

# Causal Associations Between Chronic Obstructive Pulmonary Disease and Common Comorbidities: Evidence from Comprehensive Genetic Methods

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**Background:** Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory lung disease with high morbidity and mortality worldwide. Observational studies have shown correlations between common extrapulmonary comorbidities and COPD, but the existence of correlations does not necessarily prove a causal association. Therefore, causal relationships between diseases need to be explored by means of causal inference methods.

**Materials and Methods:** Genetic correlation and two-sample Mendelian randomization (MR) analysis were explored to assess the causal relationship between exposures and outcomes with the genome-wide association studies (GWAS) dataset. Different sensitivity analyses were conducted to verify the robustness and consistency of results.

**Results:** The linkage disequilibrium score regression showed that cardiovascular disease (CVD), hypertension (HTN) and type 2 diabetes mellitus (T2DM) were significantly genetically associated with COPD. T2DM and HTN were found to have a positive causal effect on COPD. The odds ratio (OR) of T2DM on COPD was 1.111 (95% CI, 1.063–1.160;  $P < 0.0001$ ) and that of HTN on COPD was 1.125 (95% CI, 1.084–1.167;  $P < 0.0001$ ). Similar results were verified by different MR methods. Furthermore, COPD had a positive causal effect on T2DM (OR 1.152 (95% CI, 1.064–1.246;  $P = 0.0005$ )).

**Conclusion:** Our findings provided evidence for the causal association between HTN, T2DM and COPD, which would render new insights into the pathogenesis, prevention and intervention for COPD.

**Keywords:** chronic obstructive pulmonary disease, cardiovascular diseases, type 2 diabetes mellitus, hypertension, Mendelian randomization, causal effect

## Introduction

Chronic obstructive pulmonary disease (COPD) is a disease characterized by airflow obstruction and respiratory symptoms arising from airway and alveolar abnormalities.<sup>1</sup> The prevalence of COPD has been projected to increase throughout the world, due to continued exposure to risk factors and the population aging, especially for middle-aged and elderly people in low and moderate income countries, making it a leading cause of global morbidity and mortality.<sup>2,3</sup> Millions of families are afflicted by it, and in 2015, approximately 3.2 million people perished worldwide due to COPD, making COPD the third-highest age-standardized mortality in the world.<sup>4</sup> The interplay that exists between genetic factors and environmental exposures combine to influence the risk of COPD.<sup>5</sup> One of the most critical and visible environmental exposure is tobacco smoking, while other factors also contribute to COPD over the lifetime like indoor and outdoor air pollution, occupational exposures and genetic factors.<sup>6,7</sup>



COPD patients often coexist with other chronic comorbid diseases<sup>8,9</sup> which have significant impact on disease prognosis.<sup>10</sup> Previous observational studies have shown that common non-respiratory comorbidities among diagnosed COPD patients include diabetes mellitus (DM), hypertension (HTN), cardiovascular disease (CVD) and other chronic conditions.<sup>11,12</sup> A logistic regression model, adjusting for many confounders shows that severe and very severe COPD patients are significantly more likely to suffer from CVD, DM and HTN.<sup>13</sup> Similar findings are supported by results from a meta-analysis including 29 datasets.<sup>14</sup> However, these findings are derived from observational research and are prone to reverse causal effect due to confounding factors such as economic and social status, lifestyle, and individual underlying health state.<sup>15</sup> The presence of measurement error in observational studies can pose a challenge in drawing scientifically valid conclusions. Therefore, correlation analyses cannot be simply equivalent to causal relationship.

