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Causal Relationship between Chronic Obstructive Pulmonary Disease and Abdominal Aortic Aneurysm: A Mendelian Randomization Study

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Abstract

Background: Chronic Obstructive Pulmonary Disease (COPD) is a chronic inflammatory lung condition associated with significant morbidity and mortality. Observational studies indicate a positive correlation between COPD and the risk of abdominal aortic aneurysm (AAA), suggesting individuals with COPD are more likely to develop AAA. However, the causal relationship between COPD and AAA remains unclear. **Method:** This study employed a bidirectional Mendelian Randomization (MR) approach to assess the causal relationship between COPD and AAA. A two-step MR analysis was conducted to evaluate the mediating effect of 1400 circulating metabolites between COPD and AAA. Expression quantitative trait loci (eQTL) were sourced from the MRC Integrative Epidemiology Unit (MRC-IEU) database, and MR analysis was performed using the TwoSampleMR R package. The results were filtered using the Inverse Variance Weighted (IVW) method to identify genes strongly associated with both COPD and AAA. Furthermore, the Super Exact Test R package was utilized to determine the overlapping genes between COPD and AAA. Enrichment analysis for Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) was conducted using the clusterProfiler R package. Protein-protein interaction (PPI) analysis was carried out using STRING v12.0. **Results:** The IVW method indicated a causal relationship between the risk increase of COPD and AAA (OR: 1.47, 95% CI: 1.16 - 1.86, p = 0.001). Among 1400 circulating metabolites, plasma-free proline was identified as mediating the relationship between COPD and AAA, with a mediation effect proportion of −4.6% (95% CI: −9.032%, −0.164%, p = 0.042). Additionally, PPI analysis revealed 20 functionally interrelated genes mediating the linkage between COPD and AAA. KEGG enrichment analysis showed functional enrichment of these genes in the pathway of aldosterone synthesis and secretion. **Conclusion:** Our study supports a causal relationship between COPD and an increased risk of AAA. Specifically, plasma-free proline and pathways related to aldosterone synthesis and secretion may play key roles in the connection between COPD and AAA.

Keywords

COPD, Abdominal Aortic Aneurysm, Circulating Metabolites, Mendelian Randomization

1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) represents a prevalent and debilitating chronic lung condition characterized by persistent airflow limitation, leading to respiratory symptoms and functional impairment [1]. It encompasses clinical phenotypes such as chronic bronchitis and emphysema and stands as a leading cause of morbidity and mortality globally [2] [3]. COPD imposes a significant burden on healthcare systems and individuals, with symptoms including cough, sputum production, dyspnea, and reduced exercise tolerance [4]. Effective management of COPD involves pharmacological treatments, non-pharmacological interventions, and lifestyle modifications. Pharmacological treatments primarily include bronchodilators, such as beta-agonists and anticholinergics, and inhaled corticosteroids to reduce inflammation and prevent exacerbations [5]. Non-pharmacological interventions, including pulmonary rehabilitation and oxygen therapy, have been shown to improve the quality of life and exercise capacity in COPD patients [6]. Lifestyle changes, particularly smoking cessation, are critical in slowing disease progression and improving overall outcomes for patients with COPD [7]. Abdominal Aortic Aneurysm (AAA) is a potentially life-threatening vascular condition characterized by the local dilation of the abdominal aorta, which can lead to rupture and fatal bleeding [8]. Primarily affecting the elderly, the prevalence of AAA increases with age [9], with risk factors including smoking, being male, a family history, and atherosclerosis [10] [11].

Smoking is a major shared risk factor for both diseases, with a clear link between long-term smoking and increased incidence of COPD and AAA [12]. Furthermore, age, gender, and other cardiovascular diseases, such as hypertension and coronary artery disease, are considered common risk factors influencing the occurrence of COPD and AAA. The presence of these common risk factors may further complicate the association between COPD and AAA. Retrospective studies have explored the potential association between COPD and AAA [13]. For instance, Takagi, H *et al.* found that individuals with COPD had a higher risk of developing AAA compared to those without COPD [14]. Similarly, Xiong, J. *et al.* reported a significant association between the severity of COPD and the incidence of AAA [15]. However, retrospective studies are susceptible to potential confounders and selection biases, leading to uncertainty in this relationship [16]. Therefore, robust epidemiological methods are necessary to elucidate the causal relationship between COPD and AAA. Mendelian Randomization (MR) analysis, utilizing genetic variants as instrumental variables for exposures, offers a potent approach to assessing causality. MR analysis minimizes confounders and reduces the possibility of reverse causality, addressing limitations inherent in retrospective studies [17]-[19].

