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ORIGINAL RESEARCH

Bidirectional Causal Association Between Chronic Obstructive Pulmonary Disease and Cardiovascular Diseases: A Mendelian Randomization Study

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Background: A large number of studies have demonstrated links between chronic obstructive pulmonary disease (COPD) and cardiovascular diseases (CVDs). However, the causal relationship between COPD and CVDs and the reverse causality remains divergent.

Methods: Exposure and outcome data from the largest available genome-wide association studies were extracted for Mendelian randomization (MR) studies. Univariate MR analysis was performed using IVW as the primary analysis method, and multiple sensitivity analyses were used to enhance the robustness of the results. Furthermore, this was followed by mediation MR analysis of positive results after excluding confounding factors with multivariable MR analysis.

Results: The MR estimation based on IVW method indicated a strong association between genetically determined COPD and heart failure (HF) (OR = 1.117, 95% CI: 1.066–1.170, p <0.001), coronary heart disease (CHD) (OR = 1.004, 95% CI: 1.002–1.006, p <0.001), essential hypertension (EH) (OR = 1.009, 95% CI: 1.005–1.013, p <0.001) as well as Stroke (OR = 1.003, 95% CI: 1.001–1.004, p <0.001). The results of multivariable MR analysis revealed that COPD is not significantly associated with CHD after adjusting for IL-6, LDL, or total cholesterol (p>0.05). Our findings indicated that BMI, smoking initiation, smoking status, obesity, and FEV1 played a role in the causal effect of COPD on HF, EH, and Stroke.

Conclusion: We found positive causal relationships between COPD and HF, EH, and Stroke essentially unaffected by other confounding factors. The causal relationship exhibited between COPD and CHD was influenced by confounding factors. BMI, obesity, initiation of smoking, smoking status, and FEV1 were the mediators between COPD and CVDs.

Keywords: chronic obstructive pulmonary disease, cardiovascular diseases, Mendelian randomization

Introduction

Chronic obstructive pulmonary disease (COPD) and cardiovascular diseases (CVDs) are two clinically frequent diseases with high morbidity and mortality in the elderly. There is no complete cure for COPD, and most people can only rely on medication and oxygen therapy to relieve symptoms and stop the progression of the disease.[1] Moreover, COPD patients have a high prevalence of CVDs, which makes treatment more difficult and the prognosis worse. So, the best solution is to prevent the disease from occurring. Both conditions share numerous risk factors in common, including smoking and age.[2] Clinical observations indicate a frequent co-occurrence of these diseases within the same patient population. Although COPD is a lung disease, patients often die from cardiovascular disease or cancer. If patients with COPD take steps to prevent the onset of these common CVDs such as heart failure (HF), coronary heart disease (CHD), essential hypertension (EH), atrial fibrillation (AF), and Stroke, or if patients with existing CVDs take steps to prevent the onset of COPD disease, the rate of disability and death from the disease can be greatly reduced.[3,4]

There has been a great deal of investigation showing that COPD has a positive causal relationship with CVDs, and that patients with COPD have a greater likelihood of having a disease associated with CVDs. However, there is still disagreement about the causal relationship between COPD and specific CVDs and whether cardiovascular disease causes an increase in the

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prevalence of COPD patients.[5] Mendelian randomization studies can avoid confounding factors and reverse causation and are suitable for application to the study of complex causal relationships between these two types of diseases.

Mendelian randomization studies are an approach that uses genetic variation, such as single nucleotide polymorphisms (SNPs), as instrumental variables to study causal relationships between risk factors and outcomes.[6] Because the two alleles on a chromosome are randomly assigned during meiosis, they are not subject to external confounding factors and essentially show whether the risk factor is causally related to the disease. Mendelian randomization studies are weaker than randomized controlled trials (RCT) and stronger than observational studies in terms of level of evidence. But they are easier to conduct than RCT, and more economical on financial resources and time.[7] In this study, we first executed a bidirectional two-sample Mendelian randomization study to determine the causal relationship between COPD and CVDs. The multivariate Mendelian randomization (MVMR) study of CVDs causally associated with COPD was further performed to calibrate potential confounding factors. Finally, we conducted a mediation Mendelian randomization study to determine whether these possible risk factors were mediators of COPD versus CVDs.

Materials and Methods

Study Design

The bidirectional two-sample MR analysis was conducted to identify any potential causal association between COPD and 5 CVDs, including HF, CHD, EH, AF, and Stroke (Figure 1). The methodology employed in this MR analysis was based on three fundamental assumptions. First, the extracted genetic variants should be strongly associated with the exposure factors(F>10). Second, SNPs cannot be causally linked through relationships with confounders and outcomes. Third, SNPs cannot be directly related to the outcomes (Figure S1).

Genetic Association Datasets

Summary statistical data for COPD with European ancestry, comprising 13,530 cases and 454,945 controls, were extracted from the genome-wide association studies (GWAS) summary datasets.[8] To our knowledge, it is the largest scale and latest GWAS study for COPD.

