides* in COPD has significantly changed.^{26,38} *Bacteroides* plays a dual role in modulating inflammatory responses. On one hand, *Bacteroides* can regulate the gut barrier through its metabolites such as SCFAs, thereby influencing the onset of systemic inflammation.⁵¹ On the other hand, certain *Bacteroides* strains may promote inflammatory responses under specific conditions. *Bacteroides fragilis* has been reported to disrupt the gut barrier, triggering systemic inflammation and promoting the development of COPD.⁵² Similarly, *Faecalibacterium* and *Coprobacter* can also influence the occurrence of inflammation and regulate disease progression by modulating SCFAs and the gut mucosal barrier.^{53–55} This suggests that maintaining gut health and preventing systemic inflammation play a critical role in the prevention and management of COPD.

Our MR results found that *Citrobacter* in the gut microbiota and *Burkholderiales* in the skin microbiota were protective factors against COPD. Conversely, *Pandoraea*, *Francisellaceae*, *Halothiobacillaceae*, and *Francisellales* in the GM, and *Acinetobacter* in the SM, were risk factors for COPD. Previous studies on the sputum microbiome of COPD patients have shown that COPD is characterized by an increased proportion of γ -*Proteobacteria*.⁵⁶ *Acinetobacter* has also been found to have increased abundance in the lung microbiome of COPD patients, particularly in those with worsening conditions.⁵⁷ The abundance of *Acinetobacter* in the airways may also be a prognostic marker for severe COPD patients.⁵⁸ This also suggests that changes in the proportions of the flora may have different effects on their function.

Although gut microbiota has been widely studied in COPD research, there is limited research on the association between skin microbiota and COPD. This study focused on skin microbiota rather than solely on gut microbiota for several key reasons. Firstly, sampling skin microbiota is more convenient. Skin microbiota can be sampled using non-invasive methods, which are simpler and less invasive compared to methods like endoscopic examination or fecal sampling. This improves the feasibility of research and facilitates the expansion of sample sizes. Secondly, skin microbiota is directly exposed to the external environment, and its composition and abundance can be significantly influenced by environmental factors. Since the pathogenesis of COPD is closely related to environmental factors such as air pollution and smoking, studying skin microbiota can help reveal how these factors influence the development and progression of COPD through microbial changes. This may provide new perspectives on the mechanisms of these environmental factors and potentially identify environmental drivers related to COPD. Furthermore, by studying skin microbiota in depth, we may develop new diagnostic markers or therapeutic targets, providing new strategies for the prevention and management of COPD. For example, modulating skin microbiota may help improve systemic inflammatory states, thereby indirectly influencing the progression of COPD. Lastly, studying skin microbiota may reveal the potential for early intervention. As the first line of defense against the external environment, understanding how early microbial imbalances in the skin relate to the pathogenesis of COPD could help us prevent COPD, especially in high-risk populations.

It is important to recognize the limitations of our study. Firstly, this study predominantly relied on data from European populations, which may limit the generalizability of our findings to other ethnic groups, regions, or nations. Genetic differences across ethnicities, as well as variations in environmental exposures, lifestyle, and diet, could influence the composition of gut and skin microbiota. These factors may result in different microbiota profiles and, consequently, distinct relationships with COPD in non-European populations. This constraint highlights the importance of incorporating varied populations in future research to achieve a more thorough insight into the connection between microbiota (gut and skin) and COPD. Second, the sample size from the skin microbiota is modest, and the number of loci examined is relatively restricted, which could introduce bias or reduce the statistical power of the analysis. Consequently, it is essential to conduct additional investigations to validate our results through the utilization of larger GWAS datasets. Third, the lack of individual-level data restricted our assessment to summary statistics alone. The dataset employed in our research does not encompass stratification by age, gender or severity of COPD. Future studies should aim to utilize more precisely segmented datasets for population stratification analyses, thereby enabling the derivation of more accurate conclusions. Lastly, given that this investigation was methodology-focused, there is a pressing need for broader longitudinal cohort studies and prolonged follow-up assessments to thoroughly explore the potential roles of gut and skin microbiota in the prevention and management of COPD.

