

# Association Between Platelet Indices and Risk of Chronic Obstructive Pulmonary Disease: A Bidirectional Mendelian Randomization Study

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**Introduction:** Platelet indices are associated with chronic obstructive pulmonary disease (COPD), their causal relationship remains unclear. This study aims to explore the causal relationship between four common platelet indices and COPD using Mendelian randomization (MR), including platelet count (PLT), plateletcrit (PCT), mean platelet volume (MPV), and platelet distribution width (PDW).

**Methods:** We analyzed summary statistics from European-ancestry genome-wide association studies (GWAS) for platelet indices (UK Biobank, n=408,112) and COPD (FinnGen, n=433,208). MR analyses were performed using Inverse Variance Weighting (IVW), MR Egger (ME), Simple Mode (SM), Weighted Median (WMe), and Weighted Mode (WMo). Heterogeneity between SNPs was assessed using Cochran's Q test in combination with a random-effects IVW approach. MR-Egger intercept test and MR-PRESSO analysis demonstrate horizontal pleiotropy. Leave-one-out analysis to assess outlier-driven bias.

**Results:** IVW analysis indicated that higher PLT was suggestively associated with increased COPD risk (OR = 1.054, 95% CI = 1.005–1.056,  $p = 0.029$ , FDR = 0.116). In the reverse direction, COPD was suggestively associated with increased PCT (OR = 1.025, 95% CI = 1.003–1.048,  $p = 0.024$ , FDR = 0.096). No significant associations were observed for MPV or PDW. Sensitivity analyses confirmed the robustness of results, with no signs of pleiotropy or reverse causality.

**Conclusion:** Our bidirectional MR analysis found no definitive causal relationship between platelet indices and COPD, but observed suggestive associations between higher PLT/PCT and an increased risk of COPD. These findings warrant further investigation into the roles of platelet indices in COPD pathogenesis and their potential as biomarkers or therapeutic targets.

**Keywords:** platelet count, plateletcrit, mean platelet volume, platelet distribution width, chronic obstructive pulmonary disease, mendelian randomization

## Introduction

COPD is a progressive pulmonary disorder characterized by persistent airflow resistance and chronic inflammation,<sup>1</sup> emerging as the third leading cause of death globally.<sup>2</sup> The rising prevalence of COPD, due to aging populations, insufficient tobacco control, and environmental pollution, results in substantial socioeconomic burden.<sup>3</sup>

In recent years, there has been increasing interest in using accessible blood biomarkers to improve the diagnosis and prognosis of COPD. Among these biomarkers, platelet indices are promising tools for the evaluation and monitoring of disease progression. Platelet alterations are known to be associated with the incidence and development of COPD. Platelets also regulate various biological processes, including inflammation, endothelial dysfunction, and immunomodulation. It may contribute to COPD pathogenesis by regulating immune responses and thrombosis pathways.<sup>4,5</sup> Platelets regulate immune responses by

interacting with leukocytes in different pathological and physiological processes such as inflammation, tissue remodeling, and autoimmune diseases, thereby influencing the pathogenesis of respiratory diseases, such as COPD, asthma, etc.<sup>6</sup> The release of platelet-derived cytokines (eg, platelet factor 4, transforming growth factor- $\beta$ ) or microvesicles that regulate vascular permeability contribute to the inflammatory regression process by promoting the synthesis of pro-regressive mediators while decreasing pro-inflammatory mediators, making platelets a key player in inflammatory diseases such as pneumonia and acute respiratory distress syndrome.<sup>7</sup> Thrombospondin (TSP-1) interaction with integrin-mediated adhesion leads to COPD exacerbations.<sup>8</sup>

Current clinical data analysis has found that platelet counts and platelet-to-lymphocyte ratios may reflect the neutrophil inflammatory response during COPD exacerbations.<sup>9</sup> PDW can be used as a diagnostic marker for COPD with pulmonary hypertension (95% CI: 1.052–1.454,  $r = 1.237$ ,  $p < 0.05$ ).<sup>10</sup> PDW and MPV are risk factors for COPD with secondary erythrocytosis.<sup>11</sup> Thrombocytopenia and high MPV predict mortality in patients with COPD.<sup>12,13</sup> However, the causal nature of this relationship remains unclear. Bidirectional Mendelian Randomization (MR) offers a powerful framework for assessing causality by utilizing genetic variants as instrumental variables.<sup>14–16</sup> MR results in more reliable causal estimates by minimizing confounding bias (e.g smoking, air pollution, or cardiovascular comorbidities) and reverse causation.<sup>17,18</sup> To further validate causality, we tested the opposite direction (from COPD to platelet indices), as platelet alterations may be secondary to COPD-related inflammation or hypoxia, rather than causality. This analysis will strengthen the inference of one-way effects.