Our study focused primarily on the causal relationship between COPD and different types of CVDs, including HF, CHD, EH, AF, and Stroke. To gather the most extensive and up-to-date information on these outcomes within the European population, we selected the largest available GWAS studies for the primary MR analysis (study information outlined in Table 1). The summary statistics for HF (case/control: 47,309/930,014),[9] CHD (case/control: 10,157/351,037), EH (case/control: 54,358/408,652), AF (case/control:3,537/481,061),[10] and Stroke (case/control: 6,146/355,048) were extracted from large scale GWAS studies respectively. Exposure and outcome populations are drawn from as many databases as possible to prevent false-positive results due to overlapping samples. For the validation analysis, we extracted summary statistics from UK Biobank, FinnGen Biobank, or other sources different from the primary analysis to check the consistency of the findings across different datasets.

Informed Consent Statement and Ethics Approval Statement

Relevant data from the GAWS database and summary statistics for the studies used for analysis were collected from published studies. All studies have received prior approval from their institutional review boards (IRBs). The Ethics Committee of Beijing Anzhen Hospital approved the study protocol and waived the requirement for informed consent.

IV Selection

We followed a two-step process to identify the instrumental variables (IVs). Firstly, we extracted single nucleotide polymorphisms (SNPs) robustly associated with the exposures ($p < 5\times10^{-6}$). Secondly, we retained only the independent SNPs (kb = 10,000, $r^2 < 0.001$) based on the linkage disequilibrium (LD) structure of European populations. To assess the strength of the IVs, we employed the F-statistics of the remaining SNPs by the following formula: $F = R^2 \times (N–k–1)/((1–R^2) \times k)$, where $R^2 = 2 \times \beta^2 \times (1–EAF) \times EAF$, N is the sample size of exposure factors, k is the number of SNPs, β is the estimate of genetic effect on exposure factors, and EAF is

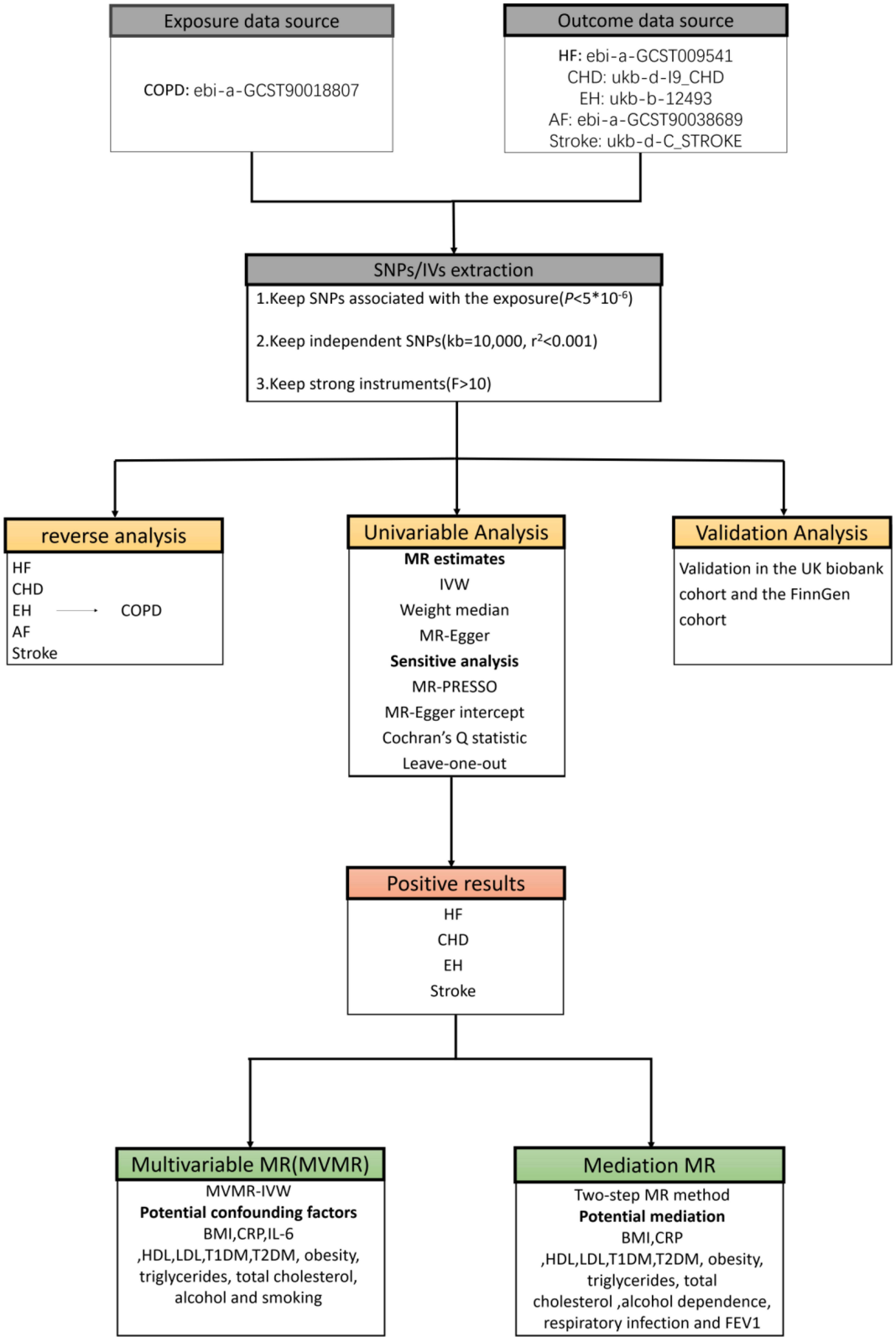

Figure 1 Flowchart of MR analysis.
Abbreviations: HF, heart failure; CHD, coronary heart disease; AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; EH, essential hypertension; SNPs, single nucleotide polymorphisms; MR, Mendelian randomization; IVW, Inverse variance weighted.

