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Causal association between gut microbiota and pulmonary embolism: a 2-sample Mendelian randomization study

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Abstract

Background: Pulmonary embolism (PE) is the third most common cause of cardiovascular-related deaths globally; however, the causal relationship between gut microbiota and PE remains unclear. This study aimed to explore the impact of gut microbiota on PE.

Methods: This study utilized a 2-sample Mendelian randomization (MR) design to analyze gut microbiota genome-wide association study data from the MiBioGen database and PE data from the FinnGen database. Statistical methods, such as inverse variance-weighted, MR-Egger, weighted median, and weighted modes, were used to investigate the causal relationship between the gut microbiota and PE. Moreover, a sensitivity analysis was conducted to assess the robustness of the results.

Results: MR analysis revealed that gut microbiota genera *Intestinimonas* (odds ratio [OR]: 0.797; 95% confidence interval [CI]: 0.666–0.952; $P = 0.013$) and *Roseburia* (OR: 0.752; 95% CI: 0.575–0.984; $P = 0.038$) have a protective effect on PE. Conversely, an increased abundance of the phylum Lentisphaerae (OR: 1.217; 95% CI: 1.033–1.434; $P = 0.019$), class Lentisphaeria (OR: 1.219; 95% CI: 1.010–1.471; $P = 0.039$), order Gastranaerophilales (OR: 1.209; 95% CI: 1.017–1.437; $P = 0.031$), order Victivallales (OR: 1.219; 95% CI: 1.010–1.471; $P = 0.039$), and the genus *Ruminococcus gauvreauii* (OR: 1.274; 95% CI: 1.015–1.599; $P = 0.037$) increases the risk of developing PE. Sensitivity analysis indicated no heterogeneity or horizontal pleiotropy.

Conclusion: Seven gut microbiotas, including the phylum Lentisphaerae, class Lentisphaeria, orders Gastranaerophilales and Victivallales, and genera *R. gauvreauii*, *Intestinimonas*, and *Roseburia*, were causally associated with PE. These findings may contribute significantly to the prevention of PE through dietary modifications and microbiome interventions.

Keywords: Causal relationship, Gut microbiota, Mendelian randomization, Pulmonary embolism

Introduction

A pulmonary embolism (PE) typically originates from venous thrombi and flows into and occludes the blood vessels of the pulmonary arteries.[1,2] The prevalence of PE is uncertain owing to the occurrence of sudden death and silent PE. Despite integrative treatment of venous thromboembolism (VTE), the 3-month mortality rate is 15% to 30% and the 5-year recurrence rate is about 22%.[3–5] Therefore, developing an early warning system is crucial for controlling the incidence of PE and the associated mortality.

Multiple risk factors for PE have been identified and are broadly classified into 3 categories.[6,7] Gene mutations were the substantial class, on the one hand, loss-of-function genetic mutations of natural anticoagulants, including PROC-encoded protein C, PROS1-encoded protein S, and SERPINC1-encoded antithrombin.[8] In contrast, gain-of-function genetic mutations of procoagulant proteins, including factor V (F5) and II (F2), which encode coagulation factor V and prothrombin, and fibrinogen-related genes (FGA, FGB, and FGG).[8] Additionally, acquired PE risk factors are more common in clinics, such as surgery, prolonged hospital stays, cancer, obesity, hyperthyroidism, chronic inflammatory bowel disease, and various types of infections, such as respiratory or urinary tract infections.[1] Nevertheless, the comprehensive high-risk factors remain unclear.

Human microbial ecosystems have shown that the gut microbiome has physiologically important effects on the maintenance of

SH and RS contributed equally to this article.

The datasets analyzed in the present study are available in the MiBioGen database (https://mibiogen.gcc.rug.nl/) and the FinnGen database (https://r7.finngen.fi/). FinnGen and pan-UKBBmeta-analysis results for PE were downloaded from https://metaresults-ukbb.finngen.fi/.

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gastrointestinal function, immune response, and neurological homeostasis mediated by the gut-brain-axis balance.[9,10] VTE is associated with imbalance in the gut microbiome characterized by a decreased commensal anaerobic bacterium. In contrast, the number of pathogenic bacteria, such as gram-negative Enterobacteriaceae (ENTERO), has markedly increased.[11] The dominant mechanism by which gram-negative bacteria cause hypercoagulability is lipopolysaccharide localized in the glycolipids of the outer membrane, which trigger the coagulation cascade by activating platelets and endothelial cells.[12–14] Bacteria can also assist in digestion, and partial metabolites such as trimethylamine-N-oxide (TMAO) increase the hyperreactivity of platelets, which is associated with thrombus formation.[15] However, whether one or more bacteria are associated with PE remains unclear.