In this study, we conducted a bidirectional MR analysis to assess the causal relationship between COPD and AAA. A two-step MR was employed to evaluate the mediating effect of 1400 circulating metabolites between COPD and AAA. Additionally, Expression quantitative trait loci (eQTL) were sourced from the the MRC Integrative Epidemiology Unit (MRC-IEU) database, and results were filtered using the IVW method to identify disease-related overlapping genes. The forestploter R package was utilized for the visual representation of the findings through forest plots. Overlapping genes were further analyzed for gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG), as well as Protein-protein interaction (PPI) network analysis.

2. Method

2.1. Study Design and Genetic Instrument Selection

This study utilized summary statistics from publicly available Genome-wide association study (GWAS) datasets, predominantly focusing on European populations. Ethical approval and informed consent were obtained in the original studies. Valid instrumental variables (IVs) were selected based on their robust association with exposure, independence from confounding factors, and absence of effects on the outcome apart from the exposure itself. The criteria for selecting instrumental variables were as follows: Instrumental variables achieving genome-wide significance ($p < 5 \times 10^{-8}$), and ensured minimal linkage disequilibrium ($r^2 < 0.001$) within a clump window exceeding 10,000 kb to ensure independence. LD levels were estimated based on the European population from the 1000 Genomes Project [20]. To ensure a strong association between instrumental variables and the exposure, the F-statistic of single nucleotide polymorphisms (SNPs) was used to assess the strength of association, with an F-statistic > 10 indicating no bias from weak instrumental variables, calculated as F-statistic = $(\beta/SE)^2$.

2.2. Data Sources for Exposure, Mediators, and Outcomes

COPD data were obtained from the MRC-IEU (https://gwas.mrcieu.ac.uk/), with the GWAS ID being finn-b-J10_COPD, including 203,824 European individuals (6915 cases and 186,723 controls) and 16,380,382 SNPs. The 1400 circulating metabolites came from 8210 individuals of European ancestry. This dataset includes absolute concentrations of 1091 biomarkers and ratios of 309 biomarkers. Complete GWAS summary statistics for all 1091 blood metabolites and 309 metabolite ratios are directly downloadable from the NHGRI-EBI GWAS Catalog (https://www.ebi.ac.uk/gwas/), with the IDs ranging from GCST90199621 to GCST902010209. Furthermore, Data on abdominal aortic aneurysms were acquired from the NHGRI-EBI GWAS Catalog (https://www.ebi.ac.uk/gwas/), with the GWAS ID being GCST90080047, including 387,930 European individuals (1184 cases and 86,746 controls).

2.3. Statistical Analysis

Mendelian Randomization analysis was performed using R software (version 4.1.2, http://www.R-project.org) and the TwoSampleM packages [21]. The bidirectional causal relationship between COPD and abdominal aortic aneurysm was assessed primarily using the Inverse Variance Weighted (IVW) method. The IVW method assumes all instrumental variables are valid; any SNP not meeting this assumption introduces bias [22]. Hence, additional analyses were conducted using the Weighted Median and MR-Egger methods. The Weighted Median approach requires at least 50% of the SNPs to be valid [23], while MR-Egger regression provides an unbiased estimate even without considering pleiotropy among instrumental variable SNP. The MR-Egger intercept test was employed to evaluate pleiotropic associations between genetic variations and potential confounders [24]. Heterogeneity among SNPs was evaluated using Cochran's Q test and funnel plots [25]. The leave-one-out approach was used to determine if any specific SNP significantly altered the results by excluding SNPs one at a time [26]. A two-step Mendelian Randomization was used to assess the mediating effect of 1400 circulating metabolites between COPD and AAA, with MR-Egger methods employed to validate the robustness of the IVW results in the MR analysis.

2.4. Knowledge-Based Analysis

All eQTL data were retrieved from the MRC-IEU database (https://gwas.mrcieu.ac.uk/). Initially, association analyses were conducted, filtering data based on a P-value threshold of less than 5^{-8} to identify SNPs associated with the exposure factor. SNPs in linkage disequilibrium were excluded using a threshold of kb = 10,000 and $r^2 = 0.001$. Subsequently, data underwent F-testing to filter SNPs with an F-test value greater than 10, mitigating the impact of weak instrumental variables. MR analysis was then performed using the TwoSampleMR R package, filtering results with IVW < 0.05 to identify genes strongly associated with these diseases. The Super Exact Test R package was used to identify overlapping genes between COPD and AAA gene sets. Finally, the cluster profile R package was employed for GO and KEGG enrichment analysis. PPI analysis was conducted using STRING v12.0.

