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Article

Causal Association Between Idiopathic Pulmonary Fibrosis and Coronary Artery Disease: A Bidirectional Two-Sample Mendelian Randomization

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Abstract

Aims/Background: Coronary artery disease (CAD) has been epidemiologically linked to idiopathic pulmonary fibrosis (IPF); however, the genetic basis of this association remains unclear. Therefore, this study aims to investigate the potential causal relationships between IPF and CAD using a bidirectional two-sample Mendelian randomization (MR) strategy. **Methods:** Inverse-variance weighted (IVW), MR-Egger, weighted median, and weighted mode approaches were applied to summary statistics obtained from CAD and IPF genome-wide association studies. Heterogeneity among instrumental variables was assessed using Cochran's Q test. Pleiotropy was assessed using MR-Egger regression and MR pleiotropy residual sum and outlier (MR-PRESSO) analyses. Additionally, the robustness and reliability of the findings were validated by applying a leave-one-out analysis. **Results:** The forward MR analysis revealed no evidence supporting a genetic causal association between IPF and CAD (odds ratio [OR] = 0.989, 95% confidence interval [CI]: 0.967–1.010, p = 0.305) after excluding an outlier single-nucleotide polymorphism (SNP) (rs7725218). However, reverse MR analysis demonstrated a significant negative genetic causal association between CAD and IPF (OR = 0.832, 95% CI: 0.711–0.975, p = 0.023). Sensitivity analysis revealed heterogeneity in the forward MR analysis, which was resolved after excluding an outlier SNP, with no evidence of horizontal pleiotropy detected. **Conclusion:** This study demonstrates a potential negative genetic influence of CAD on the risk of IPF, providing valuable insights that may guide the development of more enhanced preventive and therapeutic strategies. Future research should further assess the interactions between CAD and IPF to improve disease management and patient outcomes.

Keywords: Mendelian randomization; coronary artery disease; idiopathic pulmonary fibrosis; causality

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive interstitial lung disease of unknown etiology, characterized by fibrotic features confined to the lungs. It is associated with the histopathologic and/or radiologic features of typical interstitial pneumonia [1]. IPF results in high mortality and substantially reduced quality of life, posing a substantial and primarily irreversible health burden [2]. This disease most frequently affects individuals aged 50 to 85 years, with a male predominance of about 54% [3,4].

Coronary artery disease (CAD), which includes myocardial infarction, angina pectoris, and ischemic heart disease, remains among the most prevalent cardiovascular diseases worldwide, contributing to hundreds of thousands of deaths annually in developed countries [5]. Emerging evidence suggests that IPF and CAD may share the common associated risk factors, such as aging and smoking. Furthermore, observational studies have reported significant epidemiological associations between these two conditions: For example, Kato et al. [6] demonstrated that individuals with IPF show a significantly higher prevalence of both CAD and heart failure compared with the general population, with heart failure serving as a crucial prognostic indicator. Similarly, CAD was found to occur more frequently in patients with IPF than in those with chronic obstructive pulmonary disease [7]. Furthermore, significantly higher coronary artery calcium levels have been observed in adults with IPF than in those with chronic obstructive pulmonary disease, even after adjusting for age and lung function impairment [8]. Collectively, these observations suggest a close link between IPF and CAD; however, the pattern and causality of this relationship remain unclear.

Several studies have identified genetic variants associated with both CAD and IPF individually, though none of them has directly assessed their shared genetic underpinnings. Mendelian randomization (MR), which employs genetic variants as instrumental variables (IVs), provides a valuable approach to infer causal relationships while minimizing confounding inherent to observational study designs. Therefore, this study aimed to employ a bidirectional two-sample MR approach to systematically assess the potential causal relationship between IPF and CAD. We hypothesized that a genetic causal link may exist between these two diseases, and that bidirectional MR analysis would elucidate both the presence and direction of this association. Such valuable insights could enhance our understanding of the underlying molecular mechanisms and

optimize clinical approaches for managing individuals affected by either or both conditions.

2. Methods

2.1 Study Design

This MR analysis followed the Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization guidelines, and the corresponding checklist has been completed to ensure methodological transparency and rigor [9]. During this study, instrument variables (IVs) selection from genetic variants followed the three fundamental assumptions of MR analysis: (1) the selected genetic variants are significantly associated with the exposure; (2) they are independent of any confounding factors; and (3) they influence the outcome exclusively through the exposure, without any direct or alternative pathways. This manuscript adheres to the Strengthening the Reporting of Observational Studies in Epidemiology–Mendelian randomization (STROBE-MR) reporting standard for Mendelian randomization research, and the completed STROBE-MR checklist is attached as **Supplementary Material**.