Based on our findings, the genetic susceptibility to specific gut and skin microbiota is causally linked to COPD risk, potentially providing novel biomarkers for early diagnosis. These microbial changes may serve as screening tools, particularly for high-risk populations. Future research could explore the clinical application of these microbiota, such as using non-invasive methods like stool samples or skin swabs for early screening. Additionally, the regulation of specific microbiota may offer new therapeutic targets for COPD. For instance, the protective role of *Bacillus* in the gut suggests that modulating the gut microbiome via probiotics or dietary interventions could help alleviate chronic inflammation and slow disease progression. Similarly, regulating the skin microbiota may offer a therapeutic approach, especially in addressing systemic inflammation. Although this study is primarily based on genetic data, it suggests that integrating microbiome and clinical data could enable personalized COPD management in the future. Personalized microbiome interventions, such as probiotics, prebiotics, or immune modulation therapies, could be developed for patients. This approach has the potential to revolutionize clinical COPD management.

Conclusion

In conclusion, we systematically evaluated the potential relationships between gut microbiota, skin microbiota, and COPD. This provides us with additional perspectives and potential research value. Through this study, we aimed to reveal the roles of gut and skin microbiota in COPD and explored their potential applications in disease prevention, diagnosis and treatment.

Abbreviations

COPD, Chronic Obstructive Pulmonary Disease; MR, Mendelian randomization; OR, odds ratio; IVs, instrumental variables; GWAS, Genome-wide association study; SNPs, single nucleotide polymorphisms; 2SMR, Two-sample Mendelian randomization; CIs, confidence intervals; SD, standard deviation; IVW, inverse-variance weighted; MR-PRESSO, MR pleiotropy residual sum and outlier; BAL, bronchoalveolar lavage; SCFAs, short-chain fatty acids.

Data Sharing Statement

The original contributions presented in the study are included in the manuscript/[Supplementary materials](#), further inquiries can be directed to the corresponding authors.

Ethical Approval

Relevant data from the GWAS database and summary statistics for the studies used for analysis were collected from published studies. All studies have received prior approval from their institutional review boards (IRBs).

The Ethics Committee of Shenzhen Hospital of Integrated Traditional Chinese and Western Medicine approved the protocol for this study, and as per their guidelines, this study exclusively utilized publicly available data without using any individual-level data. Therefore, no additional IRB approval was necessary.

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.

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Disclosure

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References

- Huang X, Guan W, Xiang B, Wang W, Xie Y, Zheng J. MUC5B regulates goblet cell differentiation and reduces inflammation in a murine COPD model. *Respir Res.* 2022;23(1):11. doi:10.1186/s12931-021-01920-8
- Alqahtani JS, Aquilina J, Bafadhel M, et al. Research priorities for exacerbations of COPD. *Lancet Respir Med.* 2021;9(8):824–826. doi:10.1016/S2213-2600(21)00227-7
- Halpin DMG, Criner GJ, Papi A, et al. Global initiative for the diagnosis, management, and prevention of chronic obstructive lung disease. the 2020 GOLD science committee report on COVID-19 and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2021;203(1):24–36. doi:10.1164/rccm.202009-3533SO
- Stolz D, Mkorombindo T, Schumann DM, et al. Towards the elimination of chronic obstructive pulmonary disease: a Lancet Commission. *Lancet.* 2022;400(10356):921–972. doi:10.1016/S0140-6736(22)01273-9
- Martinez FJ, Agusti A, Celli BR, et al. Treatment trials in young patients with chronic obstructive pulmonary disease and pre-chronic obstructive pulmonary disease patients: time to move forward. *Am J Respir Crit Care Med.* 2022;205(3):275–287. doi:10.1164/rccm.202107-1663SO
- Budden KF, Gellatly SL, Wood DL, et al. Emerging pathogenic links between microbiota and the gut-lung axis. *Nat Rev Microbiol.* 2017;15(1):55–63. doi:10.1038/nrmicro.2016.142
- Wypych TP, Wickramasinghe LC, Marsland BJ. The influence of the microbiome on respiratory health. *Nat Immunol.* 2019;20(10):1279–1290. doi:10.1038/s41590-019-0451-9
- Lai HC, Lin TL, Chen TW, et al. Gut microbiota modulates COPD pathogenesis: role of anti-inflammatory Parabacteroides goldsteinii lipopolysaccharide. *Gut.* 2022;71(2):309–321. doi:10.1136/gutjnl-2020-322599
- Li N, Dai Z, Wang Z, et al. Gut microbiota dysbiosis contributes to the development of chronic obstructive pulmonary disease. *Respir Res.* 2021;22(1):274. doi:10.1186/s12931-021-01872-z
- Song J, Wu Y, Yin X, Ma H, Zhang J. The causal links between gut microbiota and COVID-19: a Mendelian randomization study. *J Med Virol.* 2023;95(5):e28784. doi:10.1002/jmv.28784
- 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
- Cheng ZX, Hua JL, Jie ZJ, Li XJ, Zhang J. Genetic insights into the gut-lung axis: mendelian randomization analysis on gut microbiota, lung function, and COPD. *Int J Chronic Obstr.* 2024;19:643–653. doi:10.2147/COPD.S441242
- Harris VC, Haak BW, Boele van Hensbroek M, Wiersinga WJ. The intestinal microbiome in infectious diseases: the clinical relevance of a rapidly emerging field. *Open Forum Infect Dis.* 2017;4(3):ofx144. doi:10.1093/ofid/ofx144