Mendelian randomization (MR) is a novel approach for probing the causal relationship between gut microbiota and PE, which refers to the causality of risk factors and outcomes by exploiting genetic variants as instrumental variables (IVs) for exposure. As genetic variants are randomly assigned at conception, the results obtained from the MR analysis greatly decreased confounding or reverse causality.[16] MiBioGen database is a bioinformatics platform for interactive and visual analysis of multi-omics data. Many genome-wide association studies (GWAS) have investigated the causal relationship between gut microbiota and various diseases such as preeclampsia-eclampsia,[17] psychiatric disorders,[18] ischemic stroke,[19] adverse pregnancy outcomes,[20] hypertension,[21] etc. The GWAS summary statistics in the present study were acquired from the MiBioGen and FinnGen consortia. A 2-sample bidirectional MR study was performed to observe the causal association between gut microbiota and PE.

Methods

Data sources

Summary data from the MiBioGen consortium, available at http://mibiogen.gcc.rug.nl, encompass the largest multi-ethnic genome-wide meta-analysis. The data comprise 16S rRNA gene sequencing and genome-wide genotyping of 24 cohorts across Europe, North America, and Asia, constituting 18,340 samples.[22] The dataset comprised 211 taxa, including 131 genera, 35 families, 20 orders, 16 classes, and 9 phyla. Twelve unknown genera and 3 unknown families were excluded, resulting in 196 taxa meeting the inclusion criteria for further analysis. Summary genetic data for PE subtypes was sourced from the FinnGen database, involving 4,185 cases and 214,288 controls, with a final selection of 16,380,466 single-nucleotide polymorphisms (SNPs). Additionally, PE GWAS summary statistics from pan-UKBB study were matched to FinnGen results based on ICD-10 code (I26) overlap and meta-analyzed together, including 17481 cases and 898088 controls. All participants were European ancestry.

Identification of instrumental variables

To ensure reliable results, the MR analysis satisfied 3 assumptions: (1) IVs included in the analysis were strongly correlated with the gut microbiome; (2) IVs used were not associated with selected confounding factors related to the gut microbiome and PE; (3) IVs affected the outcome solely through exposure without any direct effects.

Following the established screening criteria from the prior literature, we adopted a rigorous $P < 1 \times 10^{-5}$ threshold to select IVs in our analysis. This stringent threshold was selected to include only genetic variants with a minimal probability of association with the outcome, thereby reducing the inclusion of SNPs with weak or spurious associations.

Additionally, to guarantee the independence of each IV, we implemented a threshold of $r^2 < 0.001$ within a window size of 10,000 kb.[23] This step aims to mitigate the impact of linkage disequilibrium (LD), a phenomenon in which genetic variants in close proximity to the chromosome are inherited. By eliminating IVs with high LD, we aimed to reduce redundancy and exclude SNPs providing essentially the same information, thus ensuring that the selected IVs were genuinely independent and contributed unique information to the analysis.

Furthermore, we excluded "echo SNPs," which are redundant due to LD and do not offer additional information beyond the already included SNPs. Additionally, SNPs that were absent in the IV results were removed, ensuring that all SNPs used in the analysis had valid and reliable data available for research.

By applying these stringent criteria, we aimed to ensure that the selected IVs were robust, independent, and minimally influenced by LD, thereby enhancing the quality and reliability of the IV analysis.

Mendelian randomization analysis

To investigate the causal relationship between gut microbiome and PE, 4 MR methods were used: inverse-variance weighted (IVW) method, MR-Egger regression, weighted median estimator, and weighted mode. The IVW test with multiplicative random effects was chosen as the primary method of MR analysis, and some causation was obtained, with the 4 methods being complementary. Additionally, a sensitivity analysis of the primary outcomes was performed. First, we applied the MR-Egger regression intercept and MR-Pleiotropy Residual Sum and Outlier (MR-PRESSO) Global test to examine the potential horizontal pleiotropy. Second, Cochrane's Q statistic was used to assess the heterogeneity of IV, and $P > 0.05$ represents no significant heterogeneity in the IVs. Next, a leave-one-out analysis was conducted to evaluate the robustness of the results. Reverse MR analysis was used to investigate whether PE is associated with different gut microbiota. To further assess the robustness of findings, we used FinnGen and pan-UKBB meta-analysis results for PE as the outcome to replicate our analysis. An overview of the MR analysis process is shown in Fig. 1.

All analyses in the present study were conducted using the TwoSampleMR package (version 0.3.17) and the MRPRESSO package (version 1.0) for 2-sample bidirectional MR analysis using R software v4.3.1 (R Core Team 2023, Vienna, Austria).

Results

Instrumental variable selection

After screening based on the criteria for large-scale gut microbiome IVs ($P < 1 \times 10^{-5}$), we identified 103, 179, 217, 339, and 464 SNPs, which are involved in the onset of PE at the phylum, class, order, family, and genus levels, respectively. The F statistics values of the IVs are all >10.