This study utilized summary-level genome-wide association study (GWAS) data for IPF and CAD. Genetic variants were initially identified to assess the causality between IPF and CAD, which represents the primary aim of this analysis. An overview of the bidirectional MR study design is presented in Fig. 1.

2.2 Data Source

GWAS data for CAD were obtained from a previously published meta-analysis that included 60,801 individuals with CAD and 123,504 controls [10]. The GWAS data for IPF were retrieved from a previous study involving 2668 cases and 8591 controls [11]. The IPF cases were classified based on the international diagnostic criteria [12].

2.3 Selection of Instrumental Variables

The selection of IVs followed a multi-step approach. Initially, single-nucleotide polymorphisms (SNPs) exhibiting genome-wide significance ($p < 5 \times 10^{-8}$) were identified [13]. SNPs with a minor allele frequency (MAF) of <0.01 were excluded to avoid the impact of rare variants. To mitigate linkage disequilibrium (LD), a relaxed threshold of $R^2 < 0.001$ within a 10,000 kb window was applied [14]. When a selected SNP was absent in the outcome dataset, a substitute (proxy) SNP in strong LD ($R^2 > 0.8$) was selected to ascertain the representativeness of the genetic signal. Each selected and proxy SNP was then validated to confirm a specific association with the exposure and compliance with the MR exclusion restriction criteria, ensuring the lack of association with other phenotypes. The reliability of the IVs was determined using F statistics, calculated as $F = R^2 \times [N - 2]/[1 - R^2]$ [14], where R^2 indicates the proportion of variance in the exposure explained by the IVs [15]. SNPs with F statistics >10 were considered robust enough for inclusion in the final analysis.

2.4 MR Analysis

The inverse-variance weighted (IVW) method was used as the primary analytical strategy to assess the correlation between exposure and outcomes, expressed as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). In such a framework, IVW determines the inverse variance for each SNP and derives a weighted average effect [15].

To assess robustness and consistency of the results, additional sensitivity analyses were conducted employing the MR-Egger regression [15], weighted median [16], and weighted mode [17]. A statistically significant IVW result ($p < 0.05$) was considered indicative of a potential causal association, even if other strategies did not achieve significance. MR-Egger analysis accounts for directional pleiotropy by including an intercept term, thereby enabling unbiased causal estimation even when pleiotropy effects are present. The weighted median approach assumes that at least 50% of the IVs are valid and offer reliable causal estimates under this condition. In the weighted mode method, SNPs are clustered into subsets based on the similarity of their causal effects, and their causal effects were then estimated accordingly [18].

2.5 Sensitivity Analysis

Sensitivity analyses were conducted to assess potential pleiotropy in the MR framework. Cochran's Q statistics were used to quantify heterogeneity among IVs in the IVW model [19]. A *p*-value less than 0.05 indicated significant heterogeneity, suggesting significant variability in the effect estimates among IVs and reducing the reliability of the IVW estimate.

This study also includes the impact of pleiotropy of genetic variation on the estimation of correlation effect, a MR-Egger regression method, and the MR-Egger intercept was used to explore the horizontal pleiotropy. The MR-Egger regression method provides unbiased causal estimates even in the presence of directional pleiotropy, as the intercept captures the average pleiotropic effect across instruments. However, this correction typically reduces statistical precision, resulting in broader confidence intervals compared with IVW estimates. Therefore, MR-Egger results are most valuable when interpreted in combination with other complementary MR approaches.

Additionally, the MR pleiotropy residual sum and outlier (MR-PRESSO) was applied to detect outlier SNPs ($p < 0.05$). These outlier SNPs were excluded from further analysis to correct for horizontal pleiotropy [20]. A leave-one-out sensitivity analysis was also performed to assess the potential impact of individual SNPs on the overall causal estimates and to account for weak instrument bias and pleiotropic effects in the IVW method [14]. This approach

