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ORIGINAL RESEARCH

Exploring the Causal Relationship Between Saliva Microbiota Abundance and Chronic Obstructive Pulmonary Disease/Idiopathic Pulmonary Fibrosis: A Two-Sample Mendelian Randomization Study

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Background: Idiopathic pulmonary fibrosis (IPF) and chronic obstructive pulmonary disease (COPD) are progressive lung diseases with overlapping risk factors but distinct pathologies. This study employed bidirectional two-sample Mendelian randomization (MR) to explore potential causal relationships between saliva microbiota abundance and the risk of both diseases.

Methods: Saliva microbiota abundance datasets were analyzed for forward and reverse causal associations with both diseases. Of 44 datasets, 43 met the inclusion criteria for instrumental variable selection. MR analyses were performed using inverse variance weighted (IVW), MR-Egger, weighted median, and weighted mode methods. Steiger filtering confirmed directionality. Sensitivity analyses included Cochran's Q, MR-Egger intercept, MR-PRESSO, and leave-one-out to assess heterogeneity, pleiotropy, and the influence of individual variants.

Results: In forward MR, higher abundance of species *parvula* was significantly associated with reduced COPD risk (IVW OR = 0.9546, 95% CI = 0.9224–0.9879, P = 0.0020; adjusted P = 0.019). Nominal inverse associations were observed for Bacilli, *Porphyromonas*, and *Fusobacterium* with IPF, though these did not remain significant after multiple testing correction. All key associations passed Steiger directionality tests, with no evidence of horizontal pleiotropy or heterogeneity. In reverse MR, COPD showed a nominal positive association with *Periodonticum* abundance.

Conclusion: This exploratory study suggests potential directional associations between specific salivary microbiota and chronic respiratory diseases. *Parvula* abundance may be protective against COPD, while Bacilli, *Porphyromonas*, and *Fusobacterium* may influence IPF risk. These findings support the salivary microbiome as a potential contributor to respiratory disease pathogenesis and warrant further validation in mechanistic and longitudinal studies.

Keywords: idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, saliva, microbiota, Mendelian randomization analysis

Introduction

Idiopathic pulmonary fibrosis (IPF) and chronic obstructive pulmonary disease (COPD) are progressive lung diseases that lead to irreversible respiratory decline.[1] COPD is significantly more prevalent, affecting an estimated 212 million people globally and contributing to over 3 million deaths annually, making it one of the leading causes of respiratory morbidity.[2] In contrast, IPF is a rarer condition, with a global annual incidence of 5–20 cases per 100,000 people, primarily affecting men over 50.[3] While COPD is characterized by airflow limitation and chronic inflammation,[4] IPF is marked by fibrosis of lung tissue, resulting in progressive respiratory dysfunction, severe breathing difficulties, and eventual respiratory failure.[5] Both diseases share overlapping risk factors such as smoking, environmental exposures, and aging,[6] yet these factors appear to direct individuals toward different pathological outcomes. In addition to environmental risks, recent evidence emphasizes the role of genetic predisposition in fibrotic lung diseases, such as familial pulmonary fibrosis.[7] This highlights the importance of

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exploring genetic and environmental interactions that may differentiate COPD and IPF pathogenesis. Investigating both diseases together allows for a deeper understanding of potential shared or divergent pathways in their pathogenesis, which may uncover novel insights into targeted prevention and treatment strategies.

Recent studies have highlighted the potential role of saliva microbiota in respiratory diseases, as it contributes to the lung microbiota through microaspiration, influencing immune responses, inflammation, and epithelial integrity, which are critical in the pathogenesis of lung diseases.[8] In COPD, changes in saliva microbiota composition are characterized by increased bacterial richness and diversity, with genera like *Veillonella, Rothia*, and *Actinomyces* frequently identified. These alterations are linked to disease progression and exacerbations through inflammatory pathways, as evidenced by associations between specific microbiota profiles and elevated salivary inflammatory markers, which correlate negatively with lung function.[9] In IPF, the oral microbiota significantly contributes to lung microbial composition, with 32.84% of lung microbiota genes traced to the oral cavity. Enriched genera like *Streptococcus, Pseudobutyrivibrio*, and *Anaerorhabdus* are associated with microbial translocation, biofilm formation, antibiotic resistance, and metabolic changes, potentially promoting lung injury, fibrosis, and reduced microbial diversity, highlighting the oral-lung axis in IPF etiology.[10] Repeated aspiration of oral or gastric contents due to gastroesophageal reflux may further contribute to lung inflammation and microbial imbalance in IPF.[11] These findings suggest that oral microbial changes may influence disease development and warrant investigation to determine their causal role in pathogenesis.

Mendelian Randomization (MR) is a robust genetic epidemiology method that utilizes genetic variants, typically single nucleotide polymorphisms (SNPs) identified through Genome-Wide Association Studies (GWAS), as instrumental variables (IVs) to assess the causal relationship between an exposure and an outcome.[12] By minimizing confounding and reverse causality, MR offers a powerful tool to identify causal links when randomized controlled trials may be impractical or unethical.[13] This study employs a two-sample MR approach to investigate the genetically causal relationships between saliva microbiota abundance and IPF or COPD, aiming to identify potential shared and disease-specific microbial influences on pathogenesis. The findings may provide novel insights into the microbial mechanisms underlying these diseases, facilitating the understanding of their progression and enabling early risk stratification for targeted interventions.

Materials and Methods

Study Design

The methodology followed the STROBE-MR statement guidelines and employed a two-sample MR framework to assess bidirectional causal relationships between saliva microbiota abundance and respiratory diseases. Forward MR was used to estimate the effects of microbial taxa on COPD and IPF, while reverse MR tested whether genetic liability to COPD or IPF influenced microbial abundance. IVs were selected based on the three key principles of MR analysis: relevance, independence, and exclusion restriction.[14] MR Steiger directionality testing was performed to validate the inferred causal direction. GWAS summary statistics for exposures and outcomes were obtained from publicly available datasets. Sensitivity analyses included heterogeneity testing, horizontal pleiotropy assessment, and outlier correction. A schematic overview of the workflow is shown in Figure 1.

Ethics Statement

All data used in this study were obtained from publicly available datasets containing de-identified human genetic or microbiome data. In accordance with Article 32, Items 1 and 2 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects (promulgated February 18, 2023, China), research using publicly available or legally obtained, de-identified human data is exempt from ethics review and informed consent. Therefore, no further institutional review board approval was required.

