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ORIGINAL RESEARCH

CD27 on IgD-CD38-B Cells Mediates the Coprococcus-COPD Link

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Background: The gut-lung axis, representing the communication between gut microbiota and the lungs, has been hypothesized to influence chronic obstructive pulmonary disease (COPD) development through modulation of the immune response. However, the causal role of gut microbiota in COPD and the potential mediating role of immune cells remain largely undetermined. This study aimed to uncover the causal relationship between gut microbiota and COPD and explore the potential mediating role of immune cells in this connection.

Methods: This study employed a two-step Mendelian randomization (MR) analysis to investigate the causal effect of gut microbiota on COPD and explore the potential mediating role of immune cells in this relationship. The inverse variance weighted method served as the primary MR analysis method.

Results: MR analyses revealed statistically significant genetic associations between 28 gut microbiota and COPD. Among these, the genus *Coprococcus* demonstrated the strongest causal effect on COPD risk, exhibiting a significant positive association (odds ratio (OR) = 1.18, 95% confidence interval (CI): 1.03–1.36, $P = 0.03$). Additionally, 15 immune cell traits displayed significant associations with *Coprococcus*. Notably, CD27 expressed on IgD^- $CD38^-$ B cells emerged as a potential contributor to COPD development (OR = 1.04, 95% CI: 1.00–1.07, $P = 0.03$). We further explored the potential mediating effect of CD27 on IgD^- $CD38^-$ B cells in the relationship between *Coprococcus* and COPD.

Conclusion: Our MR analysis provided evidence for a causal association between gut microbiota and COPD, potentially mediated by immune cells.

Plain Language Summary: This study aimed to investigate whether gut bacteria could cause chronic obstructive pulmonary disease (COPD) and the potential role of immune cells in this process. We delved into the genetic associations between gut microbiota and COPD by employing Mendelian randomization analysis. The findings revealed a significant link between the genus *Coprococcus* and an increased risk of COPD. Additionally, the study identified 15 immune cell traits significantly associated with *Coprococcus*, among which CD27 expressed on IgD-CD38-B cells emerged as a potential key factor in COPD development. This study provides evidence for a causal relationship between gut microbiota and COPD, and suggests that immune cells may play a potential mediating role in this relationship.

Keywords: chronic obstructive pulmonary disease, gut microbiota, immune cells, Mendelian randomization, gut-lung axis

Introduction

Chronic obstructive pulmonary disease (COPD) is a group of heterogeneous diseases characterized by chronic respiratory symptoms (dyspnea, cough, phlegm, and acute exacerbation) caused by airway (bronchitis and bronchiolitis) and/or alveolar abnormalities (emphysema), resulting in progressive and aggravated airflow restriction.[1,2] COPD affects over 300 million people globally and has become a leading contributor to morbidity, mortality, and healthcare resource utilization.[3,4] Estimates suggest that COPD was responsible for 74.43 million disability-adjusted life-years and 3.28 million deaths globally in 2019,[5] with China accounting for about a quarter of all cases worldwide.[6] COPD encompasses several distinct phenotypes, which can be broadly categorized based on age of onset, clinical presentation, and underlying pathophysiological mechanisms. Among these, early-

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onset COPD and later-onset COPD are two notable phenotypes. Early-onset COPD typically presents in younger individuals, often with a history of smoking or other environmental exposures, and may be associated with a more rapid decline in lung function.[7] In contrast, later-onset COPD tends to occur in older individuals, often without a clear history of significant environmental exposures, and may be more closely linked to aging-related changes in lung structure and function, as well as comorbidities such as cardiovascular disease.[8] Later-onset COPD represents a significant and growing proportion of the COPD burden, particularly in aging populations.[9] Research has identified a growing number of factors that contribute to both the initial development and progressive worsening of COPD over time.[4] Among these emerging factors, recent studies highlight immune system imbalances as a critical player in COPD pathogenesis (ie, the origin and development of the disease).[10–12]