14. Gribonika I, Band C VI, L P-CPJ, et al. Skin autonomous antibody production regulates host-microbiota interactions. *Nature*. 2024.
15. Ubags ND, Trompette A, Pernot J, et al. Microbiome-induced antigen-presenting cell recruitment coordinates skin and lung allergic inflammation. *J Allergy Clin Immunol*. 2021;147(3):1049–1062.e1047. doi:10.1016/j.jaci.2020.06.030
16. Holmes MV, Ala-Korpela M, Smith GD. Mendelian randomization in cardiometabolic disease: challenges in evaluating causality. *Nat Rev Cardiol*. 2017;14(10):577–590. doi:10.1038/nrcardio.2017.78
17. Pang L, Ding Z, Chai H, Shuang W. The causal relationship between immune cells and different kidney diseases: a Mendelian randomization study. *Open Med*. 2023;18(1):20230877. doi:10.1515/med-2023-0877
18. Lawlor DA. Commentary: two-sample Mendelian randomization: opportunities and challenges. *Int J Epidemiol*. 2016;45(3):908–915. doi:10.1093/ije/dyw127
19. Skrivankova VW, Richmond RC, Woolf BAR, et al. Strengthening the reporting of observational studies in epidemiology using Mendelian randomization: the STROBE-MR statement. *JAMA*. 2021;326(16):1614–1621. doi:10.1001/jama.2021.18236
20. Qin Y, Havulinna AS, Liu Y, et al. Combined effects of host genetics and diet on human gut microbiota and incident disease in a single population cohort. *Nature Genet*. 2022;54(2):134–142. doi:10.1038/s41588-021-00991-z
21. Holle R, Happich M, Löwel H, Wichmann HE. KORA—a research platform for population based health research. *Gesundheitswesen*. 2005;67(Suppl 1):S19–25. doi:10.1055/s-2005-858235
22. Nöthlings U, Krawczak M. [PopGen. A population-based biobank with prospective follow-up of a control group]. *Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz*. 2012;55(6–7):831–835. doi:10.1007/s00103-012-1487-2.
23. Rokadia HK, Agarwal S. Serum cystatin C and emphysema: results from the national health and nutrition examination survey (NHANES). *Lung*. 2012;190(3):283–290. doi:10.1007/s00408-012-9374-z
24. Bowden J, Holmes MV. Meta-analysis and Mendelian randomization: a review. *Res Synthesis Methods*. 2019;10(4):486–496. doi:10.1002/jrsm.1346
25. 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(2):512–525. doi:10.1093/ije/dyv080
26. Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nature Genet*. 2018;50(5):693–698. doi:10.1038/s41588-018-0099-7
27. Shi H, Zhao T, Geng R, Sun L, Fan H. The associations between gut microbiota and chronic respiratory diseases: a Mendelian randomization study. *Front Microbiol*. 2023;14:1200937. doi:10.3389/fmicb.2023.1200937
28. Kim HS, Arellano K, Park H, et al. Assessment of the safety and anti-inflammatory effects of three Bacillus strains in the respiratory tract. *Environ Microbiol*. 2021;23(6):3077–3098. doi:10.1111/1462-2920.15530
29. Angulo M, Guerra K, Arevalo P, Trujillo E, Monreal-Escalante E, Angulo C. Probiotic potential of bacillus sp. 62A isolated from a marine extreme environment. *Probiotics Antimicrob Proteins*. 2023. doi:10.1007/s12602-023-10182-3
30. Reyes-Cortes JL, Azaola-Espinosa A, Lozano-Aguirre L, Ponce-Alquicira E. Physiological and genomic analysis of bacillus pumilus UAMX isolated from the gastrointestinal tract of overweight individuals. *Microorganisms*. 2021;9(5):1076. doi:10.3390/microorganisms9051076
31. Murugesan GR, Romero LF, Persia ME. Effects of protease, phytase and a Bacillus sp. direct-fed microbial on nutrient and energy digestibility, ileal brush border digestive enzyme activity and cecal short-chain fatty acid concentration in broiler chickens. *PLoS One*. 2014;9(7):e101888. doi:10.1371/journal.pone.0101888