In this study, we performed bidirectional MR to investigate the genetic causal relationship between common platelet indices and COPD risk as well as their directional influence. These findings provide insights into the potential application of platelet indices for early diagnosis, prevention, and treatment of COPD.

## Methods

### Study Design

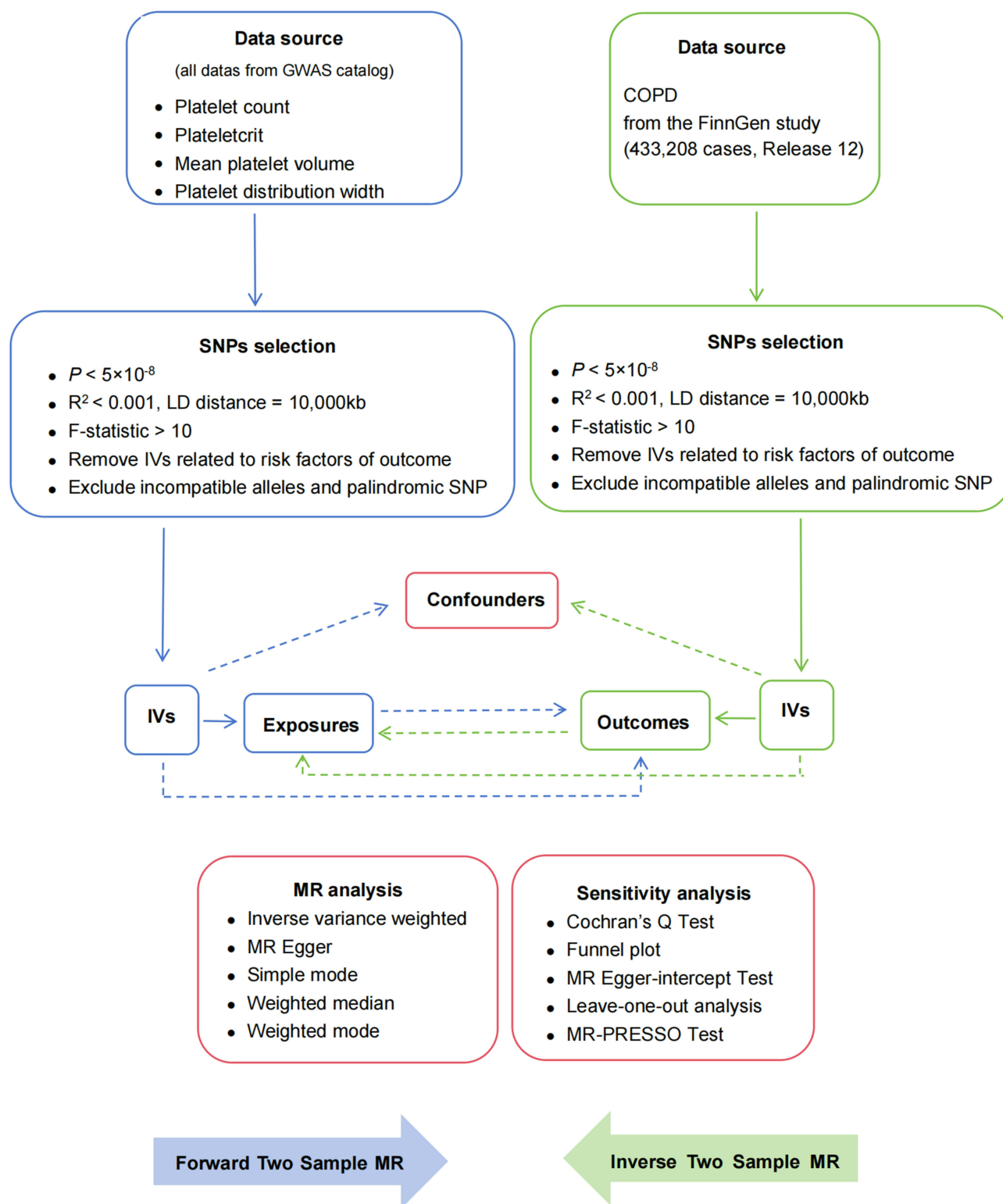
A bidirectional two-sample MR study was conducted to investigate the causal relationship between platelet indices and COPD using single-nucleotide polymorphisms (SNPs) as instrumental variables (IVs). MR analysis relies on three fundamental assumptions: 1) genetic instruments must be highly associated with exposure; 2) genetic instruments should not be linked to confounding factors; and 3) genetic instruments must affect the outcome only through exposure.<sup>15,19,20</sup> These assumptions ensure the validity and reliability of the causal inferences derived from the MR analyses. The overall design of the MR used in this study is illustrated in [Figure 1](#).