The gut microbiota is a diverse group of microbes present in the human digestive tract, hosting approximately 90% of the body's symbiotic microbes, whose structure and diversity are influenced by many factors such as diet, antibiotic use, and diseases.[13] Often referred to as the "second genome" of the human body, the gut microbiota plays a crucial role not only in digestion and nutrient absorption but also in immune and inflammatory responses.[14,15] Emerging evidence suggests that dysregulation of the gut microbiota may contribute to the onset and progression of COPD. Li et al revealed that patients with COPD showed altered gut microbiota composition and diversity, characterized by a predominance of *Prevotella*, and such altered gut microbiota could accelerate COPD progression in mice.[16] Alternations in some gut microbiota, such as enhanced abundance of *Firmicutes* and reduced abundance of the genus *Alloprevotella* was found to correlate with declined lung function in COPD patients under regular treatment.[17] Changes in gut microbiome composition and function hold promise as non-invasive biomarkers for identifying individuals across the spectrum of COPD, from mild to advanced stages.[11] Current evidence suggests that baseline gut microbiota may offer superior predictive capabilities compared to conventional risk factors.[18]

In COPD, dysregulation of the gut microbiota coincides with a reduction in gut microbial diversity and immune system dysfunction, both of which contribute to chronic inflammation.[19–22] For instance, dysregulated gut microbiota can trigger a mucosal immune response that is transferred to the lungs via the "gut-lung axis", potentially disrupting the balance between T helper 17 (Th_{17}) cells and regulatory T cells (T_{regs}) within the lungs.[23–25] Patients with COPD often exhibit decreased T_{regs} and increased Th_{17} cells, and gut microbiota dysregulation significantly amplifies this immune response, leading to diffuse structural changes in the lungs and accelerating the inflammatory process in COPD.[23,26,27] These findings highlight the strong link between the gut microbiota, the immune system, and COPD. While research in this area is expanding, the precise roles of the gut microbiota and immune cells in COPD remain to be fully elucidated.

Mendelian randomization (MR) constitutes a methodological approach that leverages genetic variations as instrumental variables (IVs) to elucidate causal relationships between exposures and outcomes.[28] Notably, MR analyses are less susceptible to confounding biases and the issues associated with reverse causality.[29,30] In this study, we employed MR analysis to investigate the genetic associations between the gut microbiota and COPD, with the further aim of exploring whether immune cells mediate the influence of the gut microbiota on COPD.

Materials and Methods

Study Design

To elucidate the causal relationship between the gut microbiota and COPD, this study employed a two-stage MR design. In the first stage, a two-sample MR approach was utilized to assess the causal effects of both the gut microbiota and immune cells on COPD susceptibility. Subsequently, the second stage investigated the potential mediation of immune characteristics in the causal pathway linking the gut microbiota to COPD. Given that the analyzed data were publicly available and had already received approval from the Institutional Review Board (IRB) of the corresponding projects, this study did not require further ethical approval. The detailed study design is depicted in Figure 1. This research was approved by the Beijing Jingmei Group General Hospital of China (Clinical Trial Number: ZZ2024-02).

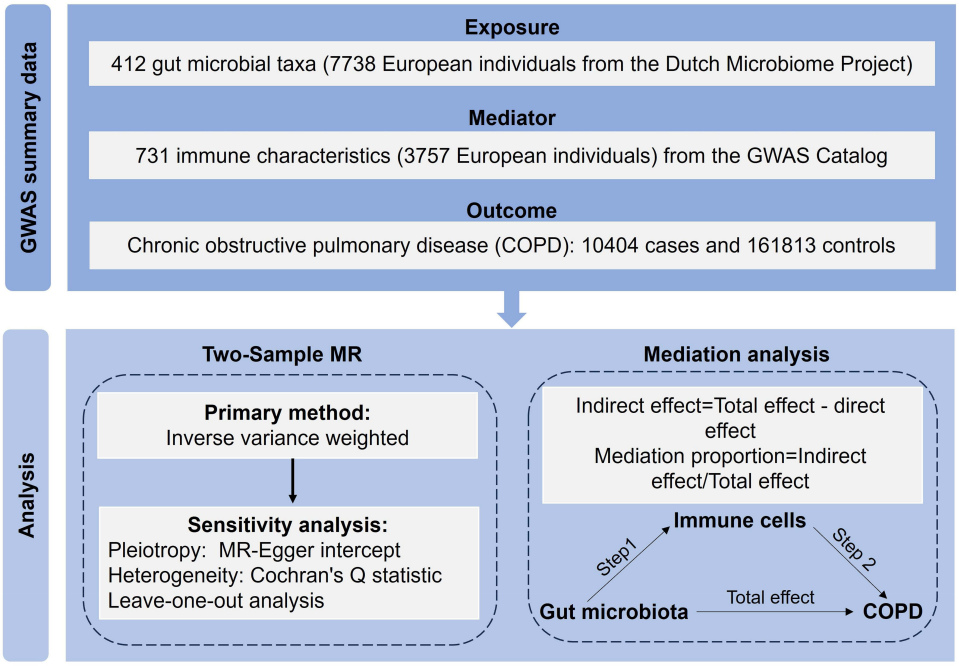

Figure 1 Study design for identifying causative role of gut microbiota on chronic obstructive pulmonary disease (COPD) risk and mediation roles of immune cells. GWAS: Genome-wide Association Studies; MR: Mendelian randomization.