3. Results

The Mendelian Randomization analysis, employing the IVW model, revealed a significant genetic correlation between the risk of developing COPD and AAA (OR: 1.47, 95% CI: 1.16 - 1.86, p = 0.001). This finding underscores a causal link between COPD and an increased risk of AAA. The results from the MR-Egger model were consistent with those from the IVW model. Our analysis found no evidence of pleiotropy and heterogeneity in any exposures (Table 1).

Table 1. MR estimates of the effect of COPD on AAA.

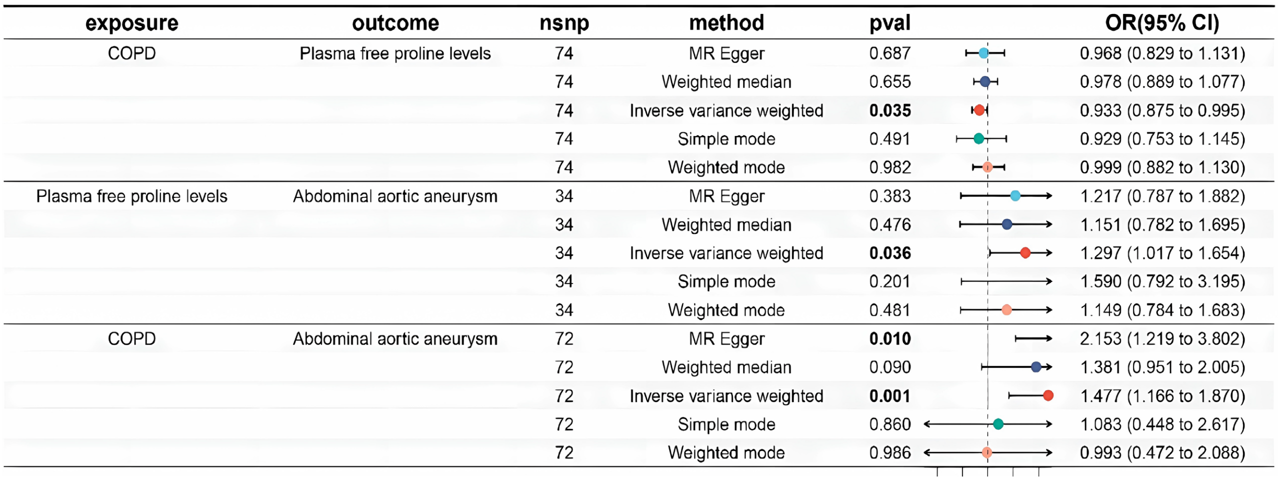
Outcome	method	OR (95% CI)	p	Q statistic	P-heterogeneity	Egger intercept	P-intercept
AAA	IVW	1.47 (1.16 – 1.86)	0.001	48.526	0.980		
	MR-Egger	2.15 (1.21 - 3.80)	0.010	46.485	0.986	−0.033	0.16
	Weighted median	1.38 (0.95 - 2.00)	0.089				
	Simple mode	1.08 (0.44 - 2.61)	0.860				
	Weighted mode	0.99 (0.47 - 2.08)	0.985				

However, the results indicate no significant genetic correlation between the risk of AAA and an increased risk of COPD (OR: 1.00, 95% CI: 0.96 - 1.04, p = 0.808). The consistency of results across different statistical models suggests that AAA does not significantly increase the risk of COPD, further validating the reliability of our conclusions (Table 2).

Table 2. MR estimates of the effect of AAA on COPD.

Outcome	method	OR (95% CI)	p	Q statistic	P-heterogeneity	Egger intercept	P-intercept
COPD	IVW	1.00 (0.96 - 1.04)	0.808	23.821	0.003		
	MR-Egger	0.97 (0.91 - 1.05)	0.609	21.927	0.002	0.015	0.462
	Weighted median	1.00 (0.96 - 1.03)	0.997				
	Simple mode	0.98 (0.93 - 1.04)	0.708				
	Weighted mode	1.00 (0.95 - 1.04)	0.995				

Among the 1400 analyzed circulating metabolites, plasma-free proline levels were significantly associated with both COPD and AAA (Figure 1). The mediation effect of COPD on AAA through plasma-free proline levels was significant, with a mediation proportion of 4.6% (95% CI: −9.032%, −0.164%, p = 0.042), suggesting that COPD may influence the development of AAA through this pathway (Table 3).