### Date Sources

Summary statistics of platelet indices were obtained from the MRBase GWAS catalog within the EBI GWAS.<sup>21</sup> Four indices (PLT, PCT, PDW, and MPV) associated with platelet phenotypes were used as the exposure factors (<https://gwas.mrcieu.ac.uk/>). COPD data were sourced from the latest version (Release 12) of the FinnGen study (<https://www.finnngen.fi/>), which included correlated genetic data from 500,000 Finnish biobank samples.<sup>22</sup> The platelet indices and COPD datasets were derived from European-ancestry GWAS studies in the UK Biobank and FinnGen to minimize potential population stratification bias. The UK Biobank and FinnGen are two independent samples.<sup>23</sup> No additional ethical approval was required as publicly available summary-level data were used. Detailed GWAS information is listed in [Table 1](#). The number of eligible SNPs that were significantly associated with each exposure variable (platelet indices or COPD) is presented in [Supplementary Tables S1](#) and [S2](#).

### Genetic IVs Selection

SNPs associated with exposure factors were selected based on their genome-wide significance ( $p < 5 \times 10^{-8}$ ). To account for linkage disequilibrium (LD), SNPs were selected using an  $R^2$  threshold of  $< 0.001$  and a clumping distance of 10,000 kb. To reduce weak instrument bias, the F-statistic was calculated using the formula ( $F = \beta^2/se^2$ , with  $\beta$  and  $se$  as allelic effect value and standard error, respectively) for each instrumental variable (IV), and  $F > 10$  indicates a strong association between the IV and exposure.<sup>24</sup> Additionally, incompatible alleles and palindromic SNPs with intermediate allele frequencies were removed to avoid potential bias. Finally, SNPs associated with potential confounders were excluded using the PhenoScanner V2 (<http://www.phenoscaner.medschl.cam.ac.uk/>).<sup>25</sup>



**Figure 1** Overview of the study design.

**Abbreviation:** SNPs, single-nucleotide polymorphisms.

**Table 1** Characteristics of GWAS Used in This Study

GWAS ID	Trait	Population	Sample size	Number of SNPs	Year	PMID
Ebi-a-GCST90002395	Mean platelet volume	European	408,112	40,299,375	2020	32888494
Ebi-a-GCST90002400	Plateletcrit	European	408,112	40,299,196	2020	32888494
Ebi-a-GCST90002401	Platelet distribution width	European	408,112	40,300,122	2020	32888494
Ebi-a-GCST90002402	Platelet count	European	408,112	40,299,783	2020	32888494
Finngen_R12_J10_COPD	COPD	European	433,208	-	2024	-

## Allele Harmonization Process

SNPs with ambiguous strand alignment (A/T or C/G) and intermediate allele frequency (MAF > 0.40) are excluded to avoid coordination errors. For the missing instrumental SNPs in the result dataset, we identified the proxy SNPs with a high LD ( $r^2 \geq 0.80$ ) using the 1000 Genomes European Reference Panel. The agent SNP with the strongest LD is replaced. Use the TwoSampleMR R software package to cross-check effect alleles and frequencies between datasets and manually verify all harmonized SNPs. Strand flipping: Use allele frequency agreement checks to flip non-palindromic SNPs with mismatched strands to the forward strand.

## Statistical Analysis

“TwoSampleMR” R package was used for MR analysis, employing methods such as Inverse Variance Weighted (IVW), MR Egger (ME), Simple Mode (SM), Weighted Median (WMe), and Weighted Mode (WMo).<sup>26–28</sup> The MR Steiger directionality test was conducted to determine the correctness of the causal effects. The fixed-effect IVW method was accepted as the primary approach for two-sample MR analysis. The MR correlation analysis employed the Benjamini-Hochberg method for multiple testing correction to generate false discovery rate (FDR)-adjusted p-values (Benjamini and Hochberg, 1995). The analysis also reported unadjusted raw p-values. Significant correlations were identified when both raw and FDR-adjusted p-values are less than 0.05. In cases where raw  $p < 0.05$  but FDR-adjusted  $p > 0.05$ , it is considered as a suggestive association between two factors.<sup>29</sup>

Heterogeneity among SNPs was assessed using Cochran’s Q test. When heterogeneity ( $Q_p > 0.05$ ) was observed, the fixed-effects IVW method was applied. Otherwise, the random effects IVW method was used.<sup>30,31</sup> The MR-Egger method and “leave-one-out” analyses were performed to evaluate the potential outlier bias.<sup>31</sup> The Mendelian randomized pleiotropic residuals and outliers (MR-PRESSO) analysis was performed using the “MRPRESSO” package to assess horizontal pleiotropy and remove influential outliers. After excluding significant outliers, the Mendelian randomization estimate was recalculated.<sup>32</sup> All statistical analyses were performed using R statistical software (version 4.3.2).