Pulmonary embolism susceptibility

We tested the causal relationship between gut microbiota and PE using 4 MR methods. Among the MR results, we found genetically predicted relative abundances of 1 phylum, 1 class, 2 orders, and 3 genera (Figs. 2,3), including phylum Lentisphaerae (odds ratio [OR]: 1.217; 95% confidence interval [CI]: 1.033–1.434; $P = 0.019$), class Lentisphaeria (OR: 1.219; 95% CI: 1.010–1.471; $P = 0.039$), order Gastranaerophilales (OR: 1.209; 95% CI: 1.017–1.437; $P = 0.031$), order Victivallales (OR: 1.219; 95% CI: 1.010–1.471; $P = 0.039$), genus *Intestinimonas* (OR: 0.797; 95% CI: 0.666–0.952; $P = 0.013$), genus *Roseburia* (OR: 0.752; 95% CI: 0.575–0.984; $P = 0.038$), and genus *R. gauvreauii* (OR: 1.274; 95% CI: 1.015–1.599; $P = 0.037$).

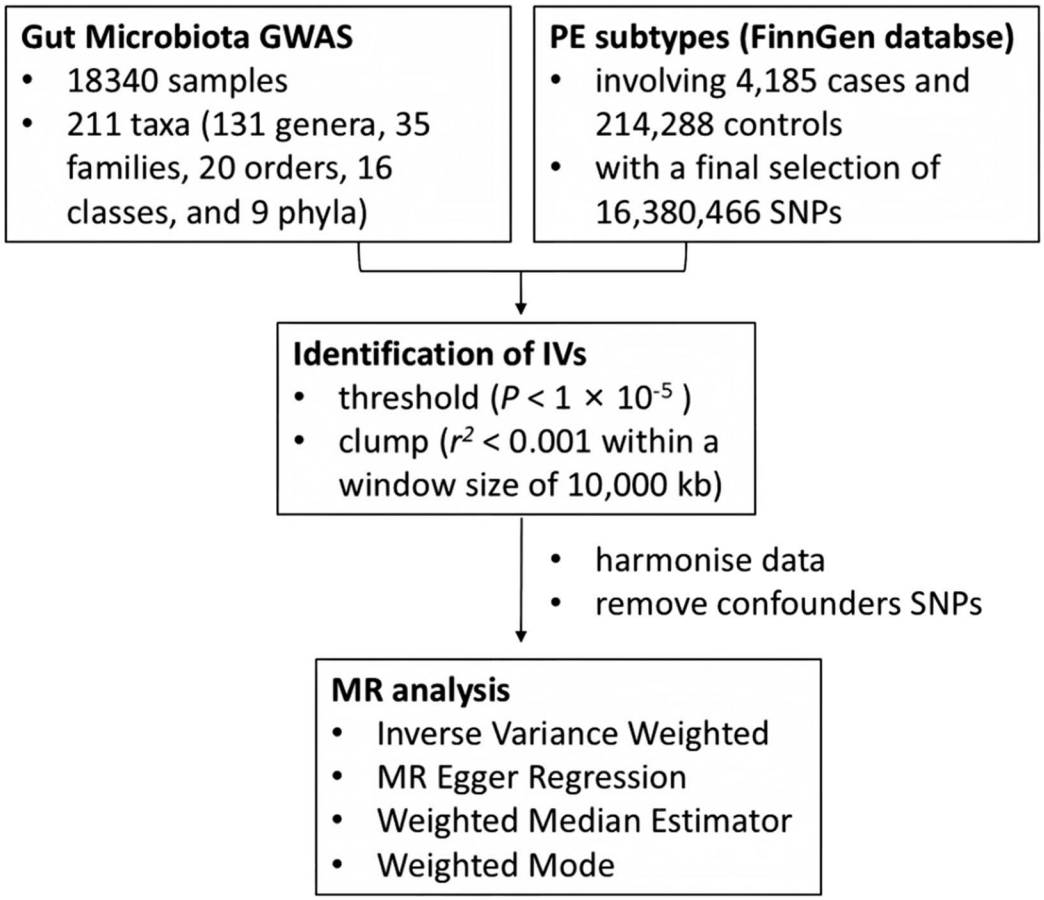
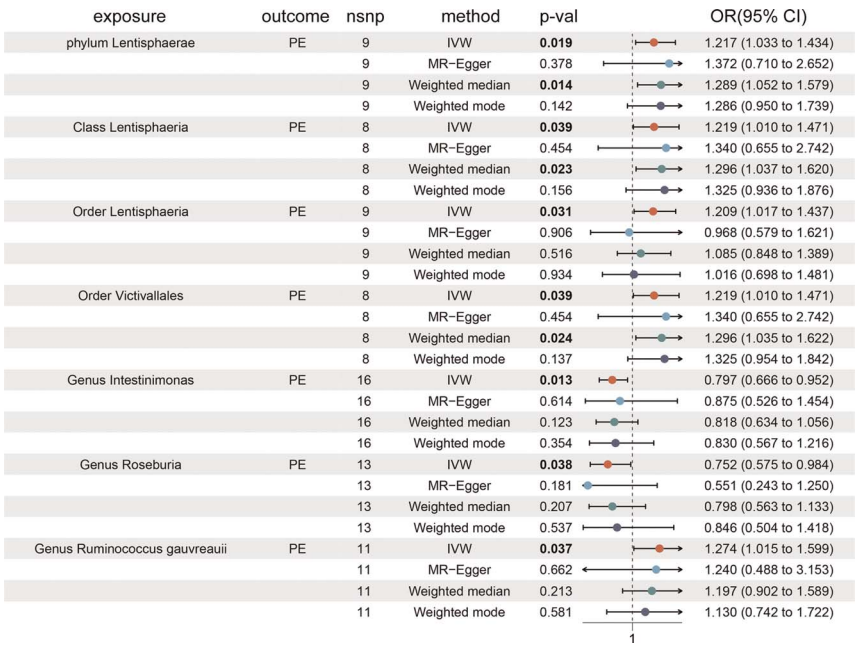