exposure	outcome	nsnp	method	pval	OR(95% CI)
COPD	Plasma free proline levels	74	MR Egger	0.687	0.968 (0.829 to 1.131)
		74	Weighted median	0.655	0.978 (0.889 to 1.077)
		74	Inverse variance weighted	**0.035**	0.933 (0.875 to 0.995)
		74	Simple mode	0.491	0.929 (0.753 to 1.145)
		74	Weighted mode	0.982	0.999 (0.882 to 1.130)
Plasma free proline levels	Abdominal aortic aneurysm	34	MR Egger	0.383	1.217 (0.787 to 1.882)
		34	Weighted median	0.476	1.151 (0.782 to 1.695)
		34	Inverse variance weighted	**0.036**	1.297 (1.017 to 1.654)
		34	Simple mode	0.201	1.590 (0.792 to 3.195)
		34	Weighted mode	0.481	1.149 (0.784 to 1.683)
COPD	Abdominal aortic aneurysm	72	MR Egger	**0.010**	2.153 (1.219 to 3.802)
		72	Weighted median	0.090	1.381 (0.951 to 2.005)
		72	Inverse variance weighted	**0.001**	1.477 (1.166 to 1.870)
		72	Simple mode	0.860	1.083 (0.448 to 2.617)
		72	Weighted mode	0.986	0.993 (0.472 to 2.088)

Figure 1. The potential causal evidence summarized from the MR analysis of Plasma-free proline levels.

Table 3. Mediated effect of COPD on AAA.

Exposure	Metabolite	outcome	Mediated effect	Mediated proportion
COPD	Plasma-free proline levels	Abdominal aortic aneurysm	−0.018 (−0.035, −6.4E−04)	−4.6% (−9.032%, −0.164%)

About 302 protein-coding risk genes within the genome were identified for COPD (136 upregulated and 174 downregulated) and 212 for AAA (126 upregulated and 86 downregulated). The overlapping genes were intersected, and Venn diagrams were created to illustrate these findings (Figure 2 and Figure 3). We assessed the gene overlap between the gene sets of COPD and AAA, eight genes were found to overlap between COPD and AAA, including TCL1A, PRKD2, BCL11A, ATP13A4, COPB1, ADARB1, LINC00243, and PARP8. The forestploter R package was used to visualize the results, producing forest plots (Figure 4 and Figure 5).

PPI analysis identified 20 functionally interrelated genes that mediate the connection between COPD and AAA (Figure 6). In the GO enrichment analysis, these shared genes showed functional enrichment in "peptidyl-serine phosphorylation" (Figure 7). In the KEGG enrichment analysis, these shared genes demonstrated functional enrichment in pathways related to "aldosterone synthesis and secretion" (Figure 8).

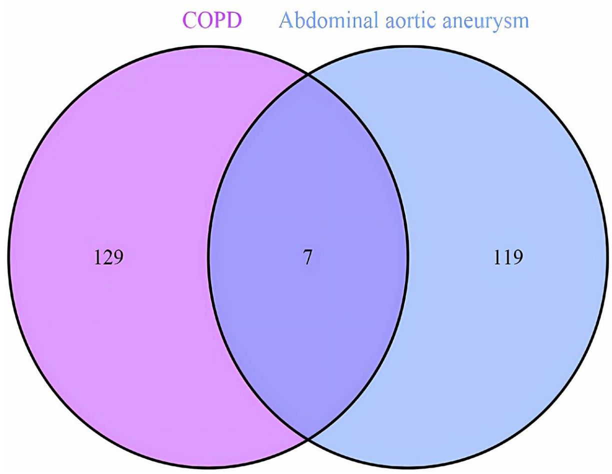


Figure 2. Venn diagram of up gene between COPD and AAA.

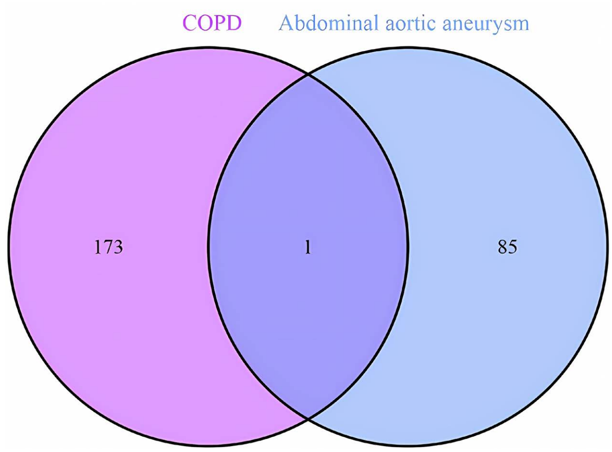


Figure 3. Venn diagram of down gene between COPD and AAA.