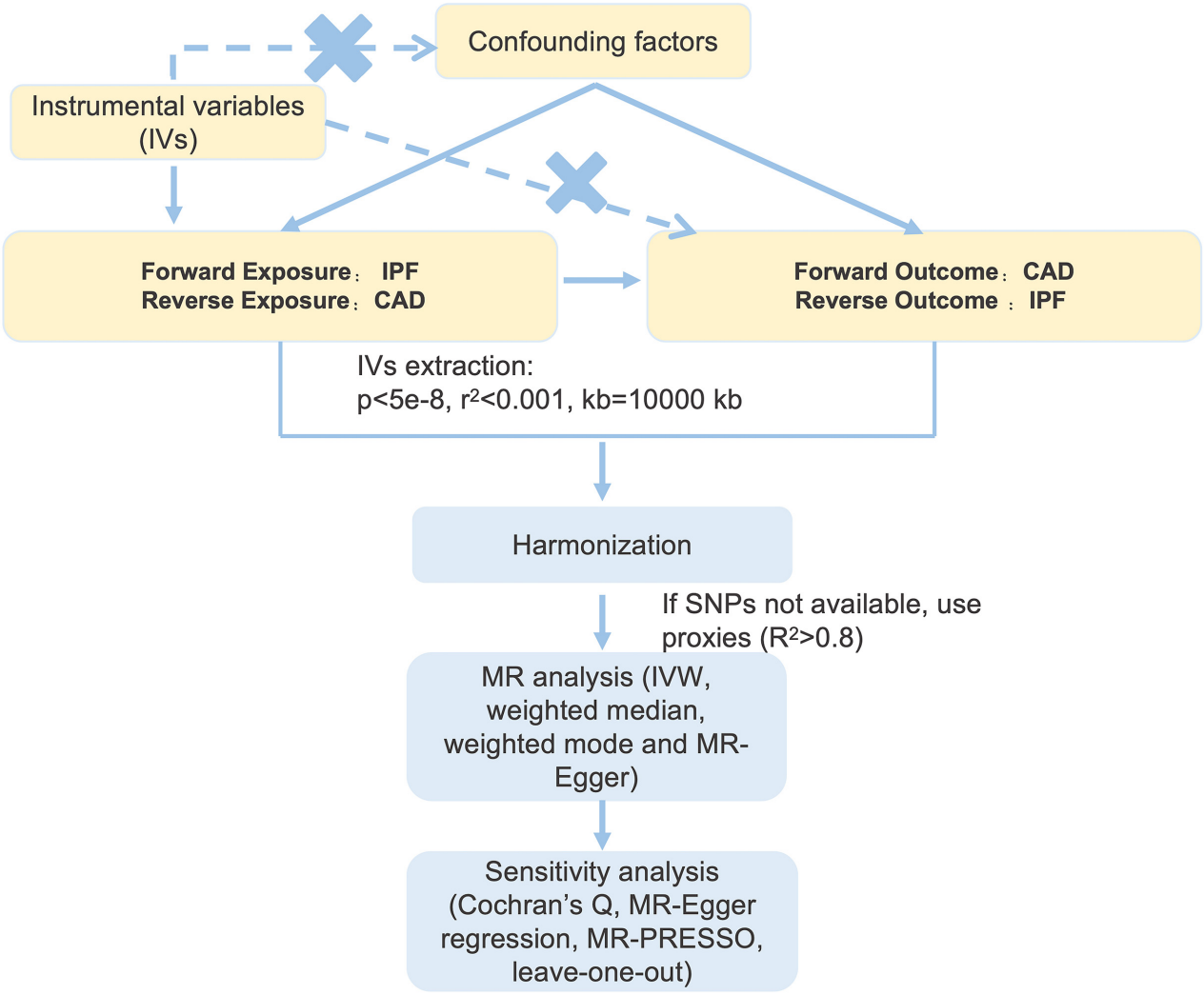

Fig. 1. An illustration of the bidirectional MR study design. MR, Mendelian randomization; IPF, idiopathic pulmonary fibrosis; CAD, coronary artery disease; SNPs, single-nucleotide polymorphisms; IVW, inverse-variance weighted; MR-PRESSO, MR pleiotropy residual sum and outlier.

systematically tested the effect of each SNP, enabling evaluation of the stability and reliability of the causal estimate.

2.6 Statistical Analysis

Data were statistically analyzed using the TwoSampleMR packages in R (version 4.0.5, R Foundation for Statistical Computing, Vienna, Austria). The statistical significance threshold was set at $p < 0.05$ for primary analyses. Since the study tested two primary causal hypotheses, IPF on CAD and CAD on IPF, a Bonferroni correction was applied to account for multiple comparisons. Accordingly, a *p*-value less than 0.025 was considered statistically significant.

Power calculations were performed using the TwoSampleMR package in R, based on the F-statistics of instrumental variables and the expected effect size (OR = 0.832).

3. Results

3.1 Mendelian Randomization Analysis Between IPF and CAD

This study identified 15 IVs associated with IPF, each with F-statistics above 10 (**Supplementary Table 1**). The IVW approach revealed no significant causal link between IPF and CAD (OR = 0.996, 95% CI: 0.971–1.022, $p = 0.767$). Consistent nonsignificant results were obtained from the MR-Egger, weighted median, and weighted mode analyses (Table 1). Sensitivity analysis further validated the robustness of these findings; reanalysis after excluding the outlier SNP (rs7725218) continued to reveal no statistically significant causal association (Table 1). The scatter plots show the distribution of SNP effects on IPF and their impact on CAD, identifying the absence of potential trends or key outliers, while forest plots summarize the overall SNP effect sizes and their 95% confidence intervals (Fig. 2A,B).