Table 1 Detailed Information for the GWAS Data

Outcomes	GWAS ID	Data Source	Sample Size	Cases/Controls	PMID	Year	Population
HF	ebi-A-GCST009541	Shah S	977,323	47,309/930,014	31,919,418	2020	European
CHD	ukb-d-I9_CHD	Neale lab	361,194	10,157/351,037	NA	2018	
EH	ukb-b-12493	Ben Elsworth	463,010	54,358/408,652	NA	2018	
AF	ebi-A-GCST90038689	D<U+00F6>nerta<U+015F> HM	484,598	3,537/481,061	33,959,723	2021	
Stroke	ukb-d-C_STROKE	Neale lab	361,194	6,146/ 355,048	NA	2018	
Exposure	**GWAS ID**	**Data Source**	**Sample Size**	**Cases/Controls**	**PMID**	**Year**	
COPD	ebi-A-GCST90018807	Sakaue S	468,475	13,530/ 454,945	34,594,039	2021	

Abbreviations: HF, heart failure; CHD, coronary heart disease; AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; EH, essential hypertension.

the frequency of the effect allele. When F>10, SNPs were taken as having a strong correlation with exposure factors.[11] Whereas the SNPs selected in our study all had F values greater than 20, reinforcing the robustness of the results.

Statistical Analysis

We used the "TwoSampleMR" software package to perform the MR principal analysis to obtain causality estimates and perform various sensitivity analyses.[12] The MR estimates were represented by odds ratios (OR) with 95% confidence intervals (CIs). MR pleiotropy residual sum and outlier (MR-PRESSO) method was used to detect outlier SNPs and adjust the horizontal pleiotropy using the 'MR-PRESSO' package.[13] The MVMR analysis was performed by the 'MVMR' and 'Mendelian Randomization' packages.[14] All statistics were calculated using R software 4.3.1 (The R Foundation for Statistical Computing).

Univariable MR Analysis

The causal effects were estimated using the inverse variance weighted (IVW) method.[15] Since the IVW method requires all the IVs to be valid to obtain an unbiased estimation, we also performed the MR analyses using two alternative MR methods (weighted median and MR-Egger) to assess the robustness of the results.[16] Moreover, the potential horizontal pleiotropy was evaluated by the MR-Egger intercept. Cochran's Q statistic was used to calculate heterogeneity in the MR study. When $p<0.05$ indicated the presence of heterogeneity, we used a random effects model to exclude or estimate SNPs. The causal effect was considered significant if the IVW p value was less than the Bonferroni-corrected threshold ($p < 0.05/5= 0.01$) while $0.01 \leq p < 0.05$ indicated suggestive significance and the results from the weighted median and MR-Egger were consistent in the same direction.

Multivariable MR Analysis

For the significant causal associations in the univariable MR analysis, the MVMR analysis was performed using the MVMR-IVW method, aiming to adjust for potential confounding factors including Body mass index (BMI), C-reactive protein (CRP), Interleukin-6(IL-6), High density lipoprotein (HDL), Low density lipoprotein (LDL), Type 1 diabetes mellitus (T1DM), Type 2 diabetes mellitus (T2DM), obesity, triglycerides, smoking initiation, Smoking status, Alcohol dependence, and Total cholesterol.[14]

Mediation MR Analysis

To clarify whether common risk factors mediate a causal relationship between COPD and CVDs, we conducted a mediation MR analysis with a two-step method.[14] In the first step, we calculated the causal effect of COPD on mediators (β1), and in the second step, we estimated the causal effect of mediators on CVDs (β2). The significance of the mediating effects (β1*β2) and the proportion of the mediation effect in the total effect were estimated using the delta method.

Results

Univariable MR Analysis

The MR estimation based on the IVW method indicated a strong association between genetically determined COPD and HF (OR = 1.117, 95% CI: 1.066–1.170, p <0.001), CHD (OR = 1.004, 95% CI: 1.002–1.006, p <0.001), EH (OR = 1.009, 95% CI: 1.005–1.013, p <0.001) as well as Stroke (OR = 1.003, 95% CI: 1.001–1.004, p <0.001). However, no significant association was found between COPD and AF (OR = 1.000, 95% CI: 0.999–1.001, p = 0.991) (Figure 2). Two alternative MR methods: weighted median and MR-Egger show similar results and the scatter plots also show consistent causal trends (Figure 3A–D). The "Leave-one-out" plot identified that none of the SNPs dominate the estimated causal association between COPD and CVDs (Figure 3E–H). Both p values of MR-Egger intercept and MR-PRESSO Global test > 0.05 reduce the potential for research results to be influenced by horizontal pleiotropy. The results of Cochran's Q statistic show weak heterogeneity exists in the MR study with the outcome of HF so random effects models are used (Table S1).