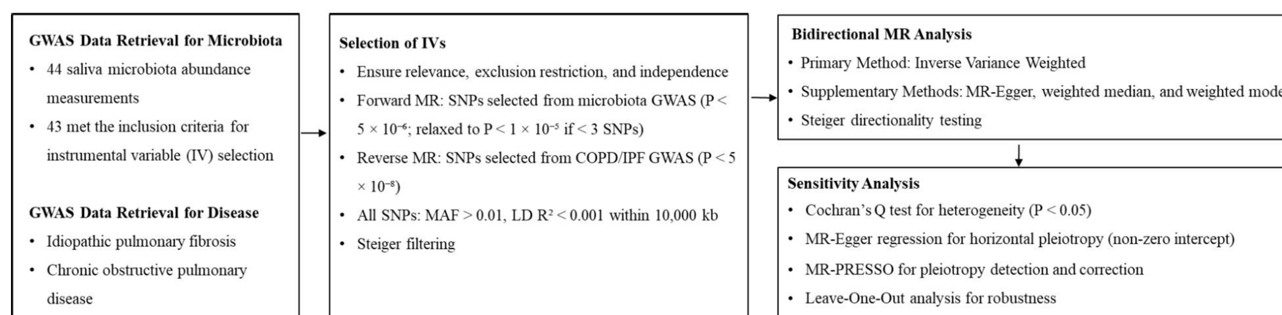

Figure 1 Study flowchart for the Mendelian randomization (MR) analysis of saliva microbiota and respiratory diseases. This flowchart summarizes the bidirectional MR framework used to investigate potential causal relationships between salivary microbiota abundance and chronic obstructive pulmonary disease (COPD) or idiopathic pulmonary fibrosis (IPF). GWAS summary statistics for 44 saliva microbiota traits were screened, with 43 traits meeting the inclusion criteria for instrumental variable (IV) selection. Forward MR used the inverse variance weighted (IVW) method as the primary analysis. Sensitivity analyses included MR-PRESSO for outlier correction, Cochran's Q test, MR-Egger intercept, and leave-one-out analysis. Steiger filtering was applied to confirm causal directionality. Reverse MR was performed using genome-wide significant SNPs from COPD and IPF GWAS to evaluate potential feedback effects on salivary microbiota composition.

Data Sources

GWAS data on IPF were obtained from a published study via https://github.com/genomicsITER/PFgenetics/tree/master. The study analyzed individuals of European ancestry, including 2668 IPF cases and 8591 controls in the discovery phase.[15] GWAS data for COPD were sourced from the FINNGEN R10 release (https://r9.risteys.finngen.fi/endpoints/J10_COPD), comprising 18,266 cases, predominantly of Finnish ancestry. Oral microbiome data were obtained from a study conducted on 610 unrelated adults of Danish ancestry from the ADDITION-PRO cohort. The study utilized 16S rRNA gene sequencing to investigate the salivary microbiota and performed GWAS to identify host genetic variants associated with oral bacterial traits. A total of 44 oral microbiome measurements were analyzed, including 43 univariate bacterial features (spanning taxonomic groups from phylum to species levels) and one multivariate bacterial community diversity metric.[16] To our knowledge, there is no sample overlap between the exposure (oral microbiota) and outcome (COPD and IPF) GWAS datasets, as these were derived from distinct cohorts (ADDITION-PRO and FinnGen/multicenter studies, respectively). The information on the datasets is summarized in Table S1.

IV Selection

For forward MR analysis, IVs were selected from GWAS summary statistics of saliva microbiota traits. An initial threshold of genome-wide significance ($P < 5\times10^{-8}$) yielded insufficient variants for most taxa; therefore, a relaxed threshold of $P < 5\times10^{-6}$ was adopted, consistent with prior MR studies on gut microbiota, inflammatory factors, and related traits.[17] To ensure adequate instrument strength and model stability, a minimum of 3 independent SNPs per exposure was required.[18] For exposures with fewer than 3 SNPs at this threshold, the criterion was further relaxed to $P < 1 \times 10^{-5}$, as previously reported.[19–21] In contrast, for reverse MR analysis, instruments for COPD and IPF were selected using the standard genome-wide significance threshold ($P < 5\times10^{-8}$) without relaxation.

To guarantee sufficient genetic variability, only SNPs with a minor allele frequency (MAF) greater than 0.01 were included.[22] Linkage disequilibrium (LD) effects were minimized by excluding SNPs with high LD ($R^2 < 0.001$) within a 10,000 kb window.[23] For cases where the selected IV was absent from the outcome summary data, proxy SNPs with strong LD ($R^2 > 0.8$) were identified and substituted to maintain integrity.[24] Furthermore, the F-statistic was calculated for each SNP to assess instrument strength and prevent weak instrument bias. The formula $F = R^2 \times (N - 2) / (1 - R^2)$ was used. R^2 represents the proportion of variance in the exposure explained by the SNP. Only SNPs with an F-statistic > 10 were included to ensure the reliability of the IVs and their ability to capture the causal effect of the exposure on the outcome.[25]

MR Analysis

In this study, the inverse variance weighted (IVW) random effects method was the primary approach for assessing the causal relationship between exposure and outcomes, providing odds ratios (ORs) with 95% confidence intervals (CIs).

The IVW method calculates a weighted average effect size using each SNP's inverse variance.[26] To ensure robustness, MR-Egger, weighted median, and weighted mode methods were also applied. MR-Egger accounts for pleiotropy by including an intercept term,[18] while the weighted median method provides reliable estimates if at least 50% of IVs are valid.[27] The weighted mode method identifies the causal effect as the mode of the effect estimates, weighted by their precision, and is robust even when most IVs are invalid, provided that the largest subset of valid instruments produces consistent estimates.[28] Associations with IVW $P < 0.05$ were considered statistically significant. P values were adjusted for multiple comparisons using the Benjamini–Hochberg false discovery rate (FDR) method.

Sensitivity Analysis

Sensitivity analyses were performed to evaluate the robustness of causal estimates and detect potential violations of MR assumptions. Heterogeneity among instrument-specific estimates was assessed using Cochran's Q test under the IVW model. A P-value > 0.05 indicated low heterogeneity, suggesting consistency across SNP effects.[29] Horizontal pleiotropy was evaluated using the MR-Egger intercept. A non-significant deviation from zero indicated the absence of directional pleiotropy.[18] MR-PRESSO identified and corrected for outlier variants contributing to pleiotropic bias.[30] Robustness was further assessed by leave-one-out (LOO) analysis, which sequentially removed individual SNPs to evaluate their influence on the overall causal estimates.[31] To ensure correct causal direction, the Steiger directionality test was applied, and SNPs explaining greater variance in the outcome than in the exposure (R^2_outcome > R^2_exposure) were excluded prior to MR. All analyses were performed using the "TwoSampleMR" package. Diagnostic plots (scatter, forest, funnel) were used for visualization.