32. van der Hee B, Wells JM. Microbial regulation of host physiology by short-chain fatty acids. *Trends Microbiol*. 2021;29(8):700–712. doi:10.1016/j.tim.2021.02.001
33. Xu Y, Yu Y, Shen Y, et al. Effects of Bacillus subtilis and Bacillus licheniformis on growth performance, immunity, short chain fatty acid production, antioxidant capacity, and cecal microflora in broilers. *Poult Sci*. 2021;100(9):101358. doi:10.1016/j.psj.2021.101358
34. Musa BB, Duan Y, Khawar H, et al. Bacillus subtilis B21 and Bacillus licheniformis B26 improve intestinal health and performance of broiler chickens with Clostridium perfringens-induced necrotic enteritis. *J Animal Physiol Animal Nutr*. 2019;103(4):1039–1049. doi:10.1111/jpn.13082
35. Yip W, Hughes MR, Li Y, et al. Butyrate shapes immune cell fate and function in allergic asthma. *Front Immunol*. 2021;12:628453. doi:10.3389/fimmu.2021.628453
36. Kinoshita M, Suzuki Y, Saito Y. Butyrate reduces colonic paracellular permeability by enhancing PPARgamma activation. *Biochem Biophys Res Commun*. 2002;293(2):827–831.
37. Chattopadhyay S, Ramachandran P, Malayil L, Mongodin EF, Sapkota AR. Conventional tobacco products harbor unique and heterogenous microbiomes. *Environ Res*. 2023;220:115205. doi:10.1016/j.envres.2022.115205
38. Yang J, Zhang Q, Zhang J, et al. Exploring the change of host and microorganism in chronic obstructive pulmonary disease patients based on metagenomic and metatranscriptomic sequencing. *Front Microbiol*. 2022;13:818281. doi:10.3389/fmicb.2022.818281
39. Shpagina LA, Kotova OS, Shpagin IS, et al. Clinic and functional features of chronic obstructive pulmonary disease after virus-induced acute exacerbations. *Terapevticheskii arkhiv*. 2023;95(3):217–222. doi:10.26442/00403660.2023.03.202086
40. Pragman AA, Lyu T, Baller JA, et al. The lung tissue microbiota of mild and moderate chronic obstructive pulmonary disease. *Microbiome*. 2018;6(1):7. doi:10.1186/s40168-017-0381-4
41. Agarwal DM, Dhotre DP, Kumbhare SV, et al. Disruptions in oral and nasal microbiota in biomass and tobacco smoke associated chronic obstructive pulmonary disease. *Arch Microbiol*. 2021;203(5):2087–2099. doi:10.1007/s00203-020-02155-9
42. Altonsy MO, Kurwa HA, Lauzon GJ, et al. Corynebacterium tuberculoearicum, a human skin colonizer, induces the canonical nuclear factor-κB inflammatory signaling pathway in human skin cells. *Immun Inflamm Dis*. 2020;8(1):62–79. doi:10.1002/iid3.284
43. Cappelli EA, Do Espírito Santo Cucinelli A, Simpson-Loureiro L, et al. Insights of OxyR role in mechanisms of host-pathogen interaction of Corynebacterium diphtheriae. *Brazilian J Microbiol*. 2022;53(2):583–594. doi:10.1007/s42770-022-00710-8
44. Zhang Y, Jiang Y, Zhan Y, Wang H, Qin T, Lu Z. First case report of human infection with Micrococcus yunnanensis identified by 16S rRNA gene sequencing: a case report. *Medicine*. 2022;101(48):e32108. doi:10.1097/MD.00000000000032108
45. Zhang Y, Hu Q, Li Z, Kang Z, Zhang L. Kocuria species: an underappreciated pathogen in pediatric patients—a single-center retrospective analysis of 10 years' experience in China. *Diagnostic Microbiol Infect Dis*. 2023;107(4):116078. doi:10.1016/j.diagmicrobio.2023.116078
46. Xu J, Zhang Y, Shi L, Wang H, Zeng M, Lu Z. Community-acquired pneumonia caused by Micrococcus antarcticus: a rare case report. *BMC Infect Dis*. 2024;24(1):1200. doi:10.1186/s12879-024-10084-x