The reverse MR analyses revealed no significant causal effect of genetic predisposition to 2 CVDs on the risk of COPD, including HF (OR = 1.062, 95% CI: 0.965–1.169, p = 0.220), Stroke (OR = 25.651, 95% CI: 0.288–2284.824 p = 0.157). Interestingly, there were strong causal inferences found in CHD (OR = 10.227, 95% CI: 1.889–55.363, p = 0.007) and EH (OR = 3.823, 95% CI: 2.291–6.382, p <0.001). The causal relationship between AF and COPD is suggestive (OR = 36.911, 95% CI: 1.839–740.732, p = 0.018) (Figure S2).

To check whether the findings were consistent across different datasets, we replicated the MR analysis using data from different databases. We found a similar significant causal association between COPD and 4 CVDs. However, no causal relationship between COPD and CHD was demonstrated after adjustment for horizontal pleiotropy (Figure S3).

MVMR Analysis

The MVMR analysis was performed to evaluate the direct effect of COPD on CVD with the adjustment of multiple other risk factors associated with CVD. The results obtained from the univariable MR analysis were partly consistent with the findings from the MVMR. However, COPD is not significantly associated with CHD after adjusting for IL-6, LDL, or total cholesterol (p>0.05) (Table 2).

Mediation MR Analysis

The two-step MR was employed to perform mediation MR analysis. We aimed to investigate whether BMI, CRP, HDL, LDL, T1DM, T2DM, obesity, triglycerides, alcohol dependence, total cholesterol, acute upper respiratory infections, acute lower respiratory infections, and FEV1 mediate the causal relationship between COPD and CVDs. Interestingly, our findings indicated that BMI, smoking initiation, smoking status, and FEV1 played a role in the causal effect of COPD on HF, EH, and Stroke. The proportions of mediation for BMI were 25.43% (95% CI: 10.31~40.54%), 33.92% (95%

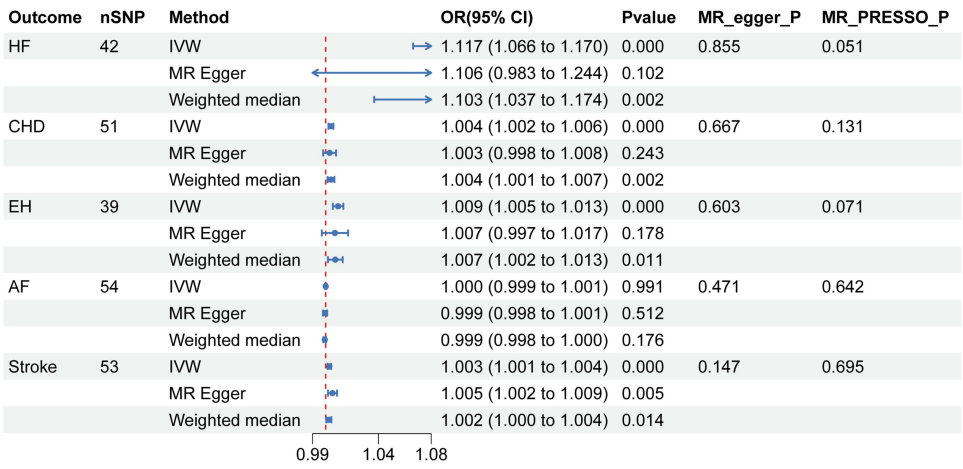

Figure 2 MR forward results between COPD and the 5 CVDs.