Randomized controlled trial (RCT) is an accepted scientific standard to evaluate causal effects, but its application is limited by the impracticality, cost and ethical considerations.<sup>16</sup> Notably, the advent of Mendelian randomization (MR), a “natural” RCT, provides an alternative way to evaluate the causality based on Mendel’s law of inheritance and the introduction of genetic instrumental variable (IV) (eg, single nucleotide polymorphisms [SNPs]).<sup>17,18</sup> MR corroborates causal associations between exposures and outcomes by excluding the interference from unobserved confounding factors and overcoming the reverse causation.<sup>19</sup> Because the offspring alleles are assigned at random by the parents during conception, the influences of factors like potential confounders and measurement errors, which are common in causal inference, can be eliminated.<sup>17</sup> Therefore, by leveraging naturally occurring genetic variations unaffected by confounders, MR analysis offers a valuable approach to address the limitations encountered in traditional observational studies, including confounding factors and reverse causality. Benefitting from the publicly available genome-wide association studies (GWAS), two-sample MR has been widespread used to interrogate the causal effect,<sup>20</sup> which address the issues of finding appropriate controls and the ethical concerns faced in RCT, and provide a reliable, convenient, efficient, and cost-effective method for assessing exposure-outcome causality.<sup>21</sup>

In the present study, we performed the bidirectional two-sample MR approach to demonstrate the causal association between COPD and common chronic diseases (CVD, type 2 DM (T2DM) and HTN) using publicly available GWAS summary data. The results could reinforce the evidence in the etiology of COPD, as well as contribute valuable insights for enhancing disease diagnosis and further exploration.

## Materials and Methods

### Study Design

Bidirectional causal relationships between COPD and three common comorbidities (CVD, T2DM and HTN) were performed by two-sample MR analysis using GWAS summary data. Further, we verified the causal relationship utilizing different MR methods based on distinguished model assumptions.

### Data Sources

The GWAS data of COPD was derived from the UK Biobank (UKBB) including 361,194 independent individuals with 26,710 cases and 334,484 controls. To avoid the sample overlap between exposure and outcome,<sup>22</sup> GWAS summary data on CVD, T2DM and HTN were from Finland – FinnGen Project comprising 453,733 samples with 2447 disease endpoints (as of June 2024). The GWAS summary statistics included in our research were all restricted to European ancestry. [Table 1](#) demonstrated the characteristics of GWASs data in our study.

### Genetic Correlation Analysis

The linkage disequilibrium score regression (LDSC) was used to estimate the SNP heritability of the two traits and the genetic correlation ( $r_g$ ) between them by regressing the product of z-statistics over the linkage disequilibrium scores.<sup>23</sup>

### Two-Sample MR Analysis

MR selected and utilized the instrumental SNP variables to investigate bidirectional causality for exposure (eg, CVD, T2DM and HTN) on the outcome (eg, COPD). To ensure the robustness and reliability of MR analysis, the SNPs as valid

**Table 1** Basic Information About the GWAS Data

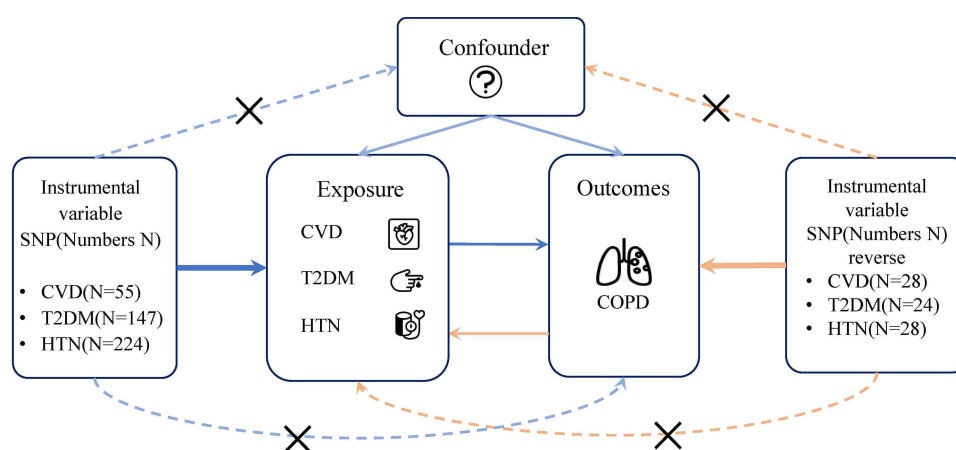
Diseases	Source	Population	Sample Size	Cases	Controls
COPD	Neale lab	European	361194	26,710	334484
T2DM	Finn Gen	European	419930	49,101	370829
HTN	Finn Gen	European	453657	137,312	316345
CVD	Finn Gen	European	453733	221,781	231,952

**Abbreviations:** COPD, chronic obstructive pulmonary disease; T2DM, type 2 diabetes mellitus; HTN, hypertension; CVD, cardiovascular disease.