## Results

### The Causal Effects of Platelet Indices on COPD

#### Selection of IVs

To mitigate the potential influence of confounding factors, the IVs for all platelet indices significantly associated with COPD were strictly selected based on a threshold of  $p < 5 \times 10^{-8}$ . For univariate MR analysis determining the relationship between PLT and COPD, 976 SNPs were identified. Following integration with the COPD dataset and subsequent exclusion of incompatible alleles and palindromic SNPs (467 SNPs removed) and 21 confounding factors, 488 SNPs were obtained ( $F$ -statistics: 37.50–99.13, median: 64.22). Using the same strategies, the 914 SNPs initially identified in PCT were refined to 457 SNPs ( $F$ -statistics: 42.67–99.85, median: 66.66). Similarly, MPV and PDW analyses yielded 453 SNPs ( $F$ -statistics: 38.88–99.71, median: 80.62) and 391 SNPs ( $F$ -statistics: 39.76–99.45, median: 66.30), respectively.

In this study, instrumental variables were selected for all platelet indices with  $F$ -statistics > 10 as the threshold, minimizing the risk of weak instrument bias and thereby strengthening the validity of the analytical findings. Furthermore, all SNPs potentially associated with outcome risk factors were excluded from the analysis.

## Two-Sample MR Analysis results

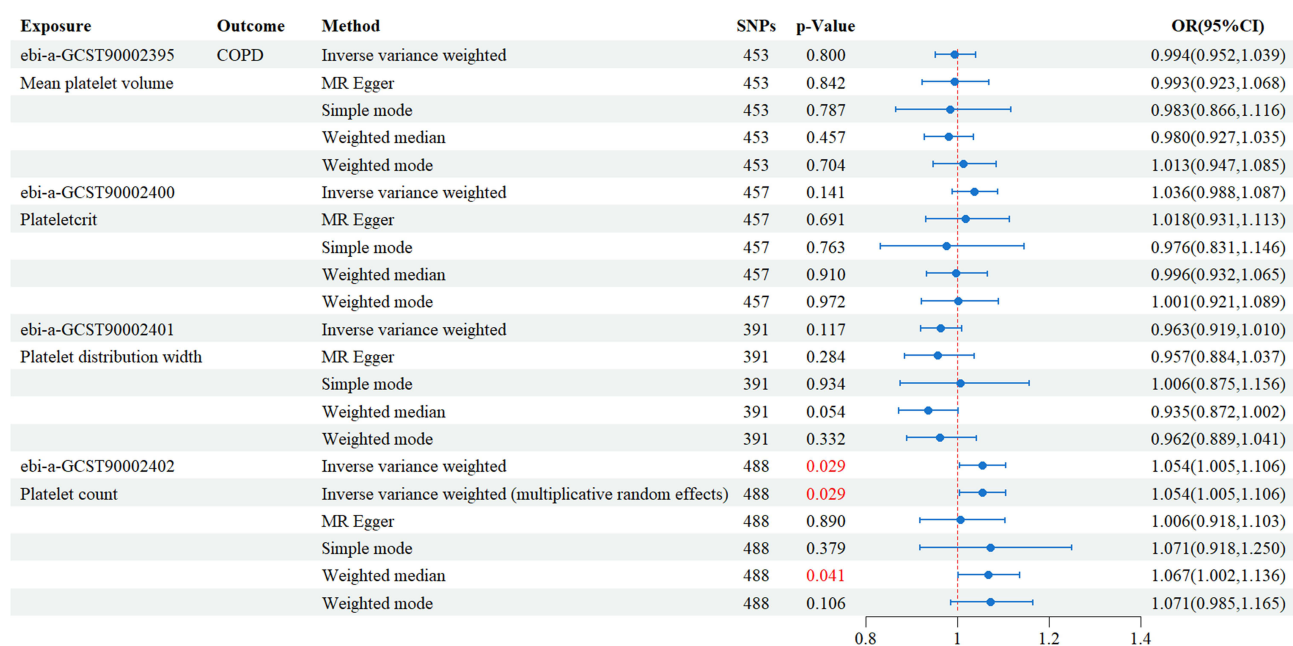
Two-sample MR analysis revealed a significant association between PLT count and COPD risk (IVW: odds ratio [OR] = 1.054, 95% CI = 1.005–1.056,  $p = 0.029$ ). After FDR correction of the obtained  $p$ -value of 0.029, the  $p$ -value was 0.116, which was not statistically significant, suggesting that PLT is a potential risk of COPD. Notably, analysis using all MR methods showed consistent directionality in their  $\beta$  values, suggesting that elevated PLT levels increased the risk of COPD. In contrast, no significant association was observed between COPD and other platelet indices including PCT (IVW: OR = 1.036, 95% CI = 0.988–1.087,  $p = 0.141$ ), PDW (IVW: OR = 0.963, 95% CI = 0.919–1.010,  $p = 0.117$ ), and MPV (IVW: OR = 0.994, 95% CI = 0.952–1.039,  $p = 0.800$ ). The results are shown in [Figure 2](#).