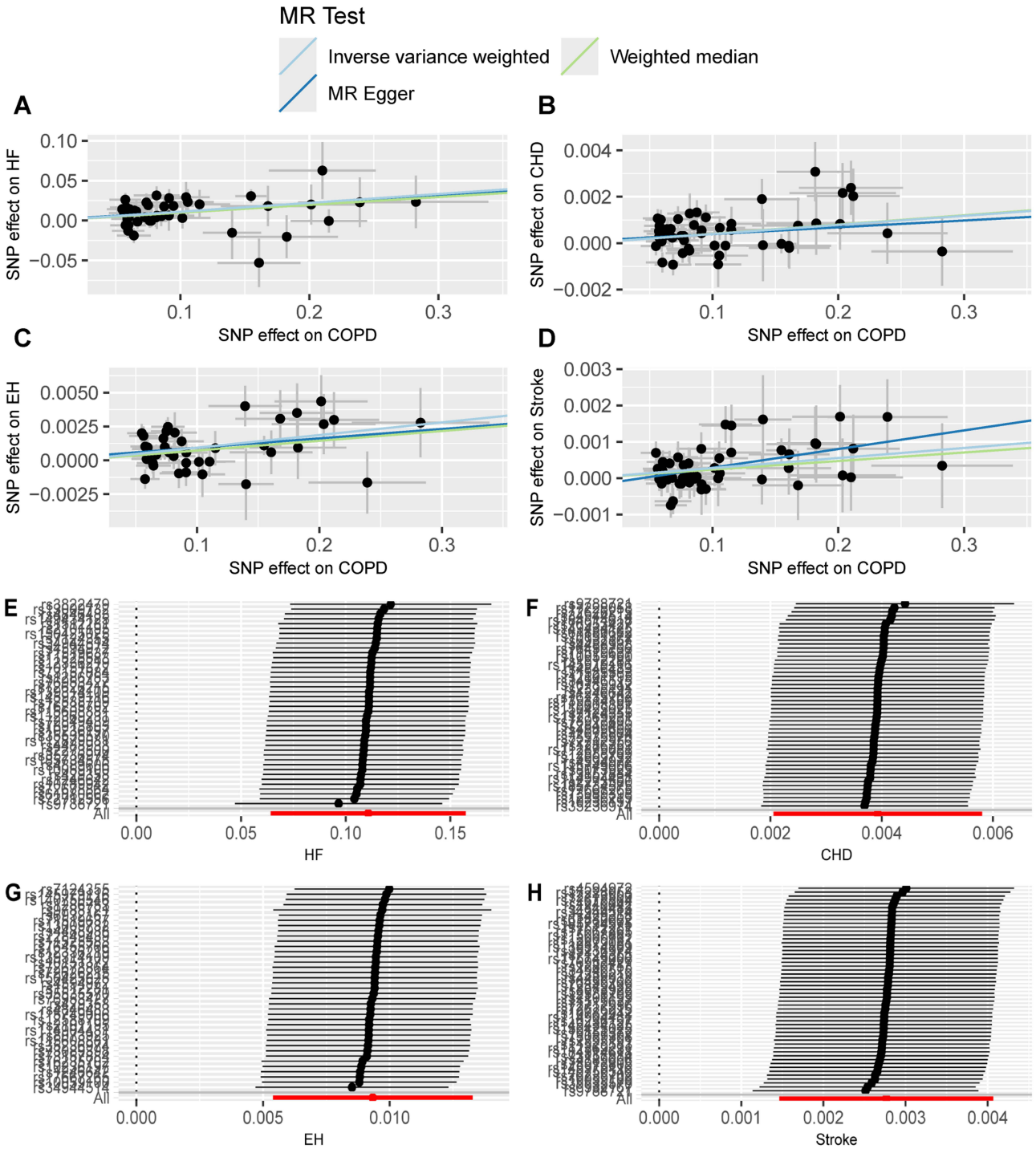

Figure 3 Plots on the 4 positive univariate MR studies. Notes: the plots of (**A**–**D**) are scatter plots of MR studies. The plots of (**E**–**H**) are the "leave-one-out" plot.

CI:11.94~55.89%) and 12.06% (95% CI:4.48~19.65%), respectively. The proportions of mediation for smoking initiation were 14.17% (95% CI: 4.16~24.18%), 11.70% (95% CI:1.57~21.83%), and 13.16% (95% CI:3.79~22.53%), respectively. The proportions of mediation for smoking status were 12.54% (95% CI:4.34~20.74%), 20.40% (95% CI: 7.04~33.76%), and 10.71% (95% CI: 3.12~18.30%), respectively. The proportions of mediation for FEV1 were 7.48% (95% CI:1.20~13.76%), 25.01% (95% CI:13.84~36.18%), and 8.68% (95% CI: 1.15~16.21%), respectively. Obesity played a role in the causal effect of COPD on HF and EH. The proportions of mediation were 30.98% (95% CI: 9.78~52.18%) and 35.59% (95% CI: 9.64~61.55%), respectively. (Table 3)

Table 2 Multivariable MR Analysis Outcomes

Potential Confounding Factors	Outcome	nsnp	Pval	OR	95% CI
BMI	HF	3	0.0023	1.077	1.027~ 1.129
	CHD	3	6.78E-05	1.004	1.002~1.006
	Stroke	3	0.0001	1.003	1.001~1.004
	EH	3	0.0002	1.008	1.004~ 1.013
CRP	HF	4	0.0002	1.169	1.076~1.271
	CHD	5	0.047	1.003	1.000~1.006
	Stroke	5	6.13E-08	1.004	1.002~1.005
	EH	5	0.00297	1.008	1.003~1.013
HDL	HF	3	6.66E-06	1.132	1.073~1.195
	CHD	4	0.0040	1.004	1.001~1.006
	Stroke	4	1.84E-07	1.004	1.003~1.006
	EH	4	4.20E-08	1.015	1.009~ 1.020
IL-6	HF	4	7.19E-05	1.171	1.083~ 1.266
	CHD	5	0.052	1.003	1.000~1.006
	Stroke	5	1.36E-09	1.004	1.003~ 1.005
	EH	5	0.0027	1.008	1.003~ 1.014
LDL	HF	5	1.63E-05	1.166	1.088~ 1.251
	CHD	6	0.141	1.003	0.999~1.006
	Stroke	6	0.0001	1.003	1.002~ 1.005
	EH	5	0.00019	1.013	1.006~ 1.020
T1DM	HF	6	0.00089	1.096	1.038~ 1.157
	CHD	7	0.0015	1.001	1.001~1.006
	Stroke	7	0.0028	1.002	1.001~ 1.004
	EH	6	0.00015	1.011	1.005~ 1.016
T2DM	HF	3	3.12E-05	1.125	1.064~ 1.189
	CHD	5	1.55E-05	1.005	1.003~1.007
	Stroke	5	0.0002	1.003	1.001~ 1.005
	EH	5	2.86E-06	1.013	1.007~ 1.018
Obesity	HF	8	0.0095	1.078	1.018~ 1.141
	CHD	8	0.0263	1.002	1.000~1.004
	Stroke	8	0.0128	1.002	1.000~ 1.003
	EH	7	0.0253	1.005	1.001~ 1.010
Triglycerides	HF	2	1.66E-08	1.187	1.118~ 1.259

(*Continued*)

Table 2 (Continued).