IVs should satisfy the following core assumptions (Figure 1): (1) the relevance assumption: IVs are strongly correlated with exposure; (2) the independence assumption: IVs are not correlated with confounders that have an effect on outcome; and (3) the exclusion restriction assumption: IVs only affect outcome through exposure.

The initial step in MR analysis was to choose the valid IVs for exposure followed by the stringent procedures: (1) we screened the SNPs significantly associated with exposure at genome-wide significance ( $P < 5 \times 10^{-8}$ ). With regard to the GWAS summary data for COPD in our study, a more lenient threshold of  $5 \times 10^{-6}$  was chosen due to the limited number of SNPs falling below the threshold of  $5 \times 10^{-8}$ . (2) selected SNPs were matched with GWAS summary dataset of outcome by chromosome and rsid. (3) independent SNPs were extracted using PLINK (version 1.90),<sup>24</sup> based on physical distance  $> 10,000$  kb or  $r^2 < 0.001$ . (4) we further excluded the SNPs which the alleles of the exposure and outcome variables mismatch or have null values. Following these steps, IVs were obtained for the next step of the analysis, with detailed information shown in the [Supplementary Tables](#).

Estimations of causal effects were predominantly carried out through the MR inverse-variance weighted (IVW) method, which assumed all IVs to be valid.<sup>25</sup> To ensure the robustness and consistence of the results, our study further selected other MR methods for sensitivity analysis: (1) weighted median method (MR-WME): consistency occurs when 50% of the weights from genetic variants are valid.<sup>26</sup> (2) weighted mode-based method (MR-MBE): a consistent estimate can be obtained if valid instruments contribute the maximal weights in the  $k$  subsets.<sup>27</sup> (3) IVW method using robust regression (MR-Robust): a regression-based robust IVW method that assigns lower weights to outliers.<sup>28</sup> (4) MR-Lasso: the method applies Lasso penalization to identify the candidate instrumental SNPs.<sup>28</sup> (5) MR Pleiotropy RESidual Sum and Outlier (MR-PRESSO): outliers can be identified using residual sums of squares and removed to estimate the causal effects.<sup>29</sup> (6) MR-Egger: some violations of the underlying assumptions of the IVs can be detected and the effect estimates can be insulated from these violations.<sup>30</sup> (7) MR Robust Adjusted Profile Score (MR-RAPS): it is robust to both systematic and specific polymorphisms.<sup>31</sup> (8) contamination mixture method (MR-CONMIX): a two-sample MR modeling method can obtain robust and effective causal estimation in case of some invalid instrumental variables.<sup>32</sup>



**Figure 1** Illustrative diagram for the MR study design in our research. The instrumental variables (IVs) required in the analysis should satisfy three assumptions. Dotted lines represent possible ways that the assumptions could be violated.

Further, SNPs were removed one by one using the leave-one-out (LOO) method to determine the impact of each genetic variant on the overall causal effect.

We calculated the proportion of variance explained (PVE) by an individual SNP and then computed the F-statistic to avoid the weak instrumental bias and evaluate the strength of IVs. An IV with an F-statistic >10 can reduce the probability of serious bias in causal inference.<sup>33</sup> Additionally, visual methods such as scatter plots, funnel plots, and LOO plots were used to identify IVs with pleiotropy.

The MR analyses were performed using R packages “MendelianRandomization”, “MRPRESSO” and “mr.raps”. The statistical analyses were conducted within the R (version 4.4.0) environment.