Table 1. Results of bidirectional Mendelian randomization analysis between IPF and CAD.

Exposure	Outcome	SNPs	Methods	OR (95% CI)	*p*-value
IPF	CAD	15	IVW	0.996 (0.971–1.022)	0.767
			MR-Egger	0.995 (0.941–1.052)	0.869
			Weighted median	0.992 (0.967–1.018)	0.531
			Weighted mode	0.994 (0.967–1.023)	0.697
IPF (after outlier removal)	CAD	14	IVW	0.989 (0.967–1.010)	0.305
			MR-Egger	0.992 (0.946–1.039)	0.726
			Weighted median	0.991 (0.967–1.017)	0.507
			Weighted mode	0.994 (0.965–1.024)	0.706
CAD	IPF	38	IVW	0.832 (0.711– 0.975)	0.023
			MR-Egger	0.656 (0.455–0.944)	0.029
			Weighted median	0.807 (0.653–0.996)	0.046
			Weighted mode	0.814 (0.641–1.032)	0.098

SNP, single-nucleotide polymorphism; MR, Mendelian randomization; OR, odds ratio; CI, confidence interval; IVW, inverse-variance weighted. Forward MR: IPF (exposure) → CAD (outcome); Reverse MR: CAD (exposure) → IPF (outcome).

Table 2. Heterogeneity and pleiotropy analysis of instrumental variables.

Exposure	Outcome	Heterogeneity		Pleiotropy	
		Q statistic (IVW)	*p*-value	MR-Egger intercept	*p*-value
IPF	CAD	29.417	0.009	<0.001	0.970
IPF (after outlier removal)	CAD	18.971	0.124	<0.001	0.893
CAD	IPF	46.844	0.129	0.026	0.164

MR, Mendelian randomization; IVW, inverse-variance weighted. Forward MR: IPF (exposure) → CAD (outcome); Reverse MR: CAD (exposure) → IPF (outcome).

Table 3. The results of the MR-PRESSO test.

Exposure	Outcome	Raw		Outlier corrected		Global *p*	Number of outliers	Distortion *p*
		OR (95% CI)	*p*-value	OR (95% CI)	*p*-value			
IPF	CAD	0.996 (0.971– 1.022)	0.771	0.989 (0.967–1.010)	0.324	0.015	1	0.62
IPF (after outlier removal)	CAD	0.989 (0.967–1.010)	0.324	NA	NA	0.176	NA	NA
CAD	IPF	0.832 (0.711–0.975)	0.029	NA	NA	0.139	NA	NA

NA, not applicable.

3.2 Heterogeneity and Pleiotropy Across IVs

Cochran's Q test revealed significant heterogeneity among IVs, indicating substantial variability across IVs (Q = 29.417, p = 0.009) (Table 2). This heterogeneity warranted further investigation to ensure the validity of our findings. However, the MR-Egger intercept test (p = 0.970) indicated no evidence of directional horizontal pleiotropy. To address the observed heterogeneity, MR-PRESSO analysis was performed, and one outlier SNP (rs7725218) was found contributing to the observed heterogeneity (Table 3).

After excluding the outlier SNP, the data were re-analyzed. The heterogeneity was substantially reduced and no longer significant (Q = 18.971, p = 0.124), while the MR-Egger intercept remained non-significant, confirming the absence of directional pleiotropy. Importantly, the primary finding remained unchanged across all MR methods, indicating no significant causal effect of IPF on CAD. Moreover, the distribution and symmetry of the SNP effects were evaluated using funnel plots, which showed no significant biases; additionally, a leave-one-out sensitivity analysis was performed to confirm that no single SNP significantly affected the overall results (Fig. 2C,D). Overall, these results confirm the robustness and reliability of the analysis.