Data Sources

This study included COPD, gut microbiome, and immune feature data from designated public databases that were complete and accurate, and excluded samples with missing, incorrect, or duplicated key information to ensure data quality. Publicly available summary data for COPD was retrieved from https://storage.googleapis.com/finngen-public-data-r9/summary_stats/finngen_R9_COPD_ LATER.gz. This dataset includes data from 392,423 individuals in the FinnGen project who were identified based on specific COPD codes, had coded events, and had event ages of ≥ 65 years. Patients with early-onset COPD, individuals who did not pass genotype quality control, and individuals in the control group who did not meet the criteria were excluded. This dataset comprised 10404 cases of late-onset COPD and 161,813 controls. Summary data for 412 gut microbiomes were obtained from the Dutch Microbiome Project (DMP).[31] This project investigates the host's genetic influence on the gut microbiota in a cohort of 7738 individuals. Summary data for 731 immune characteristics (accession numbers: GCST9001391–GCST9002121) were derived from the Genome-wide Association Studies (GWAS) Catalog (https://gwas.mrcieu.ac.uk/), encompassing data from 3757 European individuals.[32] These immune cell traits encompassed four categories: median fluorescence intensity (MFI; 389 measures), relative cell count (RC; 192 measures), absolute cell count (AC; 118 measures), and morphological parameters (MP; 32 measures). Notably, the MP data included panels for dendritic cells (DC) and T, B, and natural killer (NK) cells (TBNK). The MFI, RC, and AC data encompassed these same panels in addition to cell populations such as B cells, mature T cells, monocytes, myeloid cells, and Tregs.

IV Selection

In MR analyses, single-nucleotide polymorphisms (SNPs) are employed as IVs to evaluate potential causal relationships between exposures and outcomes. The selection of appropriate IVs hinges on three critical assumptions: (1) a robust correlation exists between the IVs and the exposure of interest, (2) the IVs are devoid of confounding factors, and (3) the IVs influence the outcome solely through their effect on the exposure. Candidate SNPs for this MR analysis were first subjected to a screening process based on genome-wide significance ($P < 1\times10^{-5}$). Subsequently, SNPs exhibiting weak instrumental strength, as indicated by an F-statistic below 10, were excluded. In instances where linkage disequilibrium (LD) was identified between SNPs ($r^2 < 0.1$), these linked SNPs were removed within a 10,000 kb window using the reference panel from the 1000 Genomes Project.[33]

Statistical Analyses

All statistical analyses were conducted using R Studio software (version 2023.09). The "TwoSampleMR" package (version 0.4.3) was employed to investigate potential causal relationships between the gut microbiota and COPD. Within this package, the inverse variance weighted (IVW) method was chosen as the primary analysis tool due to its well-established precision and robustness. A significance level of $P < 0.05$ was adopted for all statistical tests. The MR-Egger intercept test[34] was utilized to assess horizontal pleiotropy among the instrumental variables. A statistically significant intercept ($P < 0.05$) was considered indicative of potential horizontal pleiotropy, and the associated SNPs were excluded from further analyses. Cochran's Q statistic was employed to evaluate the presence of heterogeneity among the included SNPs. Additionally, a leave-one-out sensitivity analysis was conducted to assess the influence of any single SNP on the overall causal estimates.

Results

Causal Associations Between Gut Microbiota and COPD

Our MR analysis identified 28 gut microbiota with significant genetic associations with COPD occurrence. The ten gut microbiota with the most robust causal effects on COPD are presented in Table 1. All ten of these gut microbiota were associated with an increased risk of COPD, and analyses revealed no evidence of heterogeneity or pleiotropy (Table 1). Among these ten, the genus *Coprococcus* (ID: GCST90027843) demonstrated the strongest causal effect on COPD risk. Specifically, individuals with a genetic predisposition for this gut microbiota exhibited a significantly elevated COPD risk (odds ratio [OR] = 1.18, 95% confidence interval [CI]: 1.03–1.36, $P = 0.03$; Figure 2). The reverse MR analysis reassuringly indicated no evidence of reverse causality for genetically predicted *Coprococcus* on COPD risk (OR = 1.03, 95% CI: 0.96–1.11, $P = 0.44$). This lack of reverse causality strengthens the validity of our findings and paves the way for further mediation analysis.