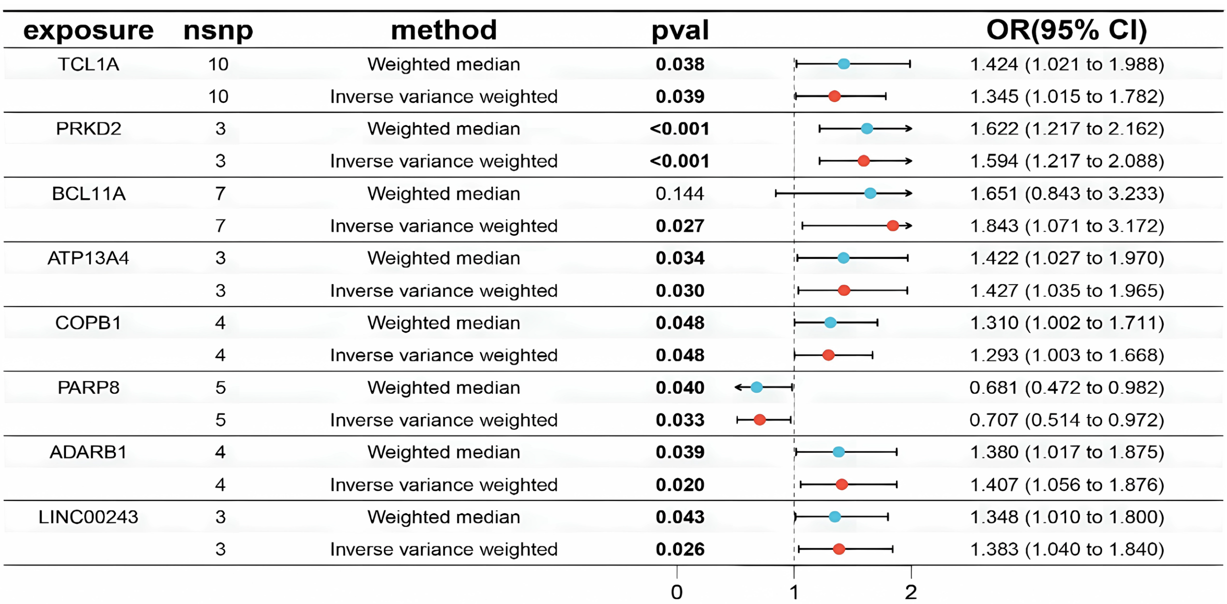
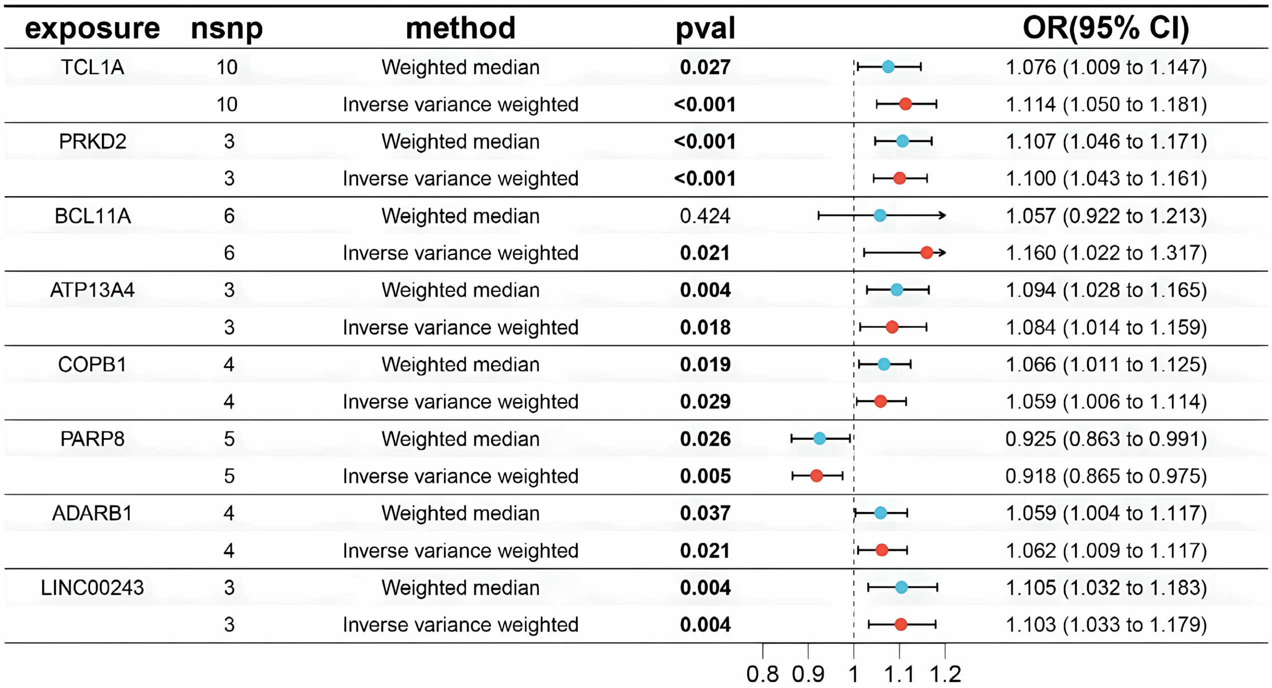