3.3 Causal Association Between CAD and IPF

During the reverse MR analysis examining the causal effect of CAD on IPF, a total of 42 SNPs associated with CAD were initially identified, all with F-statistics above 10. In the harmonization process, four SNPs were excluded: two (rs7212798 and rs180803) did not match the outcome GWAS dataset, and two additional SNPs (rs10139550 and rs7568458) were removed due to being palindromic with intermediate allele frequencies. As a result, 38 IVs were

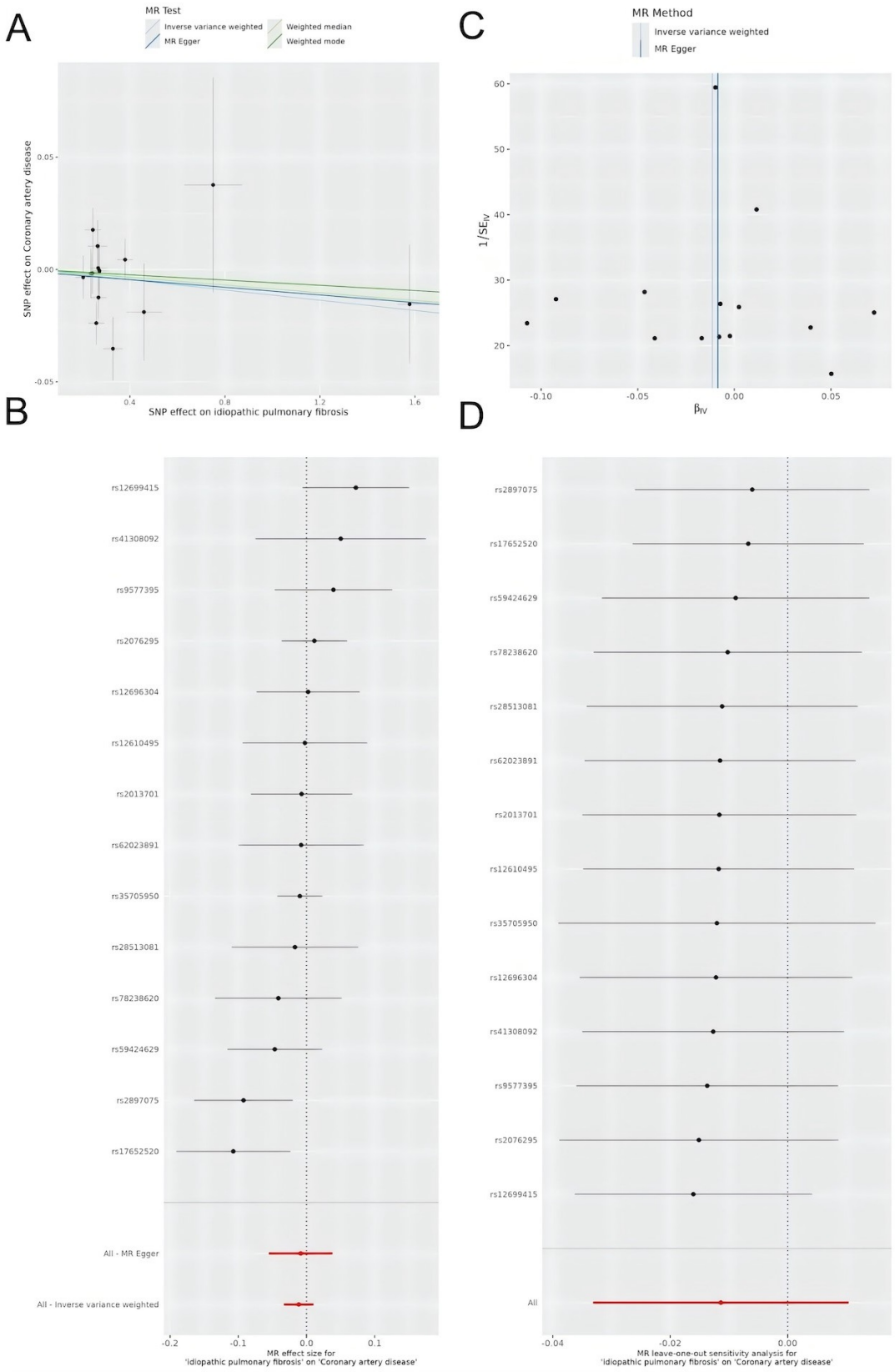

Fig. 2. The genetic association of IPF with CAD. The scatter plot (A), forest plot (B), funnel plot (C), and leave-one-out sensitivity analysis (D). SE, standard error.

retained for the final causal analysis (**Supplementary Table 2**).

The IVW analysis (Table 1) demonstrated a significant causal effect of CAD on IPF (OR = 0.832, 95% CI: 0.711–0.975, $p = 0.023$), suggesting that a higher genetic predisposition to CAD may be associated with reduced IPF risk. This link remained statistically significant after Bonferroni correction. The MR-Egger ($p = 0.029$) and weighted median ($p = 0.046$) analyses showed directionally consistent but only nominally significant associations that did not meet the corrected threshold, whereas the weighted mode method yielded a non-significant outcome ($p = 0.098$). These discrepancies, particularly the result from the weighted median method, which is usually more resistant to pleiotropy bias, suggest that the potential causal association may be modest in magnitude or partially influenced by pleiotropic effects. Hence, while it shows a potential causal association, the findings should be interpreted with caution and need further validation in an independent cohort.