Potential Confounding Factors	Outcome	nsnp	Pval	OR	95% CI
	CHD	2	0.0091	1.004	1.001~1.007
	Stroke	2	4.35E-06	1.004	1.002~ 1.006
	EH	2	6.76E-06	1.015	1.008~ 1.022
Alcohol dependence	HF	10	1.35E-05	1.104	1.056~ 1.154
	CHD	12	0.0013	1.003	1.001~1.005
	Stroke	12	0.0010	1.002	1.001~ 1.003
	EH	11	8.17E-06	1.008	1.004~ 1.011
Smoking initiation	HF	9	0.0003	1.088	1.039~ 1.140
	CHD	10	0.0006	1.003	1.001~1.005
	Stroke	10	0.0009	1.002	1.001~ 1.004
	EH	9	3.85E-06	1.010	1.006~ 1.015
Smoking status	HF	9	0.0001	1.095	1.045~ 1.148
	CHD	8	3.49E-05	1.005	1.002~1.007
	Stroke	10	0.0055	1.002	1.001~ 1.003
	EH	9	6.57E-05	1.009	1.005~ 1.014
Total cholesterol	HF	2	6.81E-05	1.163	1.080~ 1.253
	CHD	4	0.3140	1.002	0.998~1.006
	Stroke	4	4.88E-05	1.004	1.002~ 1.005
	EH	4	0.0014	1.012	1.005~ 1.020

Abbreviations: BMI, Body mass index; CRP, C-reactive protein; HDL, High density lipoprotein; IL-6, Interleukin-6; LDL, Low density lipoprotein; T1DM, Type 1 diabetes mellitus; T2DM, Type 2 diabetes mellitus.

Table 3 Mediation MR Analysis Outcomes

Mediators	Outcomes	Mediation Effect in Total Effect	95% CI
BMI	HF	25.43%	10.31~40.54%
	Stroke	12.06%	4.48~ 19.65%
	EH	33.92%	11.94~55.89%
CRP	HF	0.31%	−18.98~19.61%
	Stroke	−5.25%	−41.54~31.04%
	EH	3.31%	−22.35~28.97%
HDL	HF	2.21%	−2.50~6.93%
	Stroke	1.05%	−1.52~3.62%
	EH	3.60%	−7.11~14.31%

(*Continued*)

Table 3 (Continued).

Mediators	Outcomes	Mediation Effect in Total Effect	95% CI
LDL	HF	−4.27%	−14.59~6.05%
	Stroke	−2.39%	−9.06~4.28%
	EH	−0.71%	−5.54~4.13%
T1DM	HF	0.23%	−6.33~6.79%
	Stroke	6.62%	−3.82~17.07%
	EH	10.40%	−5.03~25.82%
T2DM	HF	3.70%	−1.18~8.58%
	Stroke	1.59%	−1.12~4.31%
	EH	6.19%	−3.21~15.59%
Obesity	HF	30.98%	9.78~52.18%
	Stroke	−3.01%	−15.32~9.30%
	EH	35.59%	9.64~61.55%
Triglycerides	HF	0.02%	−4.28~4.24%
	Stroke	−0.06%	−1.46~1.33%
	EH	1.28%	−10.58~8.03%
Alcohol dependence	HF	2.35%	−3.24~7.94%
	Stroke	2.15%	−4.37~8.68%
	EH	1.74%	−3.47~6.96%
Smoking initiation	HF	14.17%	4.16~24.18%
	Stroke	13.16%	3.79~22.53%
	EH	11.70%	1.57~21.83%
Smoking status	HF	12.54%	4.34~20.74%
	Stroke	10.71%	3.12~18.30%
	EH	20.40%	7.04~33.76%
Total cholesterol	HF	−3.80%	−11.07~3.48%
	Stroke	−1.33%	−5.11~2.45%
	EH	0.15%	−3.57~3.88%
Acute upper respiratory infections	HF	9.09%	−1.26~19.45%
	Stroke	−3.19%	−11.80~5.43%
	EH	6.07%	−4.46~16.60%
Acute lower respiratory infection	HF	−4.20%	−12.63~4.24%
	Stroke	−0.41%	−13.46~12.64%
	EH	7.53%	−4.46~19.53%

(*Continued*)

Table 3 (Continued).

Mediators	Outcomes	Mediation Effect in Total Effect	95% CI
FEV1	HF	7.48%	1.20~13.76%
	Stroke	8.68%	1.15~16.21%
	EH	25.01%	13.84~36.18%

Abbreviations: BMI, Body mass index; CRP, C-reactive protein; HDL, High density lipoprotein; IL-6, Interleukin-6; LDL, Low density lipoprotein; T1DM, Type 1 diabetes mellitus; T2DM, Type 2 diabetes mellitus; FEV1, Forced expiratory volume in the first second.