Screening of Immune Mediators

To elucidate potential mediating factors, a set of 731 immune cell characteristics was initially selected for investigation. We subsequently assessed the relationships between the genus *Coprococcus* and these immune characteristics, identifying statistically significant associations with 15 of them (Table 2). The IVW method revealed a positive correlation between the genus *Coprococcus* and eight immune characteristics, including: ebi-a-GCST90002109 (HLA DR on CD33br HLA DR^+ $CD14^{dim}$, OR = 1.35), ebi-a-GCST90002110 (HLA DR on $CD33^{dim}$ HLA DR^+ $CD11b^+$, OR = 1.34), and ebi-a-GCST90001913 (CD45 on granulocytes, OR = 1.29) (Table 2). Conversely, negative correlations were observed between the genus *Coprococcus* and seven immune characteristics, including ebi-a-GCST90001832 (CD62L on $CD62L^+$ plasmacytoid DC, OR = 0.68), ebi-a-GCST90002019 (CD14 on Mo MDSC, OR = 0.73), and ebi-

Table 1 The Causality Between Gut Microbiome and COPD

Gut Microbiota		SNPs	IVW			Pleiotropy	Heterogeneity
ID	Name		OR	95% CI	P	P	P
GCST90027593	Bacteria in PWY.6690 metabolic pathway	8	1.12	1.02–1.22	0.013	0.95	0.83
GCST90027768	Parabacteroides johnsonii	7	1.09	1.03–1.16	0.003	0.56	0.64
GCST90027829	Bacteroides intestinalis	3	1.15	1.04–1.27	0.01	0.45	0.5
GCST90027798	Ruminococcaceae bacterium D16	10	1.09	1.02–1.15	0.01	0.35	0.25
GCST90027717	Ruminococcaceae bacterium D16	10	1.09	1.02–1.16	0.01	0.36	0.23
GCST90027536	Bacteria in PWY.5005 synthetic pathway	11	1.12	1.02–1.22	0.01	0.76	0.88
GCST90027689	Adlercreutzia	7	1.15	1.03–1.29	0.01	0.51	0.66
GCST90027758	Adlercreutzia equolifaciens	7	1.15	1.03–1.29	0.01	0.49	0.66
GCST90027843	Coprococcus	5	1.18	1.03–1.36	0.03	0.52	0.86
GCST90027572	Bacteria in PWY.6151 metabolic pathway	11	1.14	1.02–1.28	0.02	0.24	0.77

Abbreviations: SNP, single-nucleotide polymorphisms; IVW, inverse variance weighted; OR, odds ratio; CI, confidence interval.