Scatter plots depict the individual effects of genetic variants on CAD, whereas forest plots summarize these effects, illustrating the overall magnitude of the causal impact (Fig. 3A,B). Power analysis confirmed that the forward MR analysis had limited statistical power (5.060%), whereas the reverse MR analysis showed adequate power (95.650%) to detect an effect of this magnitude (**Supplementary Table 3**).

As shown in Table 2, Cochran's Q test and MR-Egger regression revealed no significant heterogeneity or evidence of horizontal pleiotropy in the sensitivity analysis. Similarly, MR-PRESSO analysis did not find any outliers among the selected IVs (Table 3). Sensitivity analyses, including leave-one-out analysis and funnel plots (Fig. 3C,D), confirmed no significant bias or single SNP influence.

4. Discussion

This MR study explored the potential causal relationship between IPF and CAD using genetic variants such as IVs. The bidirectional MR analysis found no evidence indicating a causal effect of IPF on CAD. Interestingly, the reverse analysis suggested a potential negative causal association between genetic predisposition to CAD and the risk of developing IPF. This finding contradicts extensive observational evidence demonstrating CAD as a common and prognostically significant comorbidity in IPF patients. This inconsistency highlights the complexity of the IPF-CAD relationship and suggests that their clinical co-occurrence may be driven by shared risk factors (e.g., smoking, aging) or other confounding mechanisms rather than a direct genetic effect of CAD on IPF. Therefore, this unexpected negative genetic association should be dealt with caution and further investigated to elucidate the potential biological mechanisms underlying it.

Several epidemiological studies have reported a strong association between interstitial lung diseases (ILD), particularly IPF, and cardiovascular co-morbidities. For example, in a study involving 630 individuals with fibrotic lung disease, including 76 IPF patients recommended for lung transplantation, Kizer et al. [21] reported an increased prevalence of CAD even after adjusting for traditional CAD risk factors. Similarly, another study revealed that individuals with IPF had higher rates of CAD and HF than those without IPF [6]. Moreover, a large cohort study across seven National Health Service hospitals in North West England, including 1662 ILD patients, reported an independent association between lung disease and cardiovascular diseases, notably ischemic heart disease and heart failure, which significantly contributed to elevated all-cause mortality [22].

Collectively, these studies underscore the coexistence of ILD, notably IPF, with CAD, which negatively affects patient prognosis. However, most of these studies primarily focus on clinical correlations and often overlook potential genetic contributions to this association. Moreover, the incidence rates of both IPF and CAD are influenced by multiple environmental, social, and other confounding factors, complicating the recognition of a direct association between these conditions in observational studies, particularly in patients presenting with both IPF and CAD.

In contrast, our MR study specifically investigated the potential genetic causal relationships between IPF and CAD, employing multiple analytical methods to ensure robustness of the results. This framework diverges significantly from previous assumptions, such as those reported by Carter et al. [22], who have generally observed IPF as a complication arising from CAD. Our estimates instead suggest a potential inverse genetic association between CAD and IPF; however, this finding should be interpreted cautiously and not as evidence of a definitive "protective effect". Several plausible and potentially overlapping explanations may underlie this unexpected link.

From a mechanistic perspective, changes in pulmonary hemodynamics secondary to coronary atherosclerosis may enhance alveolar vascular remodeling and angiogenesis [23], mechanisms that could modulate fibrogenesis. Furthermore, CAD-associated modulation of systemic humoral and cellular immune responses may counterbalance profibrotic pathways involved in IPF [24]. Additionally, the downstream effects of CAD management—such as long-term exposure to statins, antiplatelet agents, and renin–angiotensin system inhibitors—might attenuate platelet- and transforming growth factor-β–mediated profibrotic signaling, potentially contributing to the observed negative association at the population level. From a methodological perspective, survival and competing-risk biases (e.g., individuals with greater genetic predisposition to CAD dying before IPF onset), index-event or selection bias within GWAS datasets, horizontal pleiotropy, and