Figure 1. Overview of MR analysis. MR, Mendelian randomization; SNPs, single-nucleotide polymorphisms.



exposure	outcome	nsnp	method	p-val	OR(95% CI)
phylum Lentisphaerae	PE	9	IVW	**0.019**	1.217 (1.033 to 1.434)
		9	MR−Egger	0.378	1.372 (0.710 to 2.652)
		9	Weighted median	**0.014**	1.289 (1.052 to 1.579)
		9	Weighted mode	0.142	1.286 (0.950 to 1.739)
Class Lentisphaeria	PE	8	IVW	**0.039**	1.219 (1.010 to 1.471)
		8	MR−Egger	0.454	1.340 (0.655 to 2.742)
		8	Weighted median	**0.023**	1.296 (1.037 to 1.620)
		8	Weighted mode	0.156	1.325 (0.936 to 1.876)
Order Lentisphaeria	PE	9	IVW	**0.031**	1.209 (1.017 to 1.437)
		9	MR−Egger	0.906	0.968 (0.579 to 1.621)
		9	Weighted median	0.516	1.085 (0.848 to 1.389)
		9	Weighted mode	0.934	1.016 (0.698 to 1.481)
Order Victivallales	PE	8	IVW	**0.039**	1.219 (1.010 to 1.471)
		8	MR−Egger	0.454	1.340 (0.655 to 2.742)
		8	Weighted median	**0.024**	1.296 (1.035 to 1.622)
		8	Weighted mode	0.137	1.325 (0.954 to 1.842)
Genus Intestinimonas	PE	16	IVW	**0.013**	0.797 (0.666 to 0.952)
		16	MR−Egger	0.614	0.875 (0.526 to 1.454)
		16	Weighted median	0.123	0.818 (0.634 to 1.056)
		16	Weighted mode	0.354	0.830 (0.567 to 1.216)
Genus Roseburia	PE	13	IVW	**0.038**	0.752 (0.575 to 0.984)
		13	MR−Egger	0.181	0.551 (0.243 to 1.250)
		13	Weighted median	0.207	0.798 (0.563 to 1.133)
		13	Weighted mode	0.537	0.846 (0.504 to 1.418)
Genus Ruminococcus gauvreauii	PE	11	IVW	**0.037**	1.274 (1.015 to 1.599)
		11	MR−Egger	0.662	1.240 (0.488 to 3.153)
		11	Weighted median	0.213	1.197 (0.902 to 1.589)
		11	Weighted mode	0.581	1.130 (0.742 to 1.722)

Figure 2. Causal estimations of gut microbiota on pulmonary embolism in the MR analysis. CI, confidence interval; IVW, inverse variance weighted; MR, Mendelian randomization; OR, odds ratio; PE, pulmonary embolism.