## Results of Sensitivity Analysis

For sensitivity analysis, both Cochran's Q test revealed significant heterogeneity among platelet indices ( $p < 0.05$ ). To address this heterogeneity and enhance the accuracy of data analysis, the multiplicative random-effects IVW model was employed ( $p < 0.05$ ), which effectively eliminated the observed heterogeneity ([Supplementary Table S3](#)). In addition, the MR-PRESSO global pleiotropy test and the MR-Egger intercept test showed no evidence of significant horizontal pleiotropy ( $p > 0.05$ ; [Table 2](#)).

The relationships between platelet indices and COPD were further visualized using scatter plots ([Figure 3A](#)), funnels ([Figure 3B](#)), and forest plots ([Supplementary Figure S1](#)). Scatter plots were particularly useful for assessing the strength of the association between selected IVs and outcomes. A clear linear trend in the scatter plot distribution indicated a strong linear relationship between the PLT and COPD risk.

The robustness of the IVW results was confirmed by leave-one-out analysis, in which the sequential exclusion of individual SNPs yielded results consistent with the overall causal effect estimates derived from the IVW method ( $p < 0.05$ ). Furthermore, the symmetry observed in the funnel plots of PLT and COPD suggested that pleiotropy did not significantly influence the analysis. Finally, leave-one-out analysis demonstrated that the causal relationship between platelet indices and COPD was not driven by a single SNP ([Supplementary Figure S2](#)).



**Figure 2** MR results of relationship between platelet indices and onset of COPD.

**Abbreviations:** SNPs, single-nucleotide polymorphisms; OR, odds ratio; CI, confidence interval.

**Table 2** MR-Egger Regression Analysis and MR-PRESSO Analysis of IVs for Platelet Indices (Exposures) and COPD (Outcome)

Exposure	Outcome	Egger_Intercept	Egger_Standard Error	Egger_P	MR-PRESSO.Global.Test_P
Ebi-a-GCST90002395(MPV)	COPD	8.38E-05	0.001	0.951	0.808
Ebi-a-GCST90002400(PCT)		0.001	0.001	0.641	0.136
Ebi-a-GCST90002401(PDW)		0.000	0.001	0.853	0.972
Ebi-a-GCST90002402(PLT)		0.002	0.001	0.240	0.762

**Abbreviations:** MPV, Mean platelet volume; PCT, Plateletcrit; PDW, Platelet distribution width; PLT, Platelet count.

## The Causal Effects of COPD on Platelet Indices

### Selection of IVs

Based on the three core assumptions of the MR two-sample analysis, 23 (F-statistics ranging from 30.62 to 369.53) of 92 SNPs (65 SNPs were removed from linkage imbalance and palindromic alleles, and 4 confounding factors) were selected for subsequent analysis, where COPD was treated as exposure and platelet indices as outcomes.

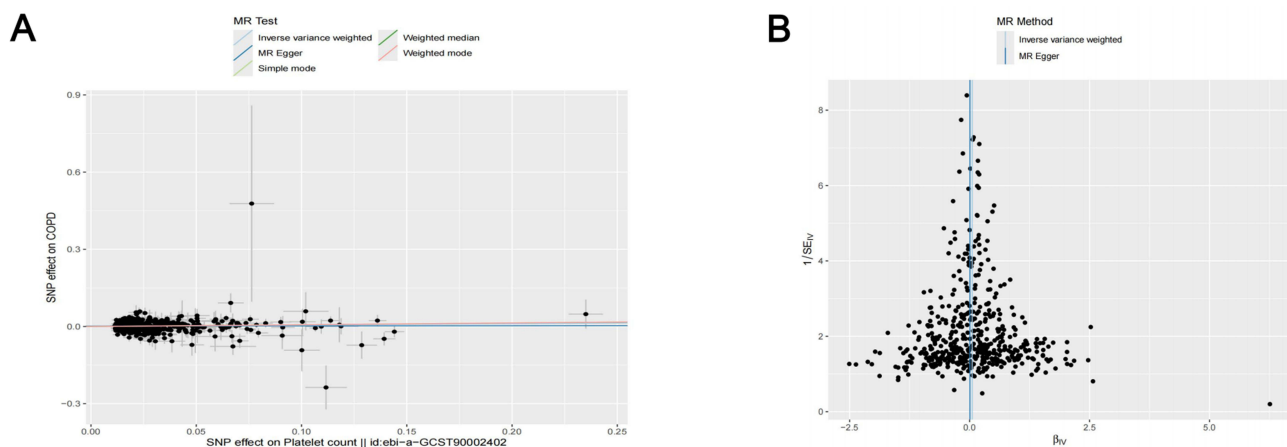
### Two-Sample MR Analysis Results

The causal effect of COPD on platelet indices was evaluated using five MR methods, as shown in Figure 4. The IVW method revealed no significant associations between COPD and PLT, MPV, or PDW ( $p > 0.05$ ). However, a minor causal relationship was identified between PCT and COPD (IVW, OR = 1.025; 95% CI, 1.003–1.048;  $p = 0.024$ ). Subsequently, the  $p$ -value of 0.024 was corrected by FDR for the given  $p$ -value using the Benjamini-Hochberg (BH) method, and the  $p$ -value was 0.096, suggesting that PCT is a potential downstream influencing factor for COPD. Moreover, all MR methods demonstrated consistent directional effects (Figure 4).