Results

IV Selection in Forward MR

For IV selection, out of 44 saliva microbiota abundance datasets, 43 were included in the final analysis. Beta diversity of salivary microbiota (GCST90429842) was excluded due to insufficient information. IVs were primarily selected using the threshold of $P < 5\times10^{-6}$. For unknown *Streptococcus* species (ASV0003, GCST90429825), species *parvula* (GCST90429829), genus *Alloprevotella* (GCST90429822), genus *Streptococcus* (GCST90429813), and unknown *Rothia* species (ASV0012, GCST90429834), fewer than 3 SNPs met this criterion. Therefore, the threshold was relaxed to $P < 1\times10^{-5}$. Unavailable SNPs in the abundance data for unknown *Schaalia* species (ASV0017), unknown *Rothia* species (ASV0016), and unknown *Neisseria* species (ASV0004) for IPF, and unknown *Rothia* species (ASV0016) and species *parvula* for COPD, were substituted with proxy SNPs, including rs73057773 for rs7807974, rs67487314 for rs61026851, rs2614710 for rs67577153, rs34837414 for rs7247650, rs4860383 for rs113621445, and rs9571821 for rs9564412. The number of IVs per dataset ranged from 3 to 13, with mean F-statistic between 20.53 and 27.10, confirming instrument strength (Table S2).

Forward MR Analysis

MR analysis using the IVW method revealed a significant inverse association between *parvula* abundance and COPD risk (OR = 0.9546, 95% CI: 0.9270–0.9831, P = 0.002). Higher abundances of class Bacilli (OR = 0.8447, 95% CI: 0.7402–0.9639, P = 0.0122) and genus *Porphyromonas* (OR = 0.8398, 95% CI: 0.7224–0.9764, P = 0.0231) were significantly associated with reduced risk of IPF (Table 1).

MR-PRESSO detected outliers in three associations: genus *Fusobacterium* with IPF (1 outlier), genus *Rothia* with COPD (1 outlier), and unknown *Rothia* species (ASV0012) with COPD (2 outliers) (Table S3). After removing outliers, a significant inverse association emerged between *Fusobacterium* and IPF (IVW OR = 0.9069, 95% CI: 0.8338–0.9865, P = 0.0227; Table 1). Other associations remained null. Notably, after FDR correction, only the association between *parvula* and COPD remained significant (adjusted P = 0.019), reinforcing its robustness. Full MR results, including post-correction estimates, are shown in Table S4. Scatter and forest plots illustrated the SNP-specific effects (Figures 2 and 3). These findings provide novel evidence linking specific salivary microbial taxa to COPD and IPF risk, suggesting disease-specific microbial contributions.

Table 1 Significant Associations Between Saliva Microbiota Abundance and Respiratory Diseases in Forward and Reverse Mendelian Randomization Analyses (IVW Method)

Exposure	Outcome	IV P-Threshold	N.SNPs	Methods	OR (95% CI)	P
Forward MR						
Saliva microbiota abundance (Species *parvula*)	COPD	$P < 1\times10^{-5}$	8	IVW	0.9546 (0.9270–0.9831)	0.002
Saliva microbiota abundance (Class Bacilli)	IPF	$P < 5 \times 10^{-6}$	4	IVW	0.8447 (0.7402–0.9639)	0.0122
Saliva microbiota abundance (Genus *Porphyromonas*)	IPF	$P < 5 \times 10^{-6}$	4	IVW	0.8398 (0.7224–0.9764)	0.0231
*Saliva microbiota abundance (Genus *Fusobacterium*)	IPF	$P < 5 \times 10^{-6}$	9	IVW	0.9069 (0.8338–0.9865)	0.0227
Reverse MR						
COPD	Saliva microbiota abundance (Species *periodonticum*)	$P < 5 \times 10^{-8}$	13	IVW	1.5446 (1.0170–2.3460)	0.041

Note: *After outlier removal.

Abbreviations: CI, Confidence Interval; COPD, Chronic Obstructive Pulmonary Disease; IPF, Idiopathic Pulmonary Fibrosis; IVW, Inverse Variance Weighted; MR, Mendelian Randomization; N.SNPs, Number of Single Nucleotide Polymorphisms; OR, Odds Ratio.

Sensitivity and Directionality Analysis in Forward MR

Sensitivity analysis confirmed the robustness of our findings. No evidence of heterogeneity (Cochran's Q P = 0.7748 for *parvula*–COPD, P = 0.7179 for Bacilli–IPF, P = 0.2210 for *Porphyromonas*–IPF, and P = 0.3145 for *Fusobacterium*–IPF) or horizontal pleiotropy (MR-Egger intercept P = 0.7327, 0.4638, 0.7139, and 0.4938, respectively) was detected in significant associations (Table S5). Funnel plots showed symmetrical SNP distributions (Figure 4). LOO analysis confirmed that no individual SNP disproportionately influenced the results (Figure 5). MR-PRESSO distortion tests supported the validity of the Bacilli–IPF association (OR = 0.8447, 95% CI: 0.7732–0.9228, P = 0.0334). No significant