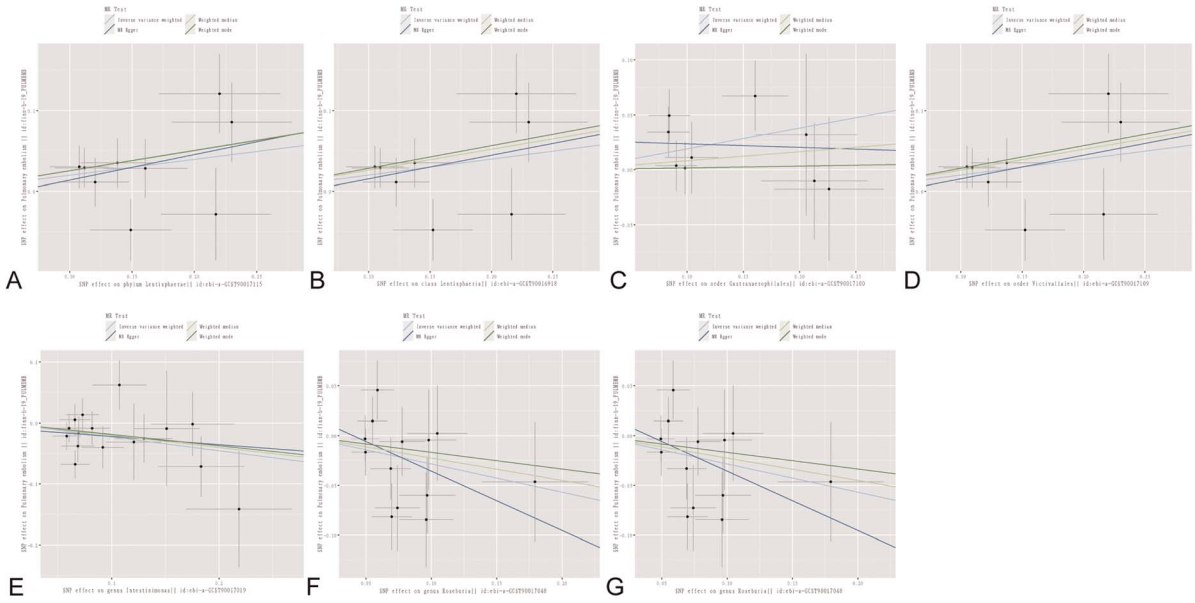


Figure 3. Scatter plots for the causal association between gut microbiota and PE. (A) Phylum Lentisphaerae. (B) Class Lentisohartia. (C) Order Gastranaerophilales. (D) Order Victivallales. (E) Genus *Intestinimonas*. (F) Genus *Roseburia*. (G) Genus *R. gauvreauii*. MR, Mendelian randomization; SNP, single-nucleotide polymorphism.

They contained 9, 8, 9, 8, 16, 13, and 11 SNPs, respectively. Furthermore, other methods were used to verify the robustness of the results, and beta values in the same direction were obtained, proving that our results were robust.

Sensitivity Analysis

We used IVW testing and MR-Egger regression to test the Q statistic; no heterogeneity was found in class Lentisphaeria (P = 0.322), phylum Lentisphaerae (P = 0.229), order Gastranaerophilales (P = 0.161), order Victivallales (P = 0.229), genus *Intestinimonas* (P = 0.451), genus *Roseburia* (P = 0.282), and genus *R. gauvreauii* (P = 0.971) (Table 1). No horizontal pleiotropy was observed in the class Lentisphaeria (P = 0.796), phylum Lentisphaerae (P = 0.723), order Gastranaerophilales (P = 0.4), order Victivallales (P = 0.796), genus *Intestinimonas* (P = 0.704), genus *Roseburia* (P = 0.446), or genus *R. gauvreauii* (P = 0.954). The MR-PRESSO results confirmed the absence of horizontal pleiotropy (Table 2). In the absence of heterogeneity and pleiotropy, the IVW results were reliable. The results of the leave-one-out analysis indicated no causal influence from a single instrumental variable (Fig. 4). Using reverse MR, we found that PE did not affect the abundance of this flora (Table 3), indicating a true causal correlation in this direction. Notably, using FinnGen and pan-UKBB meta-analysis results for PE, we found that, among the 7 gut microbiotas, only genus *Intestinimonas* was still nominally associated with PE in the sensitivity analysis (Table 4).

Discussion

In the present study, we report a systematic MR analysis to determine the relationship between the gut microbiota and the risk of PE. Using GWAS summary statistics from the MiBioGen and

Table 1

Heterogeneity Test of Gut Microbiota on PE

Id. Exposure	Exposure	MR Method	*Q*	Q_df	Q_pval	*F*
ebi-a-GCST90017115	Phylum Lentisphaerae	MR-Egger	9.071	7	0.248	21.281
		IVW	9.247	8	0.322	22.715
ebi-a-GCST90016918	Class Lentisphaeria	MR-Egger	9.226	6	0.161	20.234
		IVW	9.338	7	0.229	21.707
ebi-a-GCST90017100	Order Gastranaerophilales	MR-Egger	5.818	7	0.561	24.834
		IVW	6.620	8	0.578	20.446
ebi-a-GCST90017109	Order Victivallales	MR-Egger	9.226	6	0.161	20.234
		IVW	9.338	7	0.229	21.707
ebi-a-GCST90017019	Genus *Intestinimonas*	MR-Egger	14.852	14	0.388	22.189
		IVW	15.011	15	0.451	24.264
ebi-a-GCST90017048	Genus *Roseburia*	MR-Egger	13.535	11	0.260	20.621
		IVW	14.304	12	0.282	21.887
ebi-a-GCST90017064	Genus *R. gauvreauii*	MR-Egger	3.375	9	0.948	21.862
		IVW	3.378	10	0.971	20.034

$P > 0.05$, no significant pleiotropy. *Q_pval* > 0.05 represents no significant heterogeneity.

GWAS, genome-wide association study; IVs, instrumental variants; IVW, inverse variance weighted; MR, Mendelian randomization; PE, pulmonary embolism.