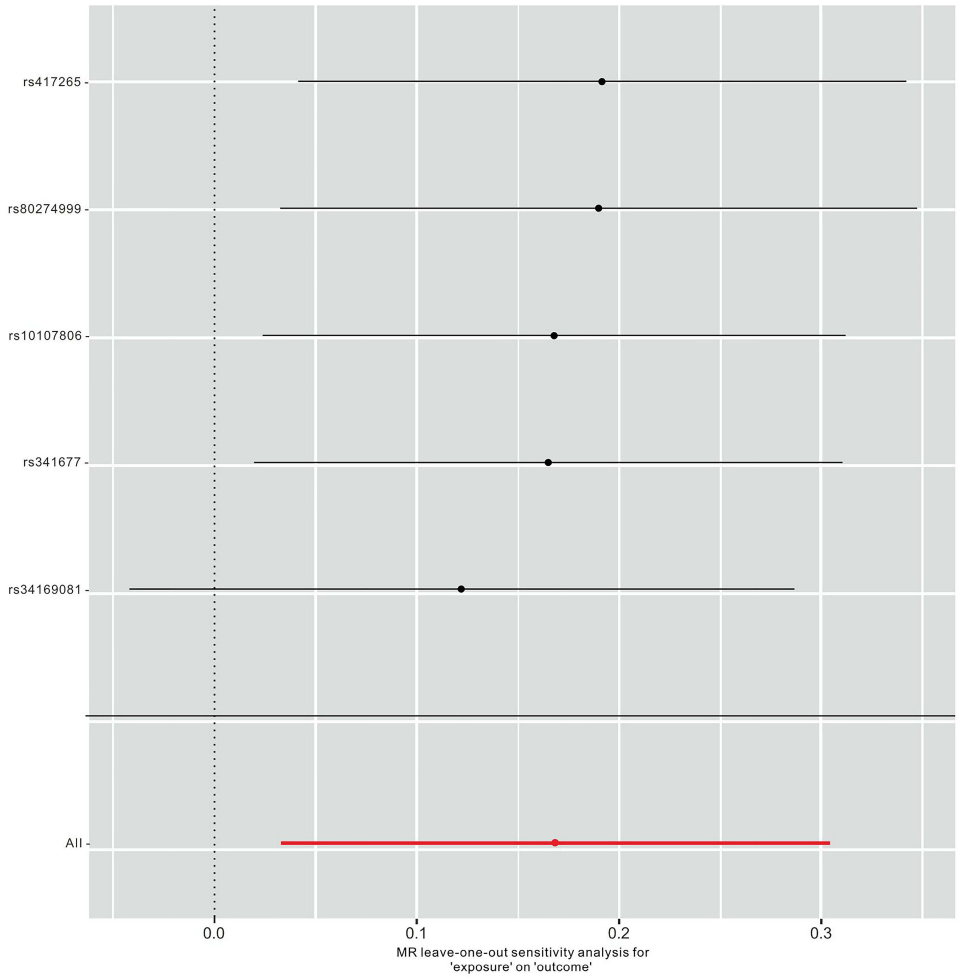

Figure 2 Forest plot showing the causal effect of each single-nucleotide polymorphism (SNP) of the genus *Coprococcus* on COPD.

a-GCST90001802 (CD27 on IgD$^-$ CD38$^-$, OR = 0.81) (Table 2). Importantly, no evidence of heterogeneity or pleiotropy was observed for any of these associations (Table 2).

We next employed MR analysis to investigate the associations between the 15 identified immune characteristics and COPD risk (Table 3). This analysis revealed two immune characteristics to be significantly associated with an increased risk of COPD

Table 2 The Causality Between Gut Microbiome and Immune Characteristics

Immune Characteristics			SNPs	IVW			Pleiotropy	Heterogeneity
ID	Panel	Name		OR	95% CI	P	P	P
ebi-a-GCST90001411	B cell	IgD+ CD24+ %B cell	6	1.28	1.04–1.58	0.02	0.85	0.36
ebi-a-GCST90001439	B cell	IgD+ CD24+ %lymphocyte	6	1.24	1.02–1.51	0.03	0.98	0.90
ebi-a-GCST90001463	cDC	CD62L- DC %DC	6	1.24	1.01–1.53	0.04	0.47	0.84
ebi-a-GCST90001583	Monocyte	Monocyte AC	6	0.82	0.68–0.99	0.04	0.34	0.89
ebi-a-GCST90001649	TBNK	HLA DR+ NK %NK	6	1.24	1.01–1.51	0.04	0.39	0.88
ebi-a-GCST90001650	TBNK	HLA DR+ NK %CD3- lymphocyte	6	1.23	1.01–1.50	0.04	0.46	0.87

(*Continued*)

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Table 2 (Continued).

Immune Characteristics			SNPs	IVW			Pleiotropy	Heterogeneity
ID	Panel	Name		OR	95% CI	P	P	P
ebi-a-GCST90001802	B cell	CD27 on IgD- CD38-	6	0.81	0.66–0.99	0.04	0.72	0.79
ebi-a-GCST90001832	cDC	CD62L on CD62L+ plasmacytoid DC	6	0.68	0.55–0.84	0.00	0.93	0.63
ebi-a-GCST90001833	cDC	CD62L on CD62L+ DC	6	0.75	0.61–0.93	0.01	0.99	0.55
ebi-a-GCST90001835	cDC	CD62L on granulocyte	6	0.80	0.65–0.99	0.04	0.67	0.46
ebi-a-GCST90001913	TBNK	CD45 on granulocyte	6	1.29	1.04–1.59	0.02	0.14	0.49
ebi-a-GCST90002004	Monocyte	CCR2 on CD14+ CD16- monocyte	6	0.80	0.66–0.98	0.03	0.40	0.53
ebi-a-GCST90002019	Myeloid cell	CD14 on Mo MDSC	6	0.73	0.55–0.97	0.03	0.79	0.52
ebi-a-GCST90002109	Myeloid cell	HLA DR on CD33br HLA DR+ CD14dim	6	1.35	1.01–1.80	0.04	0.67	0.71
ebi-a-GCST90002110	Myeloid cell	HLA DR on CD33dim HLA DR+ CD11b+	6	1.34	1.01–1.79	0.05	0.38	0.79

Abbreviations: SNP, single-nucleotide polymorphisms; IVW, inverse variance weighted; OR, odds ratio; CI, confidence interval; TBNK, T cells, B cells, and NK cells; cDC, conventional dendritic cells.