## Result

### Genetic Correlation Analysis

In the genetic correlation analysis, the positive association was found between COPD and CVD ( $r_g = 0.305$ ,  $SE=0.054$ ,  $P<0.001$ ). The estimated genetic correlation size between COPD and T2DM was 0.321 ( $SE=0.043$ ,  $P<0.001$ ). For COPD and HTN, the genetic correlation was 0.297 ( $SE=0.042$ ,  $P<0.001$ ).

### Two-Sample Mendelian Randomization Analysis

#### Causal Effect of CVD on COPD

We selected 55 SNPs as valid IVs, with overall F statistic of 36.50, suggesting that there was no weak instrumental variable bias ([Supplementary Table S1](#)). The causal effect was reported as odds ratio (OR) which represent the increase in COPD risk per unit increase in log odds of CVD. MR-Egger intercept term ( $P=0.196$ ) showed no existence of horizontal pleiotropy. As shown in [Figure 2](#), no causal effect of CVD on COPD was found. Similarly, insignificant results were derived from other MR methods. The LOO plot funnel plot and scatter plots and were seen in [Figure S1A](#), [S1C](#) and [S1E](#), which indicated nonexistence of outlier.

#### Causal Effect of T2DM on COPD

In the causal analysis for T2DM on COPD, 147 SNPs included and overall F-statistic was 39.44 ([Supplementary Table S2](#)). The IVW-random effects model showed that the OR value was 1.111 (95% CI, 1.063–1.160;  $P<0.0001$ , [Figure 2](#)). Taken into account multiple MR analysis, the OR was estimated to be 1.130 (95% CI, 1.071–1.193;  $P<0.0001$ ) by MR-WME, 1.216 (95% CI, 1.083–1.366;  $P=0.0009$ ) by MR-MBE, 1.074 (95% CI, 1.021–1.131;  $P=0.0062$ ) by MR-Robust, 1.103 (95% CI, 1.063–1.145;  $P<0.0001$ ) by MR-Lasso, 1.067 (95% CI, 1.019–1.117;  $P=0.0061$ ) by MR-PRESSO, 1.075 (95% CI, 1.022–1.130;  $P=0.0054$ ) by MR-RAPS and 1.301 (95% CI, 1.250–1.354;  $P<0.0001$ ) by MR-CONMIX. [Figure S2A](#), [S2C](#) and [S2E](#) indicated no heterogeneity and outlier. No horizontal pleiotropy existed from MR-Egger intercept term ( $P=0.560$ ).

#### Causal Effect of HTN on COPD

There were 224 SNPs for the causal analysis of HTN on COPD, and overall F-statistic was 40.36 ([Supplementary Table S3](#)). IVW-random effects model indicated the OR value was 1.125 (95% CI, 1.084–1.167;  $P<0.0001$ , [Figure 2](#)). The positive association was consistent across sensitivity analysis. The OR value was 1.144 (95% CI, 1.094–1.197;  $P<0.0001$ ) by MR-WME, 1.202 (95% CI, 1.090–1.326;  $P=0.0002$ ) by MR-MBE, 1.095 (95% CI, 1.050–1.142;  $P<0.0001$ ) by MR-Robust, 1.165 (95% CI, 1.131–1.201;  $P<0.0001$ ) by MR-Lasso, 1.089 (95% CI, 1.048–1.130;  $P<0.0001$ ) by MR-PRESSO, 1.096 (95% CI, 1.051–1.144;  $P<0.0001$ ) by MR-RAPS and 1.316 (95% CI, 1.277–1.356;  $P<0.0001$ ) by MR-CONMIX. No heterogeneity and outlier were observed ([Figure S3A](#), [S3C](#) and [S3E](#)). MR-Egger intercept term ( $P=0.796$ ) showed no existence of horizontal pleiotropy.

#### Causal Effect of COPD on CVD

Twenty-eight SNPs were totally obtained for the analysis with details shown in the [Supplementary Table S4](#). The F-statistic of each IV exceeded 10 with an overall F-statistic of 24.55. We observed no casual effect of COPD on CVD through different MR methods ([Figure 3](#)). MR-Egger intercept term ( $P=0.056$ ) indicated no horizontal pleiotropy.