Table 2

Horizontal Pleiotropy Test of Gut Microbiota on PE

Id. Exposure	Exposure	egger_intercept	SE	*P*	MR-PRESSO
ebi-a-GCST90016918	Class Lentisphaeria	–0.014	0.052	0.796	0.281
ebi-a-GCST90017115	Phylum Lentisphaerae	–0.018	0.049	0.723	0.354
ebi-a-GCST90017100	Order Gastranaerophilales	0.027	0.030	0.400	0.587
ebi-a-GCST90017109	Order Victivallales	–0.014	0.052	0.796	0.27
ebi-a-GCST90017019	Genus *Intestinimonas*	–0.009	0.022	0.704	0.474
ebi-a-GCST90017048	Genus *Roseburia*	0.024	0.030	0.446	0.33
ebi-a-GCST90017064	Genus *R. gauvreauii*	0.002	0.035	0.954	0.973

IVW, inverse variance weighted; MR, Mendelian randomization; PE, pulmonary embolism; SE, standard error.

FinnGen consortia, we found that an increased abundance of *Intestinimonas* and *Roseburia* in the gut protected against PE. In contrast, an increase in the abundance of some gut microbiota was associated with an increased risk of PE, including the phylum Lentisphaerae, class Lentisphaeria, orders Gastranaerophilales and Victivallales, and the genus *R. gauvreauii*.

Thrombosis is a physiological process that maintains vascular integrity and hemostatic function. Once thrombosis exceeds this balance, it can also obstruct blood vessels, leading to arterial or venous thrombosis.[24,25] PE occurs when the embolus breaks off, sheds, and obstructs pulmonary arteries.[26] Hypoxia aggravates vasoconstriction of the pulmonary vasculature, accompanied by vascular remodeling, leading to pulmonary hypertension, impairment of right ventricular function, and cardiac dysfunction.[27] Thrombosis is regulated by a multistep coagulation cascade involving multiple factors, including vascular endothelial injury or inflammation, platelet hyperaggregation, excessive activation of coagulation factors, fibrin formation, and thrombus remodeling.[1] Many high-risk factors for VTE are well-established and can be categorized as genetic, acquired, or mixed-origin factors.[1,7,22] Otherwise, common but clinically irrelevant SNPs might also have underlying impact on the risk of thrombosis.[8,28]

Metagenomic evidence indicates that genomic variation and strain-specific functional adaptations exist widely in the human gut microbiome.[29] The abundances and genetic polymorphisms of the intestinal microflora are intimately associated with human health.[30] An accumulating number of studies in recent years have demonstrated that gut microbiota alterations are linked to immune function and are implicated in the pathogenesis and progression of numerous diseases such as tumor,[31] neurodegenerative diseases,[32] psychiatric disorders,[33] and sarcopenia.[34] The potential impact of the gut microbiota on PE has also attracted attention. However, studies involving gut microbiota and PE are relatively limited.

Observational studies have reported an association between intestinal microecology and PE. Reshaping the gut microbiota structure through antibiotic treatment or fecal microbiota transplantation (FMT) could increase intestinal colonization by *Parasutterella* and eventually inhibit the pathogenesis of PE.[35] Gut microbiota–dependent metabolite TMAO can enhance platelet hyperreactivity and thrombosis risk, thus increasing the risk of arterial thrombotic events, including PE, myocardial infarction, stroke, and mortality.[36–39] Furthermore, TMAO remains potentially associated with postincident VTE, suggesting a possible involvement of the gut microbiota in VTE occurrence and recurrence.[40]