Table 3 The Causality Between Immune Characteristics and COPD

Immune Characteristics			SNPs	IVW			Pleiotropy	Heterogeneity
ID	Panel	Name		OR	95% CI	P	P	P
ebi-a-GCST90001411	B cell	IgD+ CD24+ %B cell	18	1.03	0.96–1.10	0.45	0.19	0.28
ebi-a-GCST90001439	B cell	IgD+ CD24+ %lymphocyte	15	1.02	0.96–1.08	0.58	0.23	0.76
ebi-a-GCST90001463	cDC	CD62L- DC %DC	20	0.99	0.96–1.02	0.38	0.27	0.40
ebi-a-GCST90001583	Monocyte	Monocyte AC	29	1.00	0.98–1.03	0.91	0.90	0.04
ebi-a-GCST90001649	TBNK	HLA DR+ NK %NK	23	0.98	0.94–1.02	0.24	0.34	0.25
ebi-a-GCST90001650	TBNK	HLA DR+ NK %CD3- lymphocyte	22	1.00	0.96–1.04	1.00	0.87	0.96
ebi-a-GCST90001802	B cell	CD27 on IgD- CD38-	29	1.04	1.00–1.07	0.03	0.75	0.08
ebi-a-GCST90001832	cDC	CD62L on CD62L+ plasmacytoid DC	15	0.97	0.92–1.03	0.33	0.75	0.06
ebi-a-GCST90001833	cDC	CD62L on CD62L+ DC	26	1.02	0.99–1.06	0.26	0.47	0.82
ebi-a-GCST90001835	cDC	CD62L on granulocyte	16	1.00	0.93–1.07	0.97	0.18	0.10
ebi-a-GCST90001913	TBNK	CD45 on granulocyte	15	1.00	0.96–1.03	0.80	0.52	0.51
ebi-a-GCST90002004	Monocyte	CCR2 on CD14+ CD16- monocyte	25	1.00	0.99–1.02	0.72	0.64	0.61
ebi-a-GCST90002019	Myeloid cell	CD14 on Mo MDSC	23	1.01	0.99–1.04	0.24	0.77	0.60
ebi-a-GCST90002109	Myeloid cell	HLA DR on CD33br HLA DR+ CD14dim	20	0.99	0.96–1.03	0.74	0.14	0.21
ebi-a-GCST90002110	Myeloid cell	HLA DR on CD33dim HLA DR+ CD11b+	23	1.03	1.01–1.05	0.01	0.29	0.31

Abbreviations: SNP, single-nucleotide polymorphisms; IVW, inverse variance weighted; OR, odds ratio; CI, confidence interval; TBNK, T cells, B cells, and NK cells; cDC, conventional dendritic cells.

onset: ebi-a-GCST90001802 (CD27 on IgD^- $CD38^-$ B cells, OR = 1.04, 95% CI: 1.00–1.07, $P = 0.03$) and ebi-a-GCST90002110 (HLA DR on $CD33^{dim}$ HLA DR^+ $CD11b^+$ B cells, OR = 1.03, 95% CI: 1.01–1.05, $P = 0.01$). Importantly, no evidence of heterogeneity or pleiotropy was observed for these associations (Table 3). Given the slightly larger OR of ebi-a-GCST90001802 (CD27 on IgD^- $CD38^-$ B cells) for COPD onset, we selected this immune characteristic for further mediation analysis to explore the potential causal pathway between the genus *Coprococcus* and COPD susceptibility.