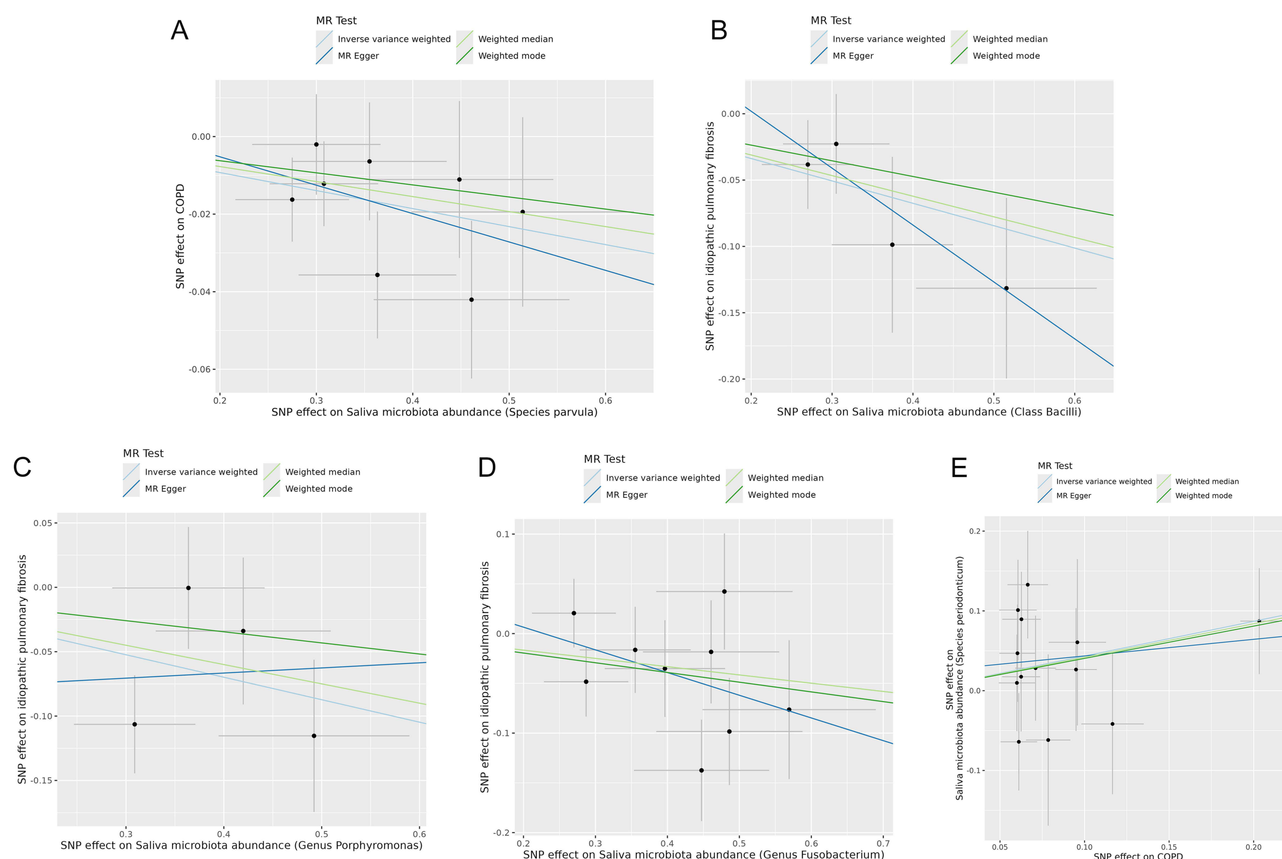

Figure 2 Scatter plots show genetic associations between saliva microbiota abundance and respiratory disease using different MR methods. Regression lines for IVW, MR-Egger, weighted median, and weighted mode methods are included when applicable. (**A**) Saliva microbiota abundance of species *parvula* and COPD risk. (**B**) Saliva microbiota abundance of class Bacilli and IPF risk. (**C**) Saliva microbiota abundance of genus *Porphyromonas* and IPF risk. (**D**) Saliva microbiota abundance of genus *Fusobacterium* and IPF risk. (**E**) COPD and saliva microbiota abundance of species *periodonticum*.

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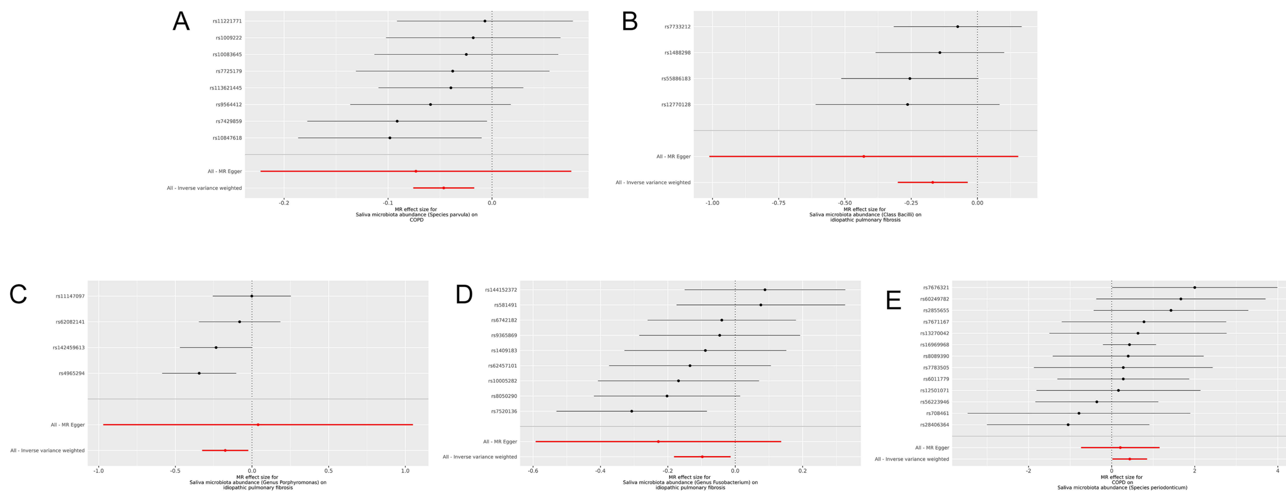

Figure 3 Forest plots demonstrate genetic associations between saliva microbiota abundance and respiratory disease. Forest plots summarize genetic associations between saliva microbiota abundance and respiratory disease risks, with odds ratios (ORs) and 95% confidence intervals (CIs). Each panel shows associations for different taxa, including individual SNP effects and the overall effect size derived from MR analyses. (**A**) *parvula* and COPD risk. (**B**) Bacilli and IPF risk. (**C**) *Porphyromonas* and IPF risk. (**D**) *Fusobacterium* and IPF risk. (**E**) COPD and saliva abundance of *periodonticum*.