47. Hou J, Sun Y. Role of regulatory T cells in disturbed immune homeostasis in patients with chronic obstructive pulmonary disease. *Front Immunol.* 2020;11:723. doi:10.3389/fimmu.2020.00723
48. Shu HM, Lin CQ, He B, et al. Pyroptosis-related genes as diagnostic markers in chronic obstructive pulmonary disease and its correlation with immune infiltration. *Int J Chronic Obstr.* 2024;19:1491–1513. doi:10.2147/COPD.S438686
49. Xiong L, Li Y, Zeng K, Wei Y, Li H, Ji X. Revealing viral diversity in the Napahai plateau wetland based on metagenomics. *Antonie van Leeuwenhoek.* 2023;117(1):3. doi:10.1007/s10482-023-01912-2
50. Leschonski KP, Mortensen MS, Hansen LBS, Krogh K, Kabel MA, Laursen MF. Structure-dependent stimulation of gut bacteria by arabinoxylo-oligosaccharides (AXOS): a review. *Gut Microbes.* 2024;16(1):2430419. doi:10.1080/19490976.2024.2430419
51. Li G, Liu L, Lu T, et al. Gut microbiota aggravates neutrophil extracellular traps-induced pancreatic injury in hypertriglyceridemic pancreatitis. *Nat Commun.* 2023;14(1):6179. doi:10.1038/s41467-023-41950-y
52. Sun F, Zhang Q, Zhao J, Zhang H, Zhai Q, Chen W. A potential species of next-generation probiotics? The dark and light sides of *Bacteroides fragilis* in health. *Food Research International.* 2019;126:108590. doi:10.1016/j.foodres.2019.108590
53. Sakamoto M, Sakurai N, Tanno H, Iino T, Ohkuma M, Endo A. Genome-based, phenotypic and chemotaxonomic classification of *Faecalibacterium* strains: proposal of three novel species *Faecalibacterium duncaniae* sp. nov. *Faecalibacterium hattorii* sp. nov. and *Faecalibacterium gallinarum* sp. nov. *Inter J Systematic Evolution Microbiol.* 2022;72(4). doi:10.1099/ijsem.0.005379
54. Verma A, Bhagchandani T, Rai A, et al. Short-chain fatty acid (SCFA) as a connecting link between microbiota and gut-lung axis-A potential therapeutic intervention to improve lung health. *ACS omega.* 2024;9(13):14648–14671. doi:10.1021/acsomega.3c05846
55. Plomp N, Harmsen HJM. Description of *Faecalibacterium wellingii* sp. nov. and two *Faecalibacterium taiwanense* strains, aiding to the reclassification of *Faecalibacterium* species. *Anaerobe.* 2024;89:102881. doi:10.1016/j.anaerobe.2024.102881
56. Diver S, Richardson M, Haldar K, et al. Sputum microbiomic clustering in asthma and chronic obstructive pulmonary disease reveals a *Haemophilus*-predominant subgroup. *Allergy.* 2020;75(4):808–817. doi:10.1111/all.14058
57. Rhoades NS, Davies M, Lewis SA, et al. Functional, transcriptional, and microbial shifts associated with healthy pulmonary aging in rhesus macaques. *Cell Rep.* 2022;39(3):110725. doi:10.1016/j.celrep.2022.110725
58. Morrow JD, Castaldi PJ, Chase RP, et al. Peripheral blood microbial signatures in current and former smokers. *Sci Rep.* 2021;11(1):19875. doi:10.1038/s41598-021-99238-4

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