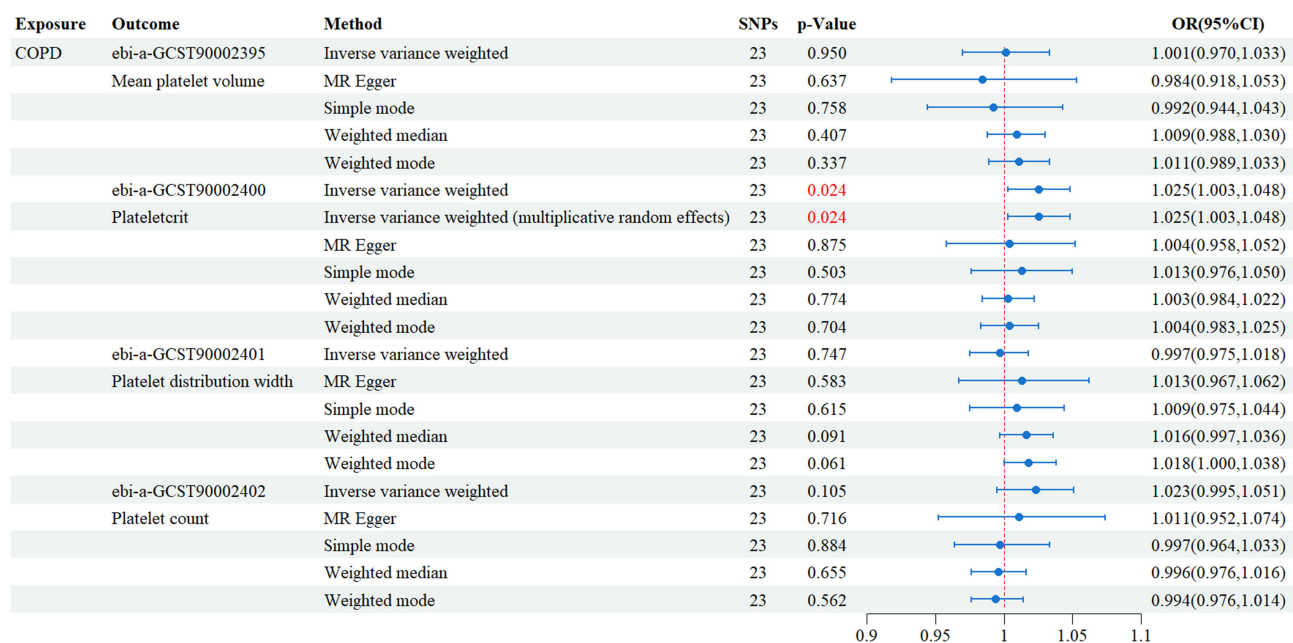
### Sensitivity Analysis Results

Sensitivity analysis revealed heterogeneity in the relationship between COPD and PCT, as evidenced by Cochran's Q test ( $p < 0.05$ ). The random-effects IVW model effectively eliminated observed heterogeneity ( $p < 0.05$ , Supplementary Table S4). In addition, the MR-PRESSO global pleiotropy test and the MR-Egger intercept test showed no significant evidence of horizontal pleiotropy in the COPD-PCT relationship ( $p > 0.05$ , Table 3).

The relationships between COPD and platelet indices were further visualized using forest plots (Figure 5A), scatter plots (Figure 5B), and funnel plots (Figure 5C). The scatter plots showed a strong linear association between IVs and outcomes, as indicated by the clear linear trend in the data point distribution, suggesting a significant linear relationship between COPD exposure and PCT.



**Figure 3** Causal effects of PLT on COPD. (A) Scatter plot of PLT on COPD. (B) Funnel plot for precision of the estimate.



**Figure 4** Results of inverse Two-sample Mendelian Randomization analysis.

**Abbreviations:** SNPs, single-nucleotide polymorphisms; OR, odds ratio; CI, confidence interval.

The symmetrical distribution of the funnel plots for COPD and PCT further supported the absence of significant pleiotropic effects in our analysis. Additionally, leave-one-out analysis demonstrated that the identified causal relationship between platelet indices and COPD was not driven by a single SNP (Figure 5D).