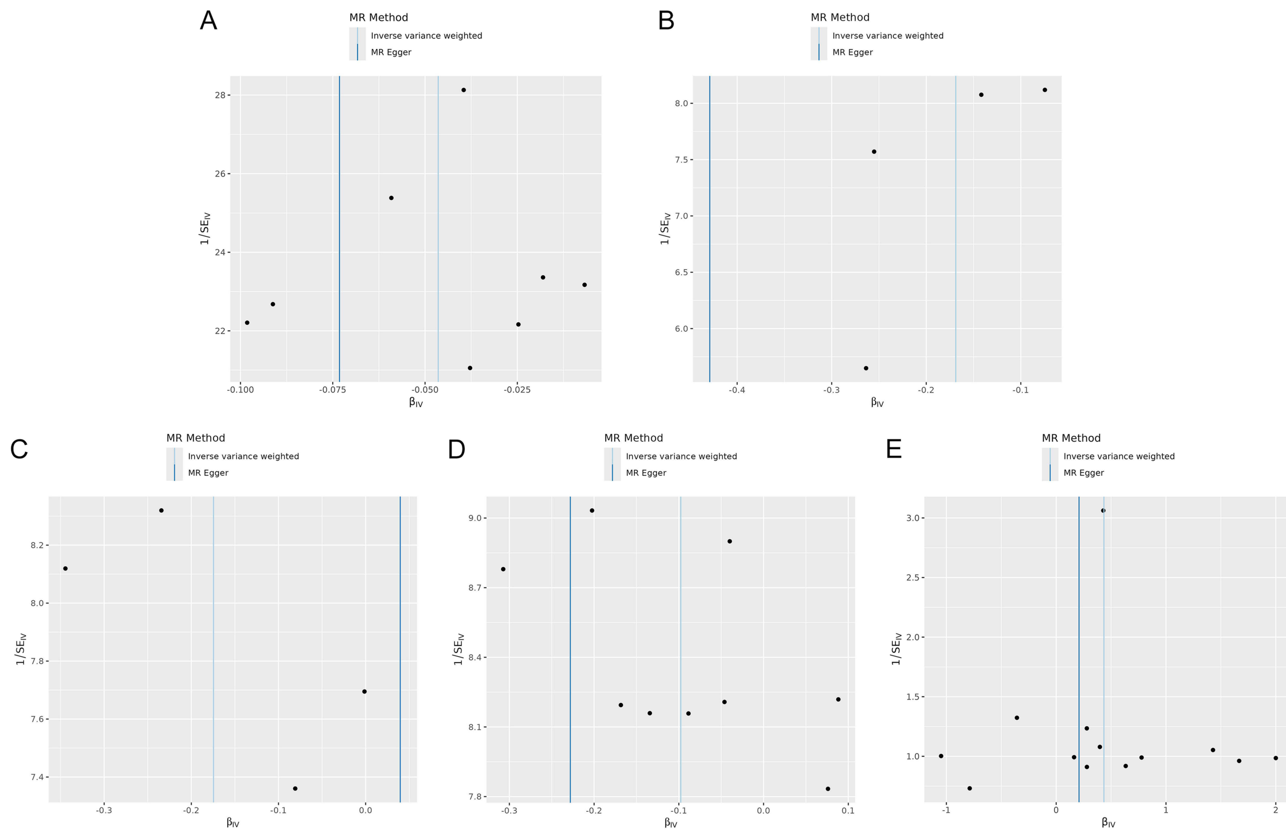

Figure 4 Funnel plots assess horizontal pleiotropy for the association between saliva microbiota abundance and respiratory disease. (**A**) *parvula* and COPD risk. (**B**) Bacilli and IPF risk. (**C**) *Porphyromonas* and IPF risk. (**D**) *Fusobacterium* and IPF risk. (**E**) COPD and saliva abundance of *periodonticum*.

pleiotropy or distortion effects were detected for the significant associations, indicating that horizontal pleiotropy is unlikely to influence these findings (Table S3). To ensure correct causal direction, SNPs explaining more variance in the outcome than in the exposure were excluded prior to MR (Table S6), and all retained associations passed the Steiger directionality test (Table 2), supporting causality from microbiota to disease.

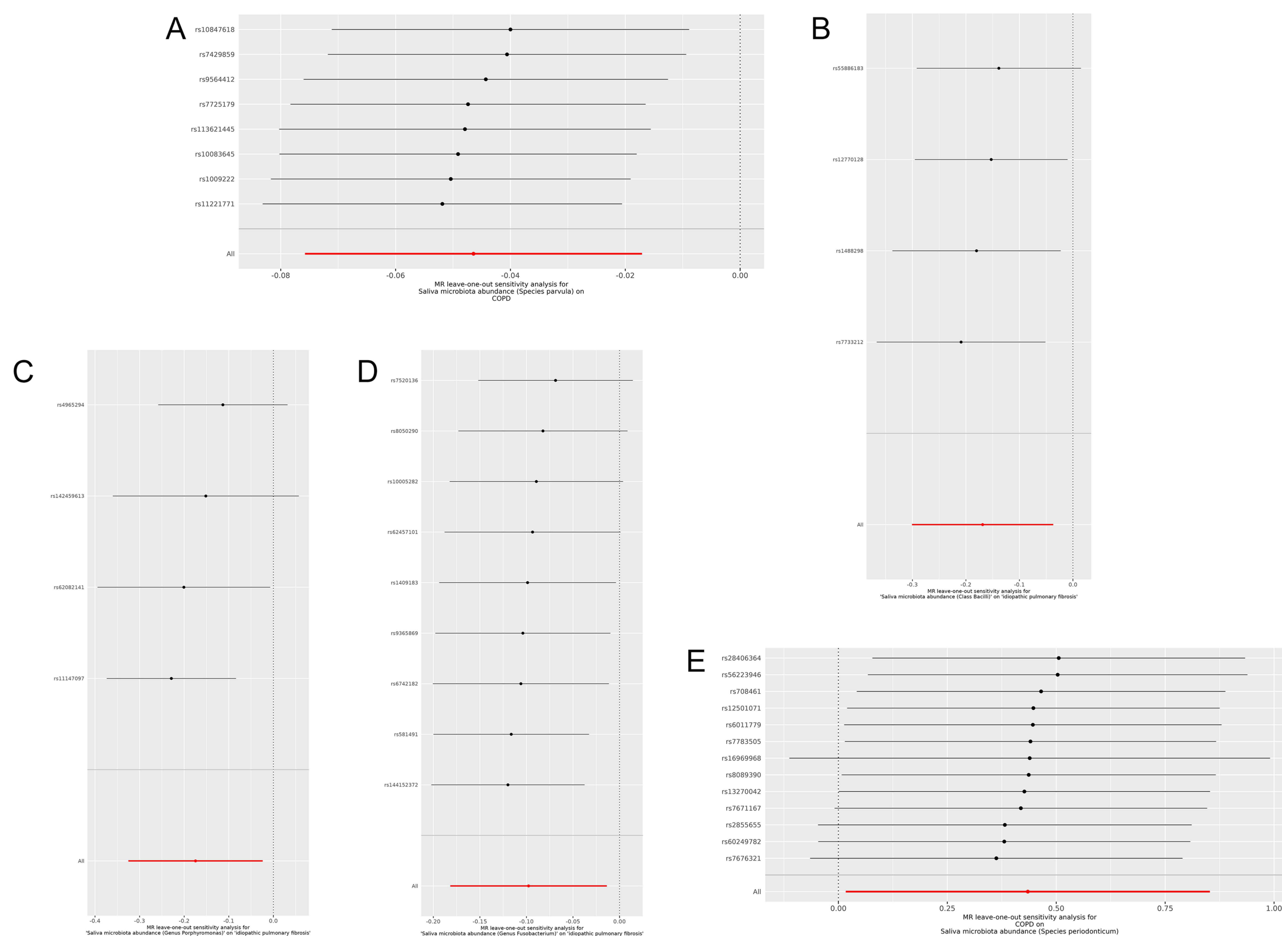

Figure 5 Leave-one-out (LOO) analysis for the association between saliva microbiota abundance and respiratory disease. (**A**) *parvula* and COPD risk. (**B**) Bacilli and IPF risk. (**C**) *Porphyromonas* and IPF risk. (**D**) *Fusobacterium* and IPF risk. (**E**) COPD and saliva abundance of *periodonticum*.