Mediating Effect of CD27 Expression on IgD^- $CD38^-$ B Cells on the Causal Associations Between Gut Microbiota and COPD

To elucidate the potential mediating role of CD27 expression on IgD^- $CD38^-$ B cells in the pathway linking the gut microbiota genus *Coprococcus* to COPD susceptibility, we conducted a mediation analysis (Figure 3). The analysis revealed a significant

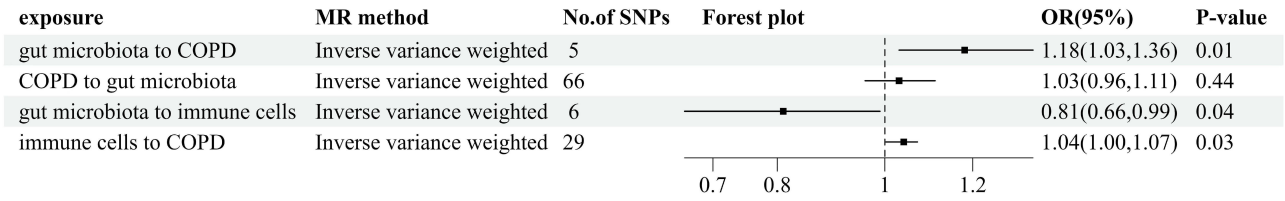

Figure 3 Forest plot showing the causal association of the genus *Coprococcus*, immune cells, and COPD.
Abbreviations: OR, odds ratio; SNPs, single-nucleotide polymorphisms.

direct effect of the genus *Coprococcus* on COPD onset (OR = 1.18, $P = 0.01$), with no evidence of reverse causality ($P = 0.44$). Furthermore, a negative association was observed between the abundance of *Coprococcus* and CD27 expression on IgD^- $CD38^-$ B cells (gut microbiota to immune cells, OR = 0.81, $P = 0.04$), suggesting a potential suppressive effect of *Coprococcus* on this immune cell marker. Importantly, a positive association was also identified between CD27 expression on IgD^- $CD38^-$ B cells and COPD risk (immune cells to COPD, OR = 1.04, $P = 0.03$). In conclusion, these findings suggest that the genus *Coprococcus* may influence COPD susceptibility by downregulating CD27 expression on IgD^- $CD38^-$ B cells, warranting further investigation into this potential mechanistic pathway.

Our analysis revealed a statistically significant direct effect of the genus *Coprococcus* on COPD risk (OR = 0.17). However, the observed mediating effect of CD27 expression on IgD^- $CD38^-$ B cells on this association was negative (OR = −0.01). Due to this negative mediating effect, it was not feasible to calculate a valid mediation proportion for the influence of CD27 expression on IgD^- $CD38^-$ B cells on the overall effect of *Coprococcus* on COPD risk.

Discussion

Importantly, COPD is a preventable and treatable condition. However, a significant burden of disease arises from missed or misdiagnoses, leading to delayed or inappropriate therapeutic interventions.[1] Early identification of COPD is crucial for effective disease prevention, diagnosis, and the implementation of timely and appropriate management strategies. This MR analysis identified a causal association between the gut microbiota genus *Coprococcus* and COPD susceptibility. Furthermore, the analysis revealed that CD27 expression on IgD^- $CD38^-$ B cells mediates the causal effect of *Coprococcus* on COPD risk.

A well-established relationship exists between the gut and lungs, characterized by shared features in both anatomical structure and physiological function.[35,36] Structurally, both the intestine with its microvilli and the respiratory tract with its cilia possess physical barriers and contribute to the development of the local immune system within lymphoid tissues. Functionally, the gut and lungs share a common mucosal immune system, characterized by the presence of secretory immunoglobulin A and mucus-secreting goblet cells.[35,36] Furthermore, these organs facilitate the exchange of signaling molecules through interconnected lymphatic and blood circulation, leading to the proposition of the "gut-lung axis" within the field of modern traditional Chinese medicine.[35] Metabolites, such as short-chain fatty acids, and immune-inflammatory factors produced by gut microbiota dysbiosis can be transported to the lungs via the gut-lung axis, potentially contributing to lung injury.[21,37] Therefore, the "gut-lung axis" presents a promising new avenue for investigation in the development of therapies for lung diseases.

Coprococcus, a gram-positive bacterium typically residing in the human gut, has garnered attention in the context of COPD due to recent research on gut bacteria and immune cell interactions. Lai et al revealed altered *Coprococcus* abundance in COPD patients compared to healthy controls, with negative correlations to smoking index and positive correlations to lung function outcomes.[38] In vivo experiments using fecal microbiota transplantation demonstrated alleviation of acute lung injury in mice through gut microbiota reconstruction, with Coprococcus abundance decreasing during the process.[39] Jia et al[26] reported a higher abundance of *Coprococcus*_2 in the COPD group compared to the control group, with this abundance decreasing after treatment with Qibai Pingfei capsules. Notably, the abundance of *Coprococcus*_2 in the COPD group positively correlated with Th17-related cytokines and the Th17/Treg ratio, while negatively correlating with Treg-related cytokines and lung function.[26] These findings suggest that *Coprococcus*, as part of the gut microbiota, may influence COPD progression through diverse mechanisms. *Coprococcus* functions as a butyrate-producing bacterium and butyrate itself may exert anti-inflammatory activity, potentially improving COPD outcomes.[40,41] Conversely, *Coprococcus* may migrate from the