## Discussion

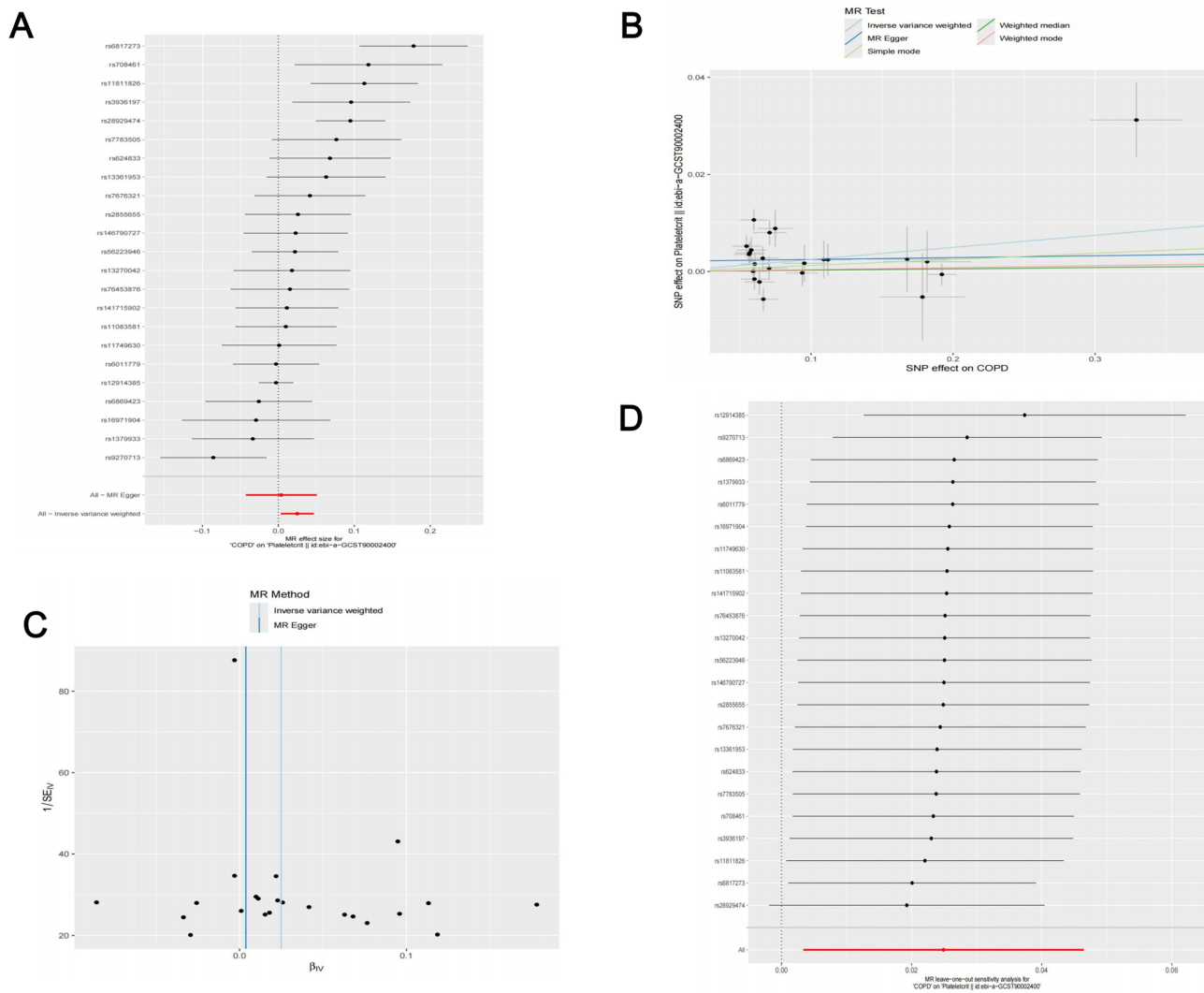
In this study, we employed a bidirectional Mendelian Randomization (MR) analysis to investigate the causal relationships between common platelet indices and COPD in European populations. We observed suggestive, but not definitive, evidence that higher PLT may increase COPD risk, and that COPD may increase PCT. No significant associations were found for MPV or PDW.

Exploring platelet index changes in COPD is beneficial for understanding underlying pathophysiological mechanisms. Platelet activation in COPD is primarily caused by chronic inflammation and endothelial dysfunction leading to hypercoagulation. Activated platelets change shape and release pro-inflammatory cytokines and mediators, mediating endothelial adhesion of circulating white blood cells and leading to endothelial cell dysfunction and disease progression in patients.<sup>33</sup> Our findings align with and expand upon previous research, providing further insights into the complex relationship between platelet indices and COPD. For instance, Ahamed et al found that PLT levels were positively correlated with COPD severity,<sup>34</sup> suggesting that elevated PLT levels may play a role in COPD disease progression. Thus, PDW may serve as a prognostic marker for patients with COPD and pulmonary arterial hypertension.<sup>10</sup> Other studies have identified lower MPV in patients with COPD, with MPV levels increasing during the recovery phase.<sup>35</sup>