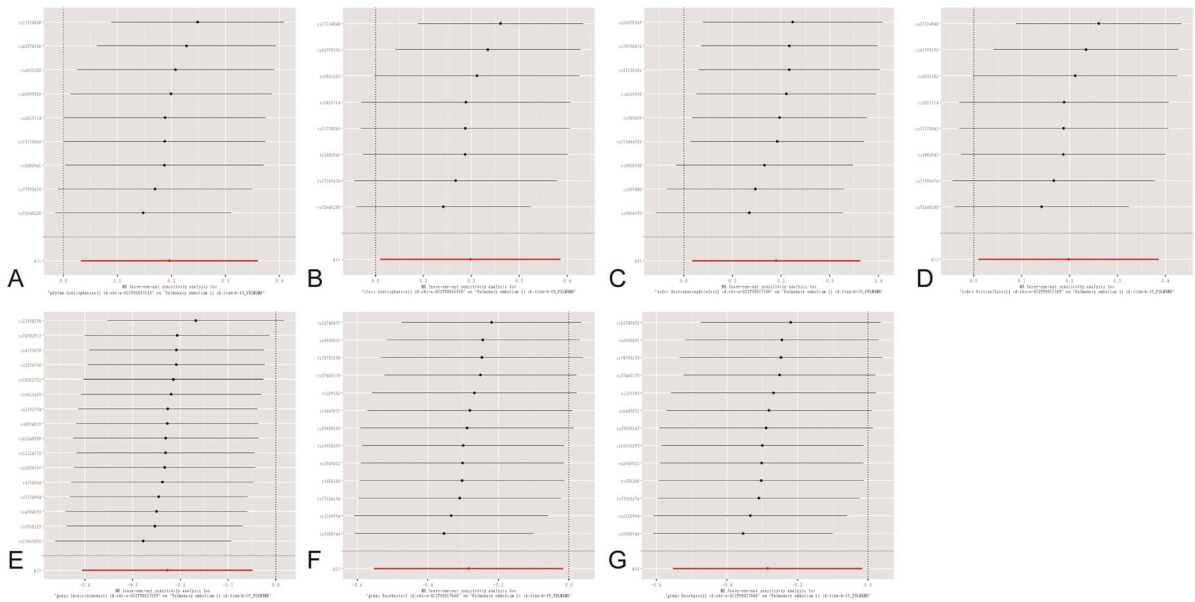


Figure 4. Leave-one-out plots for the causal association between gut microbiota and PE. (A) Phylum Lentisphaerae. (B) Class Lentisohartia. (C) Order Gastranaerophilales. (D) Order Victivallales. (E) Genus *Intestinimonas*. (F) Genus *Roseburia*. (G) Genus *R. gauvreauii*. MR, Mendelian randomization.

Table 3

Causal Estimations of Pulmonary Embolism on Gut Microbiota in the MR Analysis

Id. Outcome	Outcome	MR Method	Nsnp	β	SE	P	OR	95% CI
ebi-a-GCST90016918	Class Lentisphaeria id.2250	IVW	4	–0.071	0.048	0.140	0.931	0.848–1.024
		MR-Egger	4	0.022	0.332	0.953	1.023	0.533–1.961
		Weighted median	4	–0.106	0.062	0.087	0.900	0.797–1.016
		Weighted mode	4	–0.134	0.098	0.266	0.875	0.722–1.06
ebi-a-GCST90017115	Phylum Lentisphaerae id.2238	IVW	4	–0.074	0.052	0.150	0.928	0.839–1.027
		MR-Egger	4	0.074	0.352	0.852	1.077	0.54–2.147
		Weighted median	4	–0.115	0.062	0.061	0.891	0.79–1.005
		Weighted mode	4	–0.134	0.095	0.254	0.875	0.726–1.054
ebi-a-GCST90017100	Order Gastranaerophilales id.1591	IVW	4	0.019	0.052	0.713	1.020	0.92–1.13
		MR-Egger	4	0.511	0.250	0.178	1.667	1.021–2.722
		Weighted median	4	0.068	0.054	0.206	1.070	0.963–1.19
		Weighted mode	4	0.066	0.060	0.350	1.068	0.95–1.2
ebi-a-GCST90017109	Order Victivallales id.2254	IVW	4	–0.071	0.048	0.140	0.931	0.848–1.024
		MR-Egger	4	0.022	0.332	0.953	1.023	0.533–1.961
		Weighted median	4	–0.106	0.059	0.073	0.900	0.802–1.01
		Weighted mode	4	–0.134	0.090	0.234	0.875	0.734–1.043
ebi-a-GCST90017019	Genus *Intestinimonas* id.2062	IVW	4	0.030	0.033	0.366	1.030	0.966–1.099
		MR-Egger	4	–0.197	0.174	0.374	0.821	0.584–1.154
		Weighted median	4	0.033	0.037	0.371	1.033	0.962–1.111
		Weighted mode	4	0.032	0.050	0.566	1.033	0.936–1.139
ebi-a-GCST90017048	Genus *Roseburia* id.2012	IVW	4	0.009	0.026	0.731	1.009	0.959–1.062
		MR-Egger	4	–0.052	0.180	0.801	0.950	0.667–1.352
		Weighted median	4	0.006	0.028	0.842	1.006	0.952–1.062
		Weighted mode	4	0.002	0.035	0.961	1.002	0.936–1.073
ebi-a-GCST90017064	Genus *R. gauvreauii* id.11342	IVW	4	–0.026	0.041	0.529	0.974	0.899–1.056
		MR-Egger	4	–0.167	0.274	0.605	0.846	0.495–1.448
		Weighted median	4	–0.041	0.032	0.204	0.960	0.9–1.023
		Weighted mode	4	–0.049	0.038	0.287	0.953	0.885–1.026

β, Size effect of the association; CI, confidence interval; IVW, inverse variance weighted; MR, Mendelian randomization; Nsnp, number of single-nucleotide polymorphism; OR, odds ratio; SE, standard error.