Discussion

We examined the causal relationship between COPD and CVDs using GWAS summary datasets and it was concluded that: (1) There were positive associations between COPD and HF, CHD, EH, and Stroke, but the causality of COPD with CHD was influenced by confounding factors such as IL-6, LDL, and total cholesterol levels. COPD did not show causality with AF. (2) HF and Stroke were not causally associated with COPD. CHD and EH were significantly causally associated with COPD and AF had a suggestive causal association. (3) BMI, smoking initiation, smoking status, and FEV1 were identified as mediators of COPD associated with HF, EH, and stroke as well. Additionally, obesity was found to be a mediator of COPD associated with HF and EH.

Relevant studies have shown that inflammation is an important factor mediating COPD complicating CVDs.[17] Inflammatory reactions in the lungs can develop into systemic inflammation through the blood circulation, and damage to blood vessels. Damage to the arterial endothelium by inflammatory factors induces atherosclerosis and thrombosis, which in turn leads to CVDs. Mills et al demonstrated that the high incidence of CVDs in patients with COPD is associated with atherosclerosis, which in turn is linked to vascular dysfunction due to inflammation.[18] Reactive oxygen species released by inflammatory cells oxidize lipids attached to the sidewalls of blood vessels, and increased levels of oxidized lipoproteins promote the progression of atherosclerosis.[19] Dysregulation of proteases and antiproteases is an important mechanism in the development of COPD, of which the main ones associated with CVDs are matrix metalloproteinases (MMPs), such as MMP-2, MMP-9, and MMP-12. At the onset of the disease, they are present in large quantities in atherosclerotic plaques, in the circulation, in lung tissues, and in patient sputum.[20–23] MMP, oxidative stress, and inflammatory cell production interact to promote plaque progression.

The present results are in agreement with most of the previous ones. In a cohort study from a Danish hospital, the percentage of HF occurrence was significantly increased in patients with COPD compared to those without COPD (13.3% vs 4.0%).[24] And, HF had the largest OR of the three positive results, implying the highest propensity to develop the disease in common CVDs. Curkendall et al discovered that, after adjusting for cardiovascular risk factors, HF (OR=3.84, CI: 3.56–4.14) had a higher likelihood of occurring compared to angina (OR=1.61, CI:1.47–1.76), acute myocardial infarction (OR=1.61, CI:1.43–1.81), and stroke (OR=1.11, CI: 1.02–1.21), with a propensity 2–3 times greater.[25] This outcome was expected due to pulmonary hypertension and right heart failure of pulmonary origin resulting from the late progression of COPD. In several observational studies, COPD has shown a clear causal relationship with CHD. COPD did not show a causal relationship with CHD after adjusting for confounders IL-6, LDL, and total cholesterol levels, respectively. Similarly, no causal relationship between COPD and CHD was shown in an MR study of COPD and cardiac traits (causal estimate = 0.004, p= 0.40).[26] In another more comprehensive bidirectional MR study of COPD and cardiac traits, Cross-trait LD score regression showed that FEV1, FEV, and FEV1/FVC correlated with CHD, but there was no causal relationship in either MR study.[27] Considering that the MR study examined the relationship at the genetic level, the influence of confounding factors was excluded. Therefore, it is hypothesized that the previous observational study may has gained a strong association between the two due to many common risk factors. Statins of traditional drugs that improve the prognosis of cardiovascular disease have anti-inflammatory and antioxidant, lipid-lowering, and immunomodulatory effects to improve endothelial cell function. A meta-analysis showed statin improved exercise tolerance, quality of life, and lung function in patients with COPD, and greater benefits are seen in patients with

COPD combined with CVDs, systemic inflammation, and hyperlipidemia.[28] However, in another RCT, simvastatin had no benefit on acute exacerbation rates or time to first acute exacerbation in COPD patients who did not have heart disease or diabetes.[29] Therefore, in conjunction with our study, we hypothesize that the benefits of statin in COPD patients may be primarily derived from lipid-lowering, antioxidant therapy for heart disease. Early clinical use of statin in patients with COPD may be able to delay the atherosclerotic process, reduce the risk of cardiovascular disease, and prevent the onset of CHD. Multivariate MR analysis of a previous study showed that very severe COPD was associated with a higher risk of developing hypertension (OR=1.6, 95% CI: 1.4–1.9).[30] But the specific mechanisms involved need further study. The present study demonstrates a causal relationship between COPD and stroke even after adjusting for multiple confounders, similar to most previous studies.[31,32] A recent cross-sectional study by Chen et al showed a higher incidence of stroke in patients with established COPD compared to patients without COPD (14.1% vs 3.9%), but there was no causal relationship between COPD and stroke after adjusting for confounders.[33] So there is still a need for further research on the independent causal relationship between the two.