Reverse MR

For reverse MR analysis, genetic instruments were selected from GWAS summary data of COPD and IPF at genome-wide significance ($P < 5\times10^{-8}$). For COPD, 20 independent SNPs were initially identified. After removing 5 SNPs

Table 2 Results of Steiger Directionality Testing for Salivary Microbiota Traits and Respiratory Disease Outcomes

Exposure	Outcome	Correct_Causal_Direction	Steiger_pval
Saliva microbiota abundance (Order Fusobacteriales)	COPD	TRUE	2.7412E-43
Saliva microbiota abundance (unknown Rothia species (ASV0012))	COPD	TRUE	4.3194E-11
Saliva microbiota abundance (Phylum Firmicutes)	COPD	TRUE	1.0756E-60
Saliva microbiota abundance (unknown Schaalia species (ASV0017))	COPD	TRUE	5.6684E-43
Saliva microbiota abundance (Species mucilaginosa)	COPD	TRUE	1.5008E-85
Saliva microbiota abundance (Species histicola)	COPD	TRUE	5.9464E-43
Saliva microbiota abundance (unknown Rothia species (ASV0016))	COPD	TRUE	2.3298E-23
Saliva microbiota abundance (unknown Streptococcus species (ASV0006))	COPD	TRUE	8.0567E-43
Saliva microbiota abundance (unknown Streptococcus species (ASV0009))	COPD	TRUE	1.8569E-30
Saliva microbiota abundance (Species micronuciformis)	COPD	TRUE	2.9291E-34
Saliva microbiota abundance (Genus Alloprevotella)	COPD	TRUE	2.6852E-16
Saliva microbiota abundance (Phylum Proteobacteria)	COPD	TRUE	5.3312E-51

(*Continued*)

Table 2 (Continued).

Exposure	Outcome	Correct_Causal_Direction	Steiger_pval
Saliva microbiota abundance (Family Pasteurellaceae)	COPD	TRUE	3.4843E-58
Saliva microbiota abundance (Genus Neisseria)	COPD	TRUE	5.9541E-29
Saliva microbiota abundance (Genus Rothia)	COPD	TRUE	9.734E-35
Saliva microbiota abundance (Genus Fusobacterium)	COPD	TRUE	1.1092E-73
Saliva microbiota abundance (unknown Porphyromonas species (ASV0008))	COPD	TRUE	4.3287E-24
Saliva microbiota abundance (unknown Gemella)	COPD	TRUE	1.1475E-34
Saliva microbiota abundance (Family Lachnospiraceae_[XIV])	COPD	TRUE	1.0519E-56
Saliva microbiota abundance (Class Bacilli)	COPD	TRUE	1.9852E-22
Saliva microbiota abundance (Genus Streptococcus)	COPD	TRUE	4.0602E-16
Saliva microbiota abundance (Genus Leptotrichia)	COPD	TRUE	4.4612E-20
Saliva microbiota abundance (unknown Neisseria species (ASV0004))	COPD	TRUE	2.7449E-22
Saliva microbiota abundance (Genus Veillonella)	COPD	TRUE	6.5914E-34
Saliva microbiota abundance (Genus Granulicatella)	COPD	TRUE	1.0783E-40
Saliva microbiota abundance (Order Actinomycetales)	COPD	TRUE	9.5963E-65
Saliva microbiota abundance (Order Bacteroidales)	COPD	TRUE	6.1776E-98
Saliva microbiota abundance (Family Veillonellaceae)	COPD	TRUE	1.6909E-22
Saliva microbiota abundance (Order Clostridiales)	COPD	TRUE	1.9961E-64
Saliva microbiota abundance (Genus Haemophilus)	COPD	TRUE	1.0144E-42
Saliva microbiota abundance (Species parainfluenzae)	COPD	TRUE	6.0482E-17
Saliva microbiota abundance (Species periodonticum)	COPD	TRUE	1.1217E-43
Saliva microbiota abundance (Species rogosae)	COPD	TRUE	3.4177E-24
Saliva microbiota abundance (Species dispar)	COPD	TRUE	1.4906E-23
Saliva microbiota abundance (unknown Veillonella species (ASV0001))	COPD	TRUE	1.5366E-30
Saliva microbiota abundance (Genus Schaalia)	COPD	TRUE	1.1117E-82
Saliva microbiota abundance (Species pallens)	COPD	TRUE	6.7692E-23
Saliva microbiota abundance (Genus Porphyromonas)	COPD	TRUE	1.9553E-23
Saliva microbiota abundance (Family Actinomycetaceae)	COPD	TRUE	2.7753E-28
Saliva microbiota abundance (Genus Prevotella)	COPD	TRUE	5.4873E-76
Saliva microbiota abundance (Family Prevotellaceae)	COPD	TRUE	7.7443E-54
Saliva microbiota abundance (Order Fusobacteriales)	Idiopathic pulmonary fibrosis	TRUE	1.1719E-38
Saliva microbiota abundance (unknown Rothia species (ASV0012))	Idiopathic pulmonary fibrosis	TRUE	1.6217E-10
Saliva microbiota abundance (Phylum Firmicutes)	Idiopathic pulmonary fibrosis	TRUE	1.4924E-55
Saliva microbiota abundance (unknown Schaalia species (ASV0017))	Idiopathic pulmonary fibrosis	TRUE	5.4295E-32
Saliva microbiota abundance (Species mucilaginosa)	Idiopathic pulmonary fibrosis	TRUE	2.1234E-96
Saliva microbiota abundance (Species histicola)	Idiopathic pulmonary fibrosis	TRUE	1.5816E-37
Saliva microbiota abundance (unknown Rothia species (ASV0016))	Idiopathic pulmonary fibrosis	TRUE	1.3242E-28
Saliva microbiota abundance (unknown Streptococcus species (ASV0006))	Idiopathic pulmonary fibrosis	TRUE	2.548E-33
Saliva microbiota abundance (unknown Streptococcus species (ASV0009))	Idiopathic pulmonary fibrosis	TRUE	3.4937E-27
Saliva microbiota abundance (Species micronuciformis)	Idiopathic pulmonary fibrosis	TRUE	1.6571E-30
Saliva microbiota abundance (Genus Alloprevotella)	Idiopathic pulmonary fibrosis	TRUE	4.5114E-15
Saliva microbiota abundance (Phylum Proteobacteria)	Idiopathic pulmonary fibrosis	TRUE	3.6054E-45
Saliva microbiota abundance (Family Pasteurellaceae)	Idiopathic pulmonary fibrosis	TRUE	1.4116E-51
Saliva microbiota abundance (Genus Neisseria)	Idiopathic pulmonary fibrosis	TRUE	2.1655E-25
Saliva microbiota abundance (Genus Rothia)	Idiopathic pulmonary fibrosis	TRUE	2.7257E-37
Saliva microbiota abundance (Genus Fusobacterium)	Idiopathic pulmonary fibrosis	TRUE	4.2026E-49
Saliva microbiota abundance (unknown Porphyromonas species (ASV0008))	Idiopathic pulmonary fibrosis	TRUE	1.6907E-20
Saliva microbiota abundance (unknown Gemella)	Idiopathic pulmonary fibrosis	TRUE	3.835E-30
Saliva microbiota abundance (Family Lachnospiraceae_[XIV])	Idiopathic pulmonary fibrosis	TRUE	1.1907E-50
Saliva microbiota abundance (Class Bacilli)	Idiopathic pulmonary fibrosis	TRUE	3.8732E-19
Saliva microbiota abundance (Genus Streptococcus)	Idiopathic pulmonary fibrosis	TRUE	1.1311E-13
Saliva microbiota abundance (Genus Leptotrichia)	Idiopathic pulmonary fibrosis	TRUE	1.5916E-17
Saliva microbiota abundance (unknown Neisseria species (ASV0004))	Idiopathic pulmonary fibrosis	TRUE	1.2563E-13
Saliva microbiota abundance (Genus Veillonella)	Idiopathic pulmonary fibrosis	TRUE	2.9365E-30