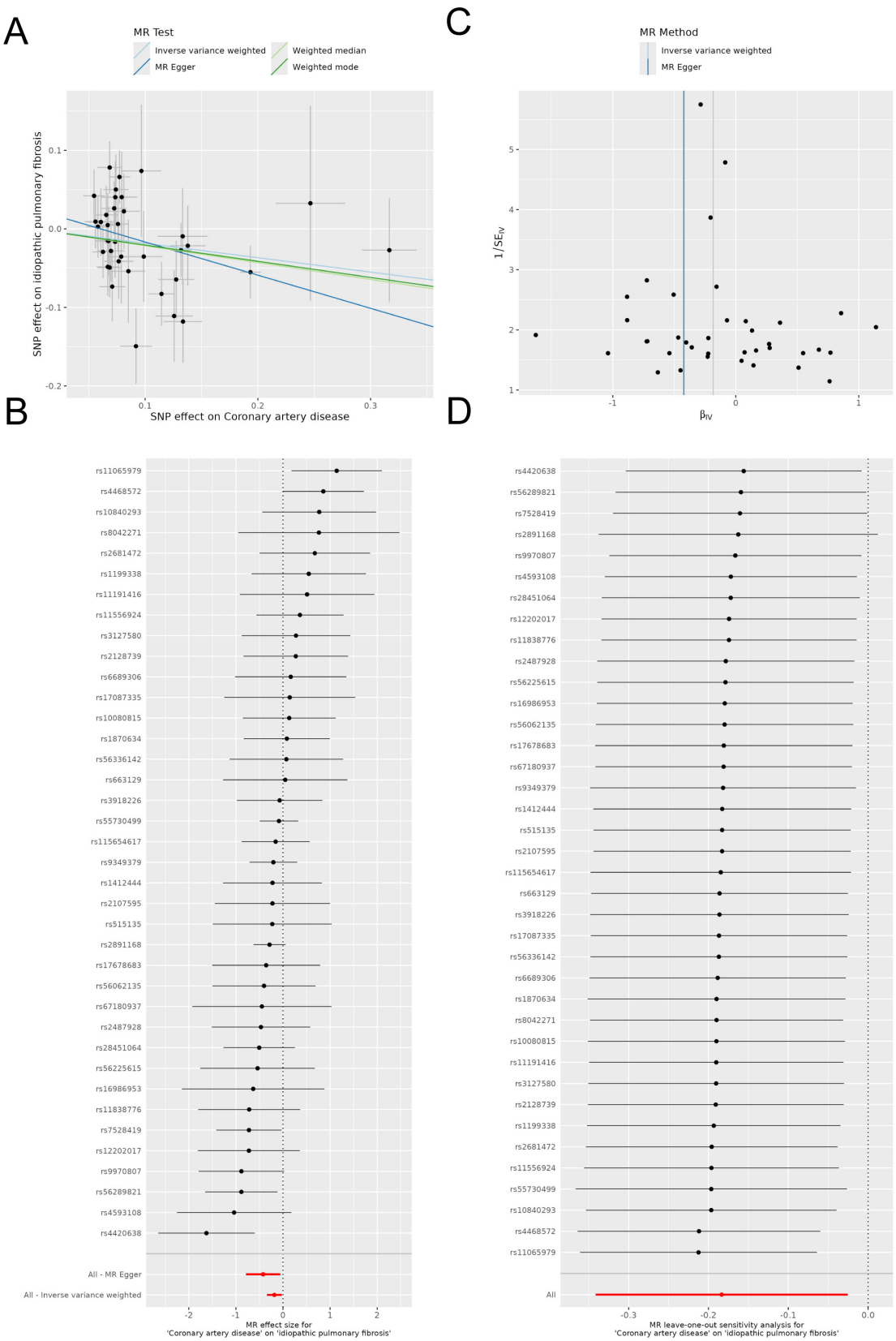

Fig. 3. The genetic association of CAD with IPF. The scatter plot (A), forest plot (B), funnel plot (C), and leave-one-out sensitivity analysis (D).

phenotypic heterogeneity or misclassification of interstitial lung disease subtypes could also produce an apparent inverse relation [25]. Further research is warranted to validate these observations and to delineate the respective contributions of genetic and environmental factors to the interaction between these two diseases.

Despite a comprehensive analysis, no significant genetic causal effect of IPF on CAD was found. The inconsistency between genetic findings and clinical observations suggests that shared environmental exposures and confounders—such as smoking and other common risk factors—may play a more substantial role in the observed association than direct genetic causation [25]. This observation demonstrates the inherent challenge of distinguishing genetic effects from environmental influences in disease comorbidity and emphasizes the need for validation in broader, more heterogeneous populations to identify additional potential underlying mechanisms.