Figure 4. The causal effects of the risk gene on COPD.



exposure	nsnp	method	pval	OR(95% CI)
TCL1A	10	Weighted median	**0.027**	1.076 (1.009 to 1.147)
	10	Inverse variance weighted	**<0.001**	1.114 (1.050 to 1.181)
PRKD2	3	Weighted median	**<0.001**	1.107 (1.046 to 1.171)
	3	Inverse variance weighted	**<0.001**	1.100 (1.043 to 1.161)
BCL11A	6	Weighted median	0.424	1.057 (0.922 to 1.213)
	6	Inverse variance weighted	**0.021**	1.160 (1.022 to 1.317)
ATP13A4	3	Weighted median	**0.004**	1.094 (1.028 to 1.165)
	3	Inverse variance weighted	**0.018**	1.084 (1.014 to 1.159)
COPB1	4	Weighted median	**0.019**	1.066 (1.011 to 1.125)
	4	Inverse variance weighted	**0.029**	1.059 (1.006 to 1.114)
PARP8	5	Weighted median	**0.026**	0.925 (0.863 to 0.991)
	5	Inverse variance weighted	**0.005**	0.918 (0.865 to 0.975)
ADARB1	4	Weighted median	**0.037**	1.059 (1.004 to 1.117)
	4	Inverse variance weighted	**0.021**	1.062 (1.009 to 1.117)
LINC00243	3	Weighted median	**0.004**	1.105 (1.032 to 1.183)
	3	Inverse variance weighted	**0.004**	1.103 (1.033 to 1.179)

Figure 5. The causal effects of the risk gene on AAA.

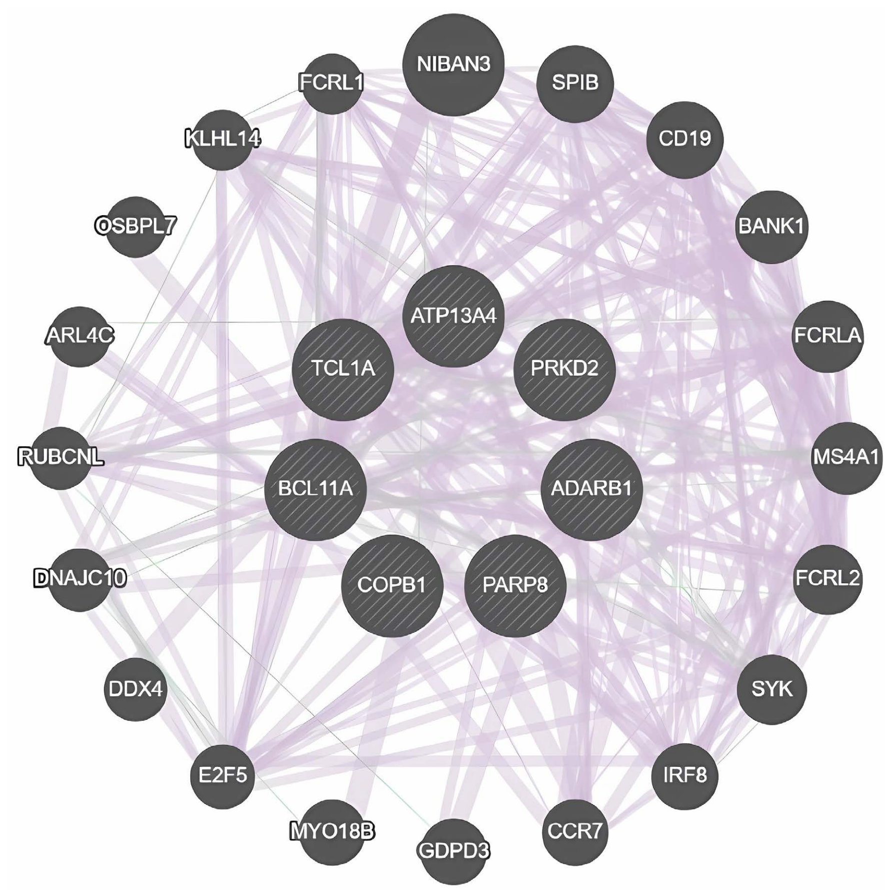


Figure 6. Protein-protein interactions among the risk genes shared between COPD and AAA.