The analysis indicated a causal relationship between the abundance of the phylum Lentisphaerae, class Lentisphaeria, order Gastranaerophilales, order Victivallales, genus *Intestinimonas*, genus *Roseburia*, and *R. gauvreauii* susceptibility to PE. There is a suggestive difference in the relative abundances of Lentisphaerae and Firmicutes at the phylum level, which holds valuable predictive potential for assessing susceptibility to PE. The phylum Firmicutes includes the orders Gastranaerophilales and Victivallales, and genera *Intestinimonas*, *Roseburia*, and *R. gauvreauii*. Firmicutes is one of the predominant bacterial phyla colonizing the intestine of healthy people. It possesses a series of genes related to fermenting dietary fiber and interacts with the intestinal mucosa, thereby maintaining intestinal homeostasis.[41,42] Our study demonstrated that susceptibility to PE decreased with an increased abundance of genera *Intestinimonas* and *Roseburia*. *Roseburia*, a probiotic, plays a positive role in attenuating inflammation in autoimmune diseases.[43] *Roseburia* is characterized by the production of propionate, which enhances gut mucosal growth, repairs compromised intestinal integrity, modulates immune function, and provides energy.[44–46] Accumulating evidence indicates the protective role of *Roseburia* in several diseases, including obesity, type 2 diabetes, allergy, and central nervous system diseases; thus, it could be considered indicative of health.[47] Moreover, the genus *Intestinimonas* has been reported to be beneficial in ischemic stroke.[19] Complementary findings from different databases collectively provide a more complete picture of this important association. Notably, Cen et al. analyzed the causal relationship between the gut microbiota and PE using the UK Biobank database and found that *Slackia*, *Oscillospira*, *Bacteroides*, and *Clostridium sensu stricto 1* may be linked to a decreased likelihood of developing PE.[48] However, in current study, we found that up to 7 microbiotas were nominally associated with PE, including genera *Intestinimonas*, *Roseburia*, and *R. gauvreauii*; phylum Lentisphaerae; class Lentisphaeria; and orders Gastranaerophilales and Victivallales. Moreover, genus *Intestinimonas* still had a protective effect on PE in the sensitivity analysis using FinnGen and pan-UKBB meta-analysis results for PE as the outcome. The sample size of our study was larger, and the results were more robust.

Based on these findings, interventions have been proposed to modulate the gut microbiota and reduce the risk of PE. First, formulations containing *Roseburia* and *Intestinimonas* could exploit their anti-inflammatory, gut barrier–repairing, and immunomodulatory effects. Second, increasing the intake of high-fiber foods to support the production of short-chain fatty acids by Firmicutes (e.g., *Roseburia*) improves gut integrity and reduces systemic inflammation. Additionally, in high-risk individuals, FMT from donors was enriched in *Roseburia* and *Intestinimonas* to restore a protective microbial profile.

Table 4

Sensitivity Analysis Using FinnGen and pan-UKBB Meta-analysis Results for PE as Outcome

Exposure	Nsnp	OR	95% CI	P
Phylum Lentisphaerae	9	1.081	0.978–1.196	0.127
Class Lentisphaeria	8	1.105	0.996–1.225	0.059
Order Gastranaerophilales	9	1.072	0.946–1.213	0.275
Order Victivallales	8	1.105	0.996–1.225	0.059
Genus *Intestinimonas*	17	0.878	0.807–0.954	0.002
Genus *Roseburia*	13	0.924	0.822–1.039	0.187
Genus *R. gauvreauii*	11	1.033	0.926–1.153	0.557

MR effects were estimated using the IVW method.

CI, confidence interval; MR, Mendelian randomization; Nsnp, number of single-nucleotide polymorphism; OR, odds ratio.

This study had several strengths. We performed the MR analysis acquired from the largest available GWAS meta-analysis to assess the causal relationship between gut microbiota and PE; to a certain extent, the interference of confounding factors and reversing causation on causal inference was excluded. Heterogeneity was detected and excluded using IVW and MR-Egger regressions to test the *Q* statistics. Potential horizontal pleiotropy was detected by using the MR-PRESSO test. Moreover, a reverse MR design was used to confirm that PE did not affect the flora abundance, indicating a true causal correlation.

Limitations

Nevertheless, this study had some limitations. Although the GWAS meta-analysis of the MiBioGen consortium for gut microbiota included more than 18,000 people of Euro-American, Middle Eastern, and East Asian ethnicities, there could be interference from population stratification. Only summary data were utilized in the present analysis, and conducting subgroup analyses, such as massive PE, submassive PE, and nonmassive PE, or exploring nonlinear relationships was not feasible. Future studies on the causal association between gut microbiota and PE should be considered in worldwide populations and subtype stratification for better generalizability and evaluation. Additionally, because microbiota-coagulation interactions are unclear, and there is a lack of standards for microbiota detection, there is hysteresis between microbiota modulation and thromboprophylactic effects. We will pursue a confirmatory exploration of these findings in future clinical studies.

Conclusion

In summary, this 2-sample MR study suggested that 7 gut microbiota, including the phylum Lentisphaerae, class Lentisphaeria, orders Gastranaerophilales and Victivallales, and genera *R. gauvreauii*, *Intestinimonas*, and *Roseburia*, were causally associated with PE.

Conflict of interest statement

The authors declare no conflict of interest.

Author contributions

He S conceived the study, completed the database search, screened and extracted data, and wrote the manuscript. Song R analyzed and interpreted the data. Li Z inspected and verified the data. Shi S revised the finished manuscript. Pang J provided suggestions on summarizations and statistical analysis. All authors have read and approved the final version of this manuscript.

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Ethical approval of studies and informed consent

This study used only publicly available data from studies involving human participants, with written informed consent and approval by their respective institutional ethics review committees.

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