The genetic basis of complex diseases such as IPF and CAD has been increasingly explored, with growing evidence implicating shared metabolic pathways. For instance, Apolipoprotein B (ApoB), a key structural protein of LDL cholesterol and a major driver of atherosclerosis, has also been linked to IPF susceptibility [26]. Despite this biological overlap, our forward MR analysis showed no evidence for a direct causal effect of genetic predisposition to IPF on CAD risk. This null finding (OR close to 1, insignificant *p*-value) may have two possible interpretations. First, it may genuinely reflect the absence of a direct causal relationship, suggesting that the observed IPF-CAD co-occurrence is primarily driven by shared risk factors like smoking, aging, or environmental exposures rather than a pathogenic effect of IPF on coronary atherosclerosis. Second, the results could be due to limited statistical power, given that current GWAS for IPF involve considerably smaller sample sizes compared to those for CAD. Therefore, the genetic instruments for IPF may lack adequate strength to detect a modest causal effect. Hence, this null association should be interpreted with caution, and future studies based on larger and more comprehensive IPF GWAS datasets are crucial to validate these observations.

In contrast to the null association observed from IPF to CAD, our reverse MR analysis revealed an unexpected negative causal relationship. This finding challenges the conventional notion that IPF occurs as a complication of CAD, a perspective often influenced by confounding factors such as obesity [27] and metabolic syndrome [28], both prevalent among CAD patients. Instead, our results suggest that genetic determinants predisposing to CAD may play a crucial role in modulating susceptibility to IPF. This observation emphasizes the need to consider both genetic predisposition and lifestyle factors when assessing the interaction between these conditions. Such a perspective invites a nuanced approach to cardiovascular and pulmonary health, promoting deeper exploration into their interplay [29].

Although the study revealed some promising outcomes, we acknowledge several limitations to this analysis. First, both the exposure and outcome GWAS were derived from European-ancestry cohorts. Differences in allele frequencies, linkage disequilibrium patterns, causal architectures, and gene-environment interactions across populations may affect instrument strength and validity. Consequently, our estimates reflect average genetic effects in European populations and should be generalized to other ancestries with caution. Replication in non-European cohorts and multi-ancestry settings—using ancestry-specific instrument selection, stratified effect estimation, and trans-ethnic colocalization or fine-mapping integrated with meta-analytic heterogeneity testing—is crucial to assess the generalizability of these findings (e.g., in East Asian, African, Hispanic/Latino, and South Asian populations). Second, this analysis was limited to IPF and did not examine other ILD subtypes; future studies incorporating additional ILD phenotypes will help clarify disease specificity. Third, the MR results were not validated in independent datasets or large clinical cohorts. Replication in external consortia and prospective cohorts is warranted before these results can be translated into clinical application.

In summary, our study highlights a potential inverse causal association between CAD and IPF, suggesting that certain genetic factors predisposing to CAD may confer a mitigating effect on IPF risk or progression. This discovery highlights the significance of integrating genetic factors alongside confounding variables when interpreting observational associations. Moreover, given the intrinsic heterogeneity of CAD, further investigations should apply a more detailed classification of CAD subtypes to uncover any subtle variations in their relationship with IPF. This approach could lead to the development of more targeted interventions and management strategies for patients affected by or at risk of these interrelated conditions.

5. Conclusion

In conclusion, our bidirectional MR analysis revealed no evidence supporting a causal effect of IPF on CAD. Interestingly, the finding demonstrated a potential negative causal association, suggesting that genetic susceptibility to CAD may not increase—and might even decrease—the risk of developing IPF. This observation challenges the assumption that their frequent clinical co-occurrence indicates a direct causal link and underscores the importance of further research to validate this genetic association across diverse populations and to elucidate the underlying molecular mechanism.

Key Points

• This MR analysis found no evidence supporting a causal effect of genetic susceptibility to idiopathic pulmonary fibrosis (IPF) on the risk of coronary artery disease (CAD).

• Conversely, genetic predisposition to CAD significantly reduced the risk of developing IPF, though this finding lacked consistency across different MR methods.

• The inconsistency between our genetic findings and clinical observations suggests that the IPF-CAD co-occurrence may be driven by shared risk factors (e.g., aging, smoking) rather than a direct causal relationship.

• These findings underscore the significance of distinguishing genetic causality from epidemiological association and highlight the need for further investigation to validate these results in diverse populations and explore underlying molecular mechanisms.

Availability of Data and Materials

All data included in this study are available from the corresponding author upon reasonable request.

Author Contributions

LY: Conceptualization, methodology, formal analysis, data curation, writing—original draft preparation, project administration. JL: Conceptualization, writing—review and editing, visualization. XZ: Software, investigation, supervision. TF: Validation, resources. All authors contributed to the important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

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Conflicts of Interest

The authors declare no conflicts of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/BJHM56025.

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