**Table 3** MR-Egger Regression Analysis and MR-PRESSO Analysis of IVs for COPD (Exposure) and Platelet Indices (Outcomes)

Exposure	Outcome	Egger Intercept	Egger Standard Error	Egger P	MR-PRESSO.Global.Test P
COPD	Ebi-a-GCST90002395(MPV)	0.002	0.003	0.573	0.122
	Ebi-a-GCST90002400(PCT)	0.002	0.002	0.326	0.569
	Ebi-a-GCST90002401(PDW)	-0.002	0.002	0.435	0.789
	Ebi-a-GCST90002402(PLT)	0.001	0.003	0.682	0.251

**Abbreviations:** MPV, Mean platelet volume; PCT, Plateletcrit; PDW, Platelet distribution width; PLT, Platelet count.



**Figure 5** Causal relationship between COPD (exposure) and PCT (outcome). **(A)** The forest plot summarizing overall effects of COPD on PCT. **(B)** Scatter plot visualizing the effects of COPD on PCT. The 95% CIs for COPD and PCT effects are shown as vertical and horizontal lines, respectively. The fit line's slope indicates the MR effect per method. **(C)** Funnel plot for the precision of the estimate. **(D)** Leave-one-out sensitivity analysis results.

Furthermore, Hakim et al observed significantly higher MPV, PDW, and PCT levels in patients with COPD, both with and without diabetes, than in the control group. Notably, COPD patients with diabetes exhibit even higher MPV levels than those without diabetes.<sup>36</sup> Several studies have shown that the increased expression of  $\alpha$  IIb  $\beta$  3 integrin leads to significant platelet activation, resulting in increased platelet counts and enhanced platelet aggregation in patients.<sup>33,37</sup> Collectively, these findings demonstrate a close relationship between platelet indices and COPD; however, they do not offer evidence for the causal influence of platelet indices on COPD pathogenesis and progression. Our study further revealed that among the platelet indices, increased PLT leads to a higher risk of COPD, while an increase in PCT is the subsequent event resulting from COPD.

This study has several advantages. First, Our MR Study validated the correlation between the platelet indices and COPD. Compared to previous observational studies, MR Analysis is an effective tool for mitigating potential biases such as confounders and reverse causation, thereby improving the reliability of causal reasoning. Second, the datasets used in this study mainly involved populations of European descent, which helps to minimize the effect of population stratification. Third, we used different estimation models and conducted rigorous sensitivity analysis to ensure the reliability and robustness of the obtained results. However, this study has several limitations. First, it was conducted in a single population and further validation was performed across ethnic groups. Second, although rigorous steps were

implemented to identify abnormal variants and mitigate horizontal pleiotropy, their effects could not be completely eliminated. This could be attributed to the complex and unclear biological functions of several genetic variants. Finally, we used data from participants of all European ancestry (minimized stratification) but did not specify whether and how each GWAS was adjusted for principal component, genotyping lot, or correlation.

## Conclusions

Our bidirectional MR analysis found no definitive causal relationship between platelet indices and COPD, but observed suggestive associations between higher PLT/PCT and increased COPD risk. These findings highlight the need for further research to clarify the roles of platelet indices in COPD pathogenesis and their potential as biomarkers or therapeutic targets. The roles of PLT/PCT in COPD can be further elucidated by longitudinal cohort validation, randomized antiplatelet therapy trials stratified by genetic risk, or functional assays of key SNPs. Moreover, integrating multi-omics data would be beneficial for uncovering the underlying molecular mechanisms accounting for the functions of PLT/PCT on COPD.

## Abbreviations

MR, Mendelian randomization; COPD, chronic obstructive pulmonary disease; PLT, platelet count; PCT, plateletcrit; MPV, mean platelet volume; PDW, platelet distribution width; IVW, Inverse Variance Weighting; GWAS, genome-wide association studies; SNPs, single-nucleotide polymorphisms; CI, confidence interval; OR, odds ratio; MR-PRESSO, MR-pleiotropy residual sum and outliers.

## Data Sharing Statement

The data that support the findings of this study are openly available in the IEU Open GWAS database (<https://gwas.mrcieu.ac.uk/>) and the FinnGen database (<https://www.finnngen.fi/fi>).

## Institutional Review Board Statement

Our study used publicly available GWAS aggregate statistics (no individual-level data). The study is eligible for exemption from ethics approval under Article 32(1) and (2) of the Chinese Measures for the Ethical Review of Life Science and Medical Research Involving Human Subjects (2023) because it involves: (1) conducting the study using legally obtained publicly available data; and (2) studies involving non-invasive observational analysis of existing data. (<http://www.nhc.gov.cn/>).

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## 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 no conflict of interest.

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