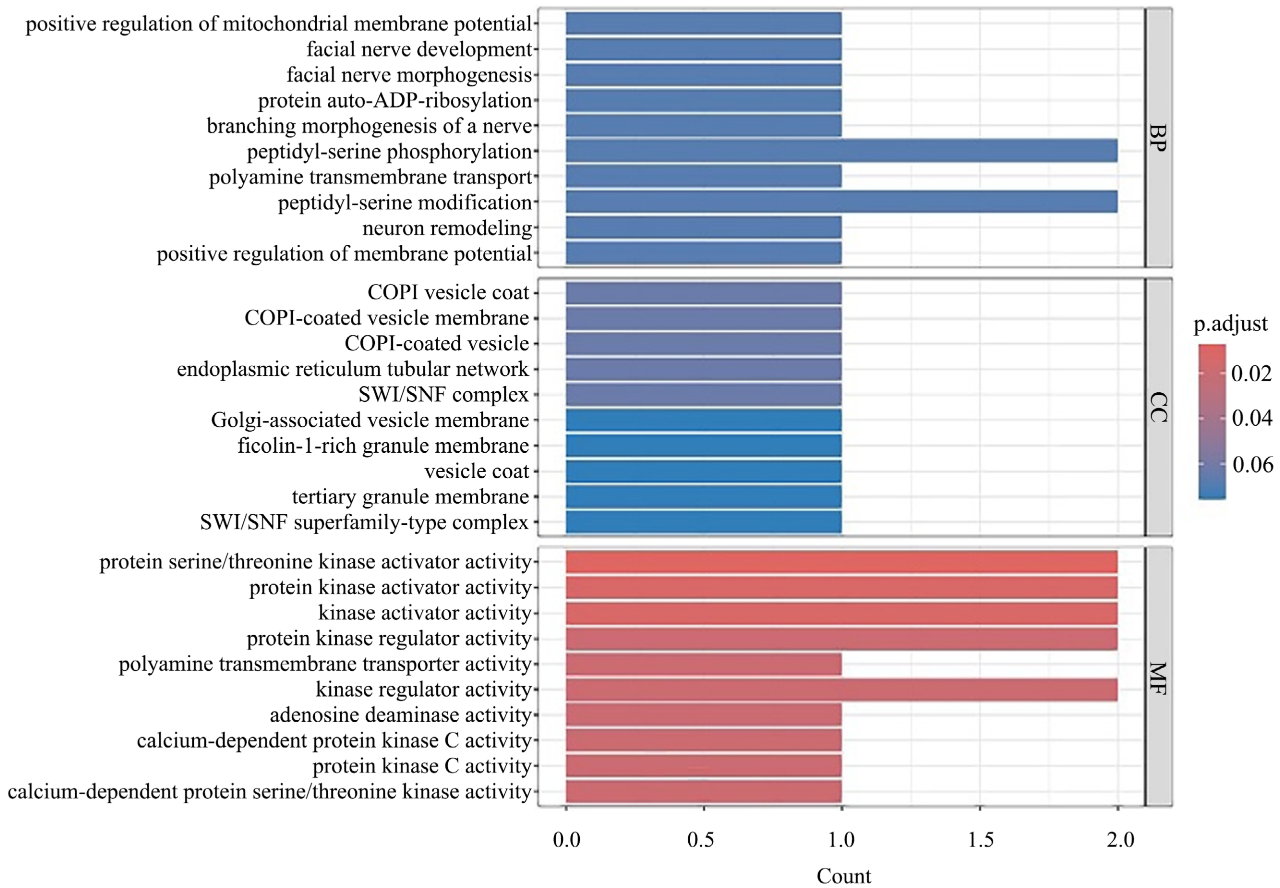


Figure 7. GO among the risk genes shared between COPD and AAA.