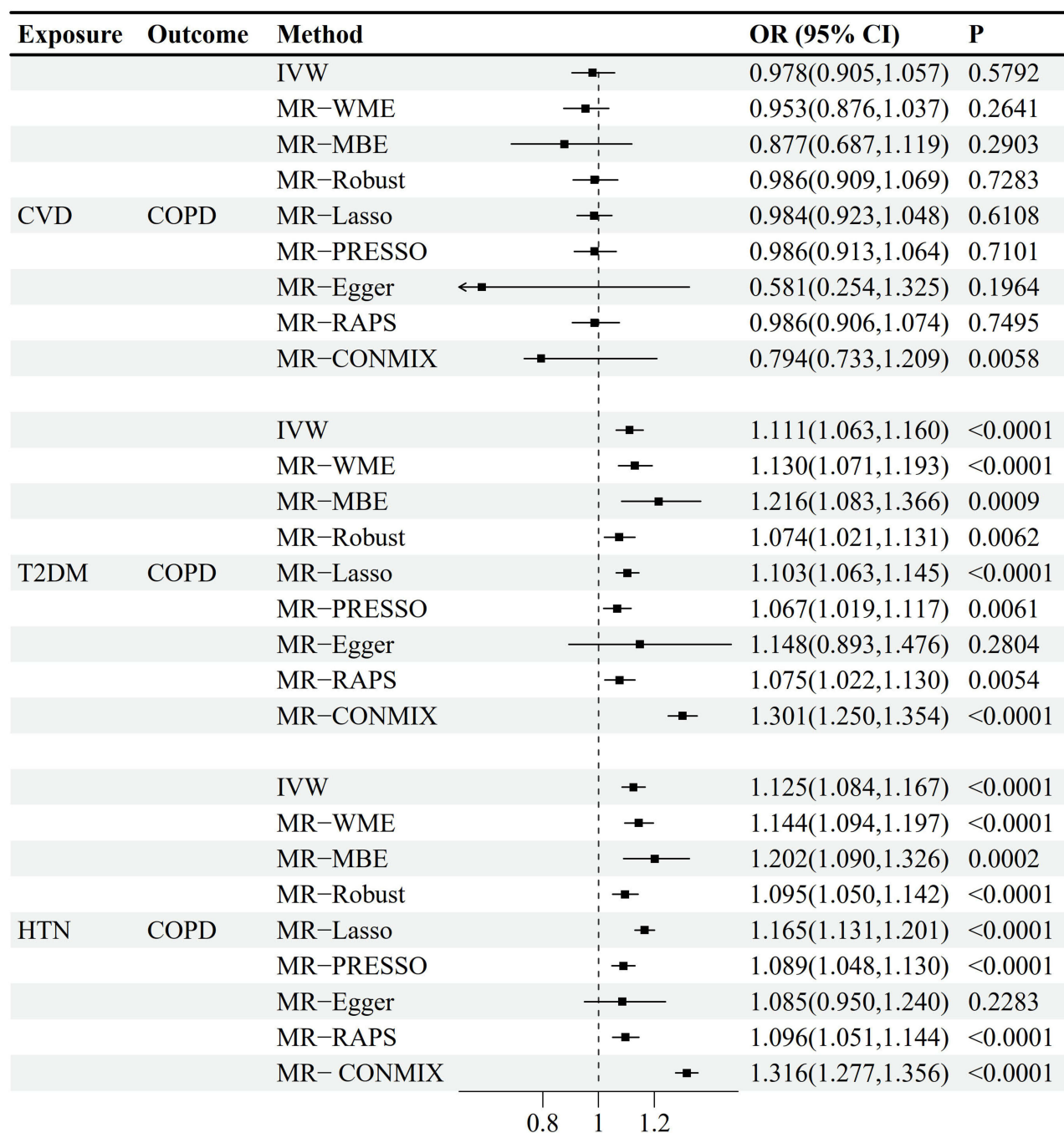