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gut to the respiratory tract during acute COPD exacerbations. This is supported by the decrease in *Coprococcus* 2 abundance observed in the bronchoalveolar lavage fluid of colitis mice treated with Gegen Qinlian decoction, which alleviated lung inflammation and injury.[42] These studies collectively highlight *Coprococcus*' potential involvement in the development and progression of COPD.

B cells have been demonstrated to be involved in COPD, as evidenced by the increased number and size of B cell-rich lymphoid follicles, as well as the presence of B cells within pulmonary lymph nodes and perivascular and parenchymal lymphoid follicles in COPD lungs.[43,44] During pulmonary infections, memory B cells can be generated in the peribronchial regions, aiding in defense against reinfection by rapidly inducing secondary immune responses.[43] Notably, IgD is mainly expressed on naïve B cells and functions to inhibit the response, whereas CD27 is a widespread marker of memory B cells that promotes their terminal differentiation. The phenotypic expression of CD27 and IgD can be used to categorize B cells into four functionally distinct subsets.[45] Doubly negative ($CD27^{-}IgD^{-}$) B cells are a unique subset with significant roles.[45] For example, the activity of the $CD27^{-}IgD^{-}$ B cell subset contributes to the release of proinflammatory cytokines.[46] This B cell subset is reported to be of low abundance in healthy controls; however, it is expanded in multiple disorders.[45] Furthermore, CD38 is a multifunctional ectoenzyme expressed on the surface of B cells, particularly in terminally differentiated plasma cells. In resting B cells, CD38 is linked to CD19, which is involved in B cell antigen receptor signaling.[47] These studies suggest that changes in the expression of these cell surface markers may affect the activity and functional phenotype of B cells. Therefore, based on the above findings, a reasonable speculation could be drawn in this study that an enhanced abundance of *Coprococcus* may affect CD27 expression on $IgD^{-}CD38^{-}$ B cells, potentially weakening secondary immune responses and increasing the release of proinflammatory cytokines, thus promoting COPD onset.

To the best of our knowledge, this is the first MR study to investigate the potential mechanisms linking gut microbiota and immune cells to COPD onset. However, several limitations warrant consideration. 1) Although no heterogeneity was found among SNPs, it is important to acknowledge the potential for heterogeneity arising from several aspects, such as experimental conditions, analytical platforms used, and population characteristics. 2) The population analyzed in this study was primarily European, which may limit the generalizability of the observed linkages between gut microbiota and immune cells to COPD onset in Asian and African populations. Finally, future studies are warranted to further elucidate the exact mechanism by which *Coprococcus* influences COPD risk and the involvement of B cells.

Conclusions

In conclusion, our current MR analysis suggests a potential causal association between gut microbiota and COPD onset. Notably, *Coprococcus* was associated with an increased risk of developing COPD, and CD27 expression on the surface of $IgD^{-}CD38^{-}$ B cells may act as a mediator in this association. This study highlights the importance of the "gut-lung axis" in COPD development and potential therapeutic strategies.

Data Sharing Statement

We would like to express our sincere gratitude to the Finnish database for providing the comprehensive summary data on Chronic Obstructive Pulmonary Disease (COPD) cases and controls, which were essential for our research (available at https://storage.googleapis.com/finngen-public-data-r9/summary_stats/finngen_R9_COPD_LATER.gz). We also extend our heartfelt thanks to the Dutch Microbiome Project (DMP) for supplying the summary data on 412 gut microbiomes, based on 7738 individuals, which were invaluable to our study.

Furthermore, we deeply appreciate the Genome-wide Association Studies (GWAS) Catalog for providing the summary data on 731 immune characteristics (accession numbers: GCST9001391–GCST9002121) derived from 3757 European individuals (accessible at https://gwas.mrcieu.ac.uk/).

Ethics Approval

I would like to formally declare that all research involving human subjects was conducted in full compliance with the ethical standards set forth by Beijing Jingmei Group General Hospital, and all necessary ethical approvals were obtained. Additionally, as mentioned earlier, the waiver of informed consent was granted due to the retrospective nature of the study and the anonymized data used.

Disclosure

The authors report no conflicts of interest in this work.

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