(*Continued*)

Table 2 (Continued).

Exposure	Outcome	Correct_Causal_Direction	Steiger_pval
Saliva microbiota abundance (Genus Granulicatella)	Idiopathic pulmonary fibrosis	TRUE	5.8076E-36
Saliva microbiota abundance (Order Actinomycetales)	Idiopathic pulmonary fibrosis	TRUE	2.3603E-58
Saliva microbiota abundance (Order Bacteroidales)	Idiopathic pulmonary fibrosis	TRUE	7.2661E-87
Saliva microbiota abundance (Family Veillonellaceae)	Idiopathic pulmonary fibrosis	TRUE	7.9744E-20
Saliva microbiota abundance (Order Clostridiales)	Idiopathic pulmonary fibrosis	TRUE	2.4176E-57
Saliva microbiota abundance (Genus Haemophilus)	Idiopathic pulmonary fibrosis	TRUE	4.8019E-38
Saliva microbiota abundance (Species parainfluenzae)	Idiopathic pulmonary fibrosis	TRUE	9.09E-15
Saliva microbiota abundance (Species periodonticum)	Idiopathic pulmonary fibrosis	TRUE	8.2624E-40
Saliva microbiota abundance (Species rogosae)	Idiopathic pulmonary fibrosis	TRUE	6.5303E-21
Saliva microbiota abundance (Species dispar)	Idiopathic pulmonary fibrosis	TRUE	2.702E-21
Saliva microbiota abundance (unknown Veillonella species (ASV0001))	Idiopathic pulmonary fibrosis	TRUE	5.792E-27
Saliva microbiota abundance (Genus Schaalia)	Idiopathic pulmonary fibrosis	TRUE	9.4417E-75
Saliva microbiota abundance (Species pallens)	Idiopathic pulmonary fibrosis	TRUE	5.6878E-21
Saliva microbiota abundance (Genus Porphyromonas)	Idiopathic pulmonary fibrosis	TRUE	2.0247E-19
Saliva microbiota abundance (Family Actinomycetaceae)	Idiopathic pulmonary fibrosis	TRUE	1.4057E-25
Saliva microbiota abundance (Genus Prevotella)	Idiopathic pulmonary fibrosis	TRUE	1.3163E-60
Saliva microbiota abundance (Family Prevotellaceae)	Idiopathic pulmonary fibrosis	TRUE	2.1418E-41
Saliva microbiota abundance (Species parvula)	COPD	TRUE	1.7661E-53
Saliva microbiota abundance (Species parvula)	Idiopathic pulmonary fibrosis	TRUE	4.3676E-49
Saliva microbiota abundance (unknown Streptococcus species (ASV0003))	COPD	TRUE	1.0373E-15
Saliva microbiota abundance (unknown Streptococcus species (ASV0003))	Idiopathic pulmonary fibrosis	TRUE	1.5844E-13

unavailable in the microbial GWAS datasets (rs538515410, rs60892124, rs9271399, rs28929474, rs141669463) and 2 additional SNPs due to palindromic structure or weak strength (rs1095705, rs6874581), a total of 13 IVs were retained. Similarly, 15 SNPs were selected for IPF, among which three (rs78238620, rs35705950, rs41308092) were not available in the outcome datasets, yielding 12 final IVs. The mean F-statistics were 51.53 (range: 29.89–330.93) for COPD and 115.52 (range: 36.96–927.06) for IPF, confirming sufficient instrument strength. COPD showed a potential positive association with species *periodonticum* abundance (IVW OR = 1.5446, 95% CI: 1.0170–2.3460, P = 0.041, adjusted P = 0.979) (Table 1). The reverse MR results are provided in Table S7.

Sensitivity analysis revealed heterogeneity (IVW Q statistic P < 0.05) or evidence of directional pleiotropy (MR-Egger P < 0.05) in several associations, including COPD with family *Pasteurellaceae* (Q P = 0.032), genus *Haemophilus* (Q P = 0.016), genus *Leptotrichia* (Q P = 0.023), genus s*chaalia* (Egger P = 0.049), and unknown *Schaalia* species (ASV0017) (Egger P = 0.048), as well as IPF with unknown *Streptococcus* species (ASV0003) (Q P = 0.037) (Table S8). MR-PRESSO identified outliers in the associations of COPD with *Haemophilus, Leptotrichia*, and *Pasteurellaceae* (Table S9). After outlier removal, these associations remained non-significant (Table S7). LOO identified rs16969968 as an influential SNP in association with *Schaalia* (genus and ASV0017). Its exclusion eliminated potential pleiotropy and heterogeneity without altering the null results (Table S7). No horizontal pleiotropy or heterogeneity was detected after correction, except for COPD–*Haemophilus* (P = 0.03) (Table S9).

Discussion

This bidirectional MR study explored potential causal links between salivary microbiota composition and two chronic respiratory diseases, COPD and IPF. In forward MR, higher abundances of species *parvula* were associated with a lower risk of COPD, while class Bacilli, genus *Porphyromonas*, and genus *Fusobacterium* were inversely associated with IPF. These associations showed no evidence of horizontal pleiotropy or heterogeneity, and all passed the Steiger directionality test, suggesting a possible causal effect of specific microbial taxa on respiratory disease risk. In contrast, reverse MR identified an association between COPD and increased abundance of species *periodonticum*. While no pleiotropy or heterogeneity was detected for this pair, several other reverse MR associations showed sensitivity to instrument outliers,

limiting interpretability. Taken together, these findings suggest microbiota-to-disease directionality is more plausible than the reverse, providing preliminary evidence for salivary microbial involvement in the pathogenesis of COPD and IPF.