Studies related to reverse causality and mechanisms between COPD and CVDs are inadequate compared to studies of forward causality. In a retrospective cohort study involving 86,795 patients, newly diagnosed HF (adjusted HR: 1.45, 95% CI: 1.30 to 1.62) and possible HF (adjusted HR: 1.65, 95% CI: 1.58 to 1.72) similarly increased acute exacerbation risk of COPD.[34] However, our study did not find a reverse causal association between COPD and HF, which is consistent with the previous MR study.[35] Reverse MR analysis in the current investigation showed that EH was able to promote the development of COPD, which may be due in part to the use of anti-hypertensive medications, such as beta-blockers.[36] The use of medications for COPD and CVDs has always been conflicting and a point of concern for clinicians, and further research is needed in this area in the future. Several studies have shown a relationship between COPD and AF, but the direction is not conclusive, and there are still studies validating the increased incidence of COPD in patients with AF.[37–44] The results of this study show reverse causation of COPD with AF and CHD, but both of them are influenced by common cardiopulmonary risk factors as well as cardiopulmonary diseases, and the exact mechanisms need to be further explored.

Mediating factors were explored in that the presence of these mediating factors in patients with COPD increased the incidence and exacerbation of CVDs in the presence of pre-existing COPD or these risk factors. FEV1 is an established independent risk factor for CVDs, and our mediator MR study corroborates the findings of previous research in this area.[45] Similar findings were obtained in a cross-sectional study, where the prevalence of hypertension and CVDs increased progressively with the increasing severity of COPD (decrease in FEV1).[30] Obesity or increased BMI may bring about a variety of metabolic disorders in the body, such as high blood glucose, high blood lipids, and increased cardiac burden due to water and sodium retention. Nicotine in cigarettes damages the vascular endothelial and causes an increase in the oxygen free radicals within the organism. Weight loss and smoking cessation have been the most important preventive and therapeutic tools in patients with COPD combined with CVDs.

Our study offers novel clinical trial evidence and insights, including the reverse causality between CVD and COPD and the impact of newly identified confounders on the COPD-CHD relationship, which may benefit future research. This study highlights the necessity of an aggressive, interdisciplinary approach to the management of cardiopulmonary disease, recognizing COPD as a major cardiovascular risk factor and incorporating tailored therapies to mitigate this risk. Concerning researchers, our MVMR study and mediator MR study open pathways for exploring pathophysiological mechanisms between COPD and CVD, urging further research into effective cardiopulmonary disease management strategies, identification of potential biomarkers for early detection, and assessment of the broader systemic impact of cardiopulmonary disease.To obtain robust results, we used multiple methods of excluding the horizontal pleiotropy and confounding factors. We used multiple datasets to validate our positive results. We derived the mediator and mediator proportions of positive outcomes through a mediation Mendelian randomization study. However, some deficiencies exist in our study. First of all, our research population is Europeans so the findings cannot be applied to other populations. Second, study bias is unavoidable. The relationship between COPD and CVDs is complex and despite our best efforts to minimize pleiotropy, unknown intrinsic and extrinsic associations between other exposures and outcomes may lead to pleiotropy. It is not practical to study all possible confounders and mediators in MVMR and mediator MR in a completely exhaustive manner. Finally, We did not prominently classify and stage COPD according to the commonly

used clinical guidelines, such as distinguishing between chronic stable COPD and acute exacerbations of COPD. Currently, no study has been able to clarify in which type of patients with impaired lung function CVDs can be more prevalent, and it is also difficult to explore the specific relationship between COPD subtypes and individual CVDs,[46] as the MR study is an emerging research methodology and the available research data are limited, more detailed MR studies need to be done in the future.

Conclusion

We found a positive causal relationship between COPD and HF, EH, and Stroke essentially unaffected by other confounders. The causal relationship exhibited between COPD and CHD was affected by confounders IL-6, LDL, and total cholesterol levels. There was an inverse causal relationship between COPD and CHD, EH.BMI, obesity, initiation of smoking, smoking status, and FEV1 were the mediators between COPD and CVDs. Intervention of intermediate factors as well as the treatment of COPD will reduce the incidence and exacerbation of CVDs and improve the prognosis of patients.

Abbreviations

COPD, Chronic obstructive pulmonary disease; CVDs, Cardiovascular diseases; HF, Heart failure; CHD, Coronary heart disease; EH, Essential hypertension; AF, Atrial fibrillation; SNPs, Single nucleotide polymorphisms; RCT, Randomized controlled trial; GWAS, Genome-wide association studies; IVs, instrumental variables; LD, linkage disequilibrium; OR, odds ratios; CIs, confidence intervals; MR-PRESSO, MR pleiotropy residual sum and outlier; MVMR, Multivariable MR; IVW, Inverse variance weighted; BMI, Body mass index; CRP, C-reactive protein; HDL, High density lipoprotein; IL-6, Interleukin-6; LDL, Low density lipoprotein; T1DM, Type 1 diabetes mellitus; T2DM, Type 2 diabetes mellitus; FEV1, Forced expiratory volume in the first second; MMP, Matrix metalloproteinase.

Data Sharing Statement

All of the datasets used in this study came from publicly accessible resources found at (https://gwas.mrcieu.ac.uk/).

Ethics Approval and Consent to Participate

Relevant data from the GAWS database and summary statistics for the studies used for analysis were collected from published studies. All studies have received prior approval from their institutional review boards (IRBs). The Ethics Committee of Beijing Anzhen Hospital approved the study protocol and waived the requirement for informed consent. As per their guidelines, this study exclusively utilized publicly available data without using any individual-level data. Therefore, no additional IRB approval was necessary.

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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 competing interests in this work.

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