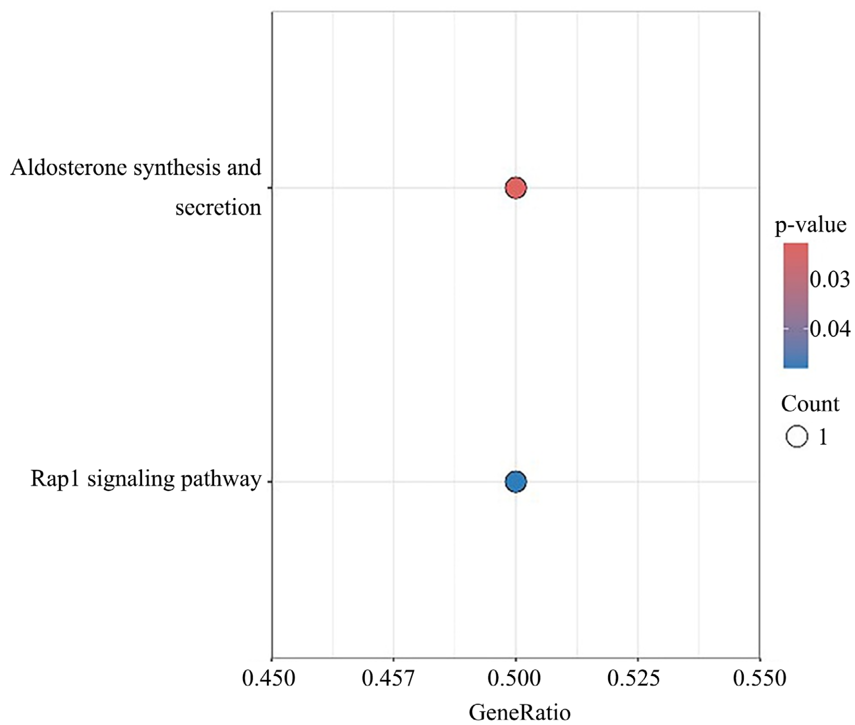


Figure 8. KEGG among the risk genes shared between COPD and AAA.

4. Discussion

This study elucidated the causal relationship between COPD and AAA through bidirectional Mendelian Randomization. We support a causal association between COPD and an increased risk of AAA. However, AAA does not significantly increase the risk of COPD. Moreover, our analysis indicates the effect of COPD on AAA through a reduction in plasma free proline levels, unveiling a potential mechanistic pathway linking the two conditions. Additionally, our study identified 20 functionally interrelated genes that mediate the link between COPD and AAA, demonstrating functional enrichment in pathways related to aldosterone synthesis and secretion.

Consistent with previous epidemiological studies, such as that by Sakamaki, F. *et al.* [27], which reported an increased risk of AAA among patients with COPD. Furthermore, research by Lindholt, J. *et al.* [28] also indicated a higher incidence of AAA among COPD patients compared to non-COPD patients. Recent studies suggest an association between proline levels and vascular structural changes [29] [30], indicating that plasma-free proline might increase the risk of AAA through alterations in inflammatory pathways or vascular structure. Furthermore, Liu *et al.* found that mineralocorticoid receptor agonists combined with a high salt diet induced the formation and rupture of abdominal and thoracic aortic aneurysms in mice. The use of mineralocorticoid receptor antagonists, such as spironolactone or eplerenone, significantly reduced these factors-induced aortic aneurysms, suggesting a potential role for aldosterone in the pathogenesis of aortic aneurysms [31]. However, direct studies on the effects of proline on aldosterone synthesis and secretion are lacking.

In the bidirectional Mendelian Randomization approach, this study provides novel evidence for the potential causal relationship between COPD and AAA. Moreover, we identified plasma-free proline as a potential mediated factor linking COPD with AAA. These findings offer new insights into the potential mechanisms underlying the association between these two diseases, crucial for understanding the complex interplay between chronic respiratory diseases and cardiovascular conditions. By elucidating the involved mechanistic pathways, clinicians can better identify high-risk patients and implement intervention measures to reduce the risk of AAA in this population.

However, this study has some limitations: Firstly, our analysis relies on GWAS data from European populations, which may limit the generalizability of our findings to other racial groups. Secondly, MR studies have inherent limitations, such as potential interactions between genes and environment that may affect the accuracy of causal inference, and measurement errors in genotype data that could impact result precision. Thirdly, If a genetic variant affects multiple traits (*i.e.*, pleiotropy), and some of these traits are associated with the exposure and outcome, it can introduce bias. Future research should consider replicating this study in diverse racial and ethnic groups to assess the universality and applicability of these results. Additionally, experimental studies are recommended to explore the exact role of proline metabolism in the progression from COPD to AAA.

5. Conclusion

In conclusion, this study supports a causal relationship between COPD and an increased risk of AAA. Specifically, our findings highlight the key role of plasma-free proline and pathways related to aldosterone synthesis and secretion in the link between COPD and AAA. This discovery emphasizes the importance of managing AAA risk among COPD patients and points to plasma-free proline as a potential biomarker, offering new perspectives for future prevention and treatment strategies.

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Data Availability Statement

Please contact the corresponding author for additional inquiries.

Ethics Statement

Because the GWAS data are accessible to the general public, ethical approval was not necessary.

Consent for Publication

All authors approved the submitted version.

Conflicts of Interest

The authors declare that they have no competing interests.

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