After multiple testing corrections, the inverse associations of Bacilli, *Porphyromonas*, and *Fusobacterium* with IPF did not remain statistically significant (all adjusted P > 0.05), suggesting limited robustness. In contrast, *parvula* exhibited a significant negative association with COPD risk (P = 0.002; adjusted P = 0.019), indicating a potentially protective role. However, this finding appears to contrast with previous observational and experimental evidence implicating *Veillonella parvula* in COPD pathogenesis. *V. parvula* isolated from the saliva of COPD frequent exacerbators has been shown to impair epithelial barrier integrity, increase cytotoxicity, and activate IL-1β/NF-κB signaling in bronchial epithelial cells.[32] It has also been identified as a dominant species enriched in the lower airways of COPD patients, positively correlated with neutrophilic inflammation and reduced lung function.[33] As a predominant subgingival species, *V. parvula* can translocate to the lower respiratory tract via microaspiration of saliva, particularly in individuals with periodontal disease or impaired mucociliary clearance.[9] This apparent discrepancy may reflect differences in taxonomic resolution, microbial niche, or study design. The MR framework infers lifetime genetic predisposition to salivary *parvula* abundance, which may not directly reflect the local effects of transient airway colonization or infection. Additionally, salivary *parvula* may serve as a proxy for broader microbial community features or immune homeostasis that modulate COPD risk. Future studies integrating strain-level metagenomics, mucosal immunity, and longitudinal sampling are needed to clarify the context-dependent role of *parvula* in respiratory health.

IPF is characterized by dysfunction of alveolar epithelial cells, leading to impaired barrier integrity, persistent inflammation, and a profibrotic microenvironment that drives fibroblast activation and irreversible lung remodeling.[34] Emerging evidence suggests that microbial communities may influence these processes. In our analysis, Bacilli, *Porphyromonas*, and *Fusobacterium* showed nominal inverse associations with IPF risk, although none remained significant after multiple testing corrections. These taxa are common components of the oral and respiratory microbiota and have been implicated in maintaining mucosal and immune balance and microbial diversity,[35] both of which are considered protective against chronic inflammation and epithelial injury in IPF.[36] Preclinical studies suggest that members of the class Bacilli, such as *Lactobacillus*, can enhance epithelial barrier function and modulate immune responses via the production of lactic acid and bacteriocins.[37] These metabolites may suppress pro-inflammatory cytokines and reduce tissue injury, potentially mitigating fibrotic progression. For example, *Lactobacillus* have been shown to stabilize epithelial monolayers and suppress inflammatory signaling in vitro.[38] These properties may counteract the inflammation and tissue remodeling observed in fibrosis.

The genus *Porphyromonas*, commonly associated with periodontal disease, produces short-chain fatty acids such as butyrate,[39] which regulate immune responses by increasing regulatory T cells and reducing pro-inflammatory cytokines.[40] Butyrate has also been shown to inhibit TGF-β1-induced myofibroblast differentiation and enhance mitochondrial function, thereby mitigating fibrotic progression.[41] These mechanisms align with the observed nominal inverse association between *Porphyromonas* abundance and IPF risk, suggesting a possible protective role in maintaining mucosal homeostasis. *Fusobacterium*, a facultative anaerobe frequently detected in the lower respiratory tract,[42] has been linked to altered lung microbiota in IPF.[10] However, our findings suggest a nominal negative association between salivary *Fusobacterium* and IPF risk. This may indicate that oral *Fusobacterium* contributes to microbial stability and barrier defense. For example, *Fusobacterium nucleatum* is known to support biofilm structure and induce antimicrobial peptides and chemokines that modulate host responses.[43] These observations raise the question of whether specific oral commensals exert context-dependent effects—protective in the oral niche but potentially pathogenic upon translocation. One hypothesis is that higher oral abundance of these genera may reflect a more balanced or resilient microbiome state, indirectly influencing systemic or mucosal immune tone relevant to lung disease. Collectively, these findings provide preliminary evidence for the potentially protective roles of specific oral taxa in fibrotic lung disease. Given the exploratory nature of our analysis, further mechanistic and longitudinal studies are needed to clarify their functional relevance and therapeutic potential.

This study establishes potential genetically causal links between specific saliva microbiota and COPD and IPF. However, several limitations should be acknowledged. The reliance on GWAS data from predominantly European populations may restrict the generalizability. Due to limited variant availability in current oral microbiota GWAS datasets

based on a relatively small sample size (n = 610), we applied a relaxed significance threshold for IV selection, which enabled broader analysis but introduced weak instrument bias. Larger, ancestry-diverse GWAS are needed to improve instrument strength. Although meta-GWAS or pooled datasets could address this, no suitable resources are currently available. Similarly, triangulation using gut or nasal microbiota is constrained by niche-specific microbial differences and the lack of harmonized cross-site data. At present, replication using independent microbiota GWAS or observational cohorts is not feasible due to the limited availability of comparable salivary microbiota datasets with genetic data. Although oral microbiome data exist for East Asian populations, they were not used for replication because of ancestry differences that may introduce bias. This limits the generalizability and reinforces the exploratory nature of the findings. Some microbial traits, such as ASV0012, remain taxonomically ambiguous. However, re-annotation was not feasible due to the absence of full-length 16S sequences, raw FASTQ files, or shotgun metagenomic data in the original dataset. Additionally, the use of salivary taxa as proxies for respiratory exposure warrants further validation. Moreover, the reliance on broad taxonomic categories may obscure the functional roles of individual microbial species. Addressing these limitations through diverse cohorts, expanded GWAS datasets, advanced microbial characterization, and functional assessments will provide deeper insights into the role of saliva microbiota in respiratory diseases.

Conclusion

This study provides exploratory evidence for genetically inferred associations between specific salivary microbiota and the risk of COPD and IPF, offering new insights into potential microbiome–host interactions in chronic respiratory disease. Increased abundance of species *parvula* was significantly associated with reduced COPD risk, while Bacilli, *Porphyromonas*, and *Fusobacterium* showed nominal inverse associations with IPF. Reverse MR provided limited evidence for disease-to-microbiota effects, further supporting a directional influence of oral microbes on disease susceptibility. These findings suggest the potential of salivary microbiota as biomarkers or modulators of chronic lung disease, warranting further validation in diverse populations and functional studies to clarify their mechanistic relevance.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article and its supplementary information files.

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

The authors declare that they have no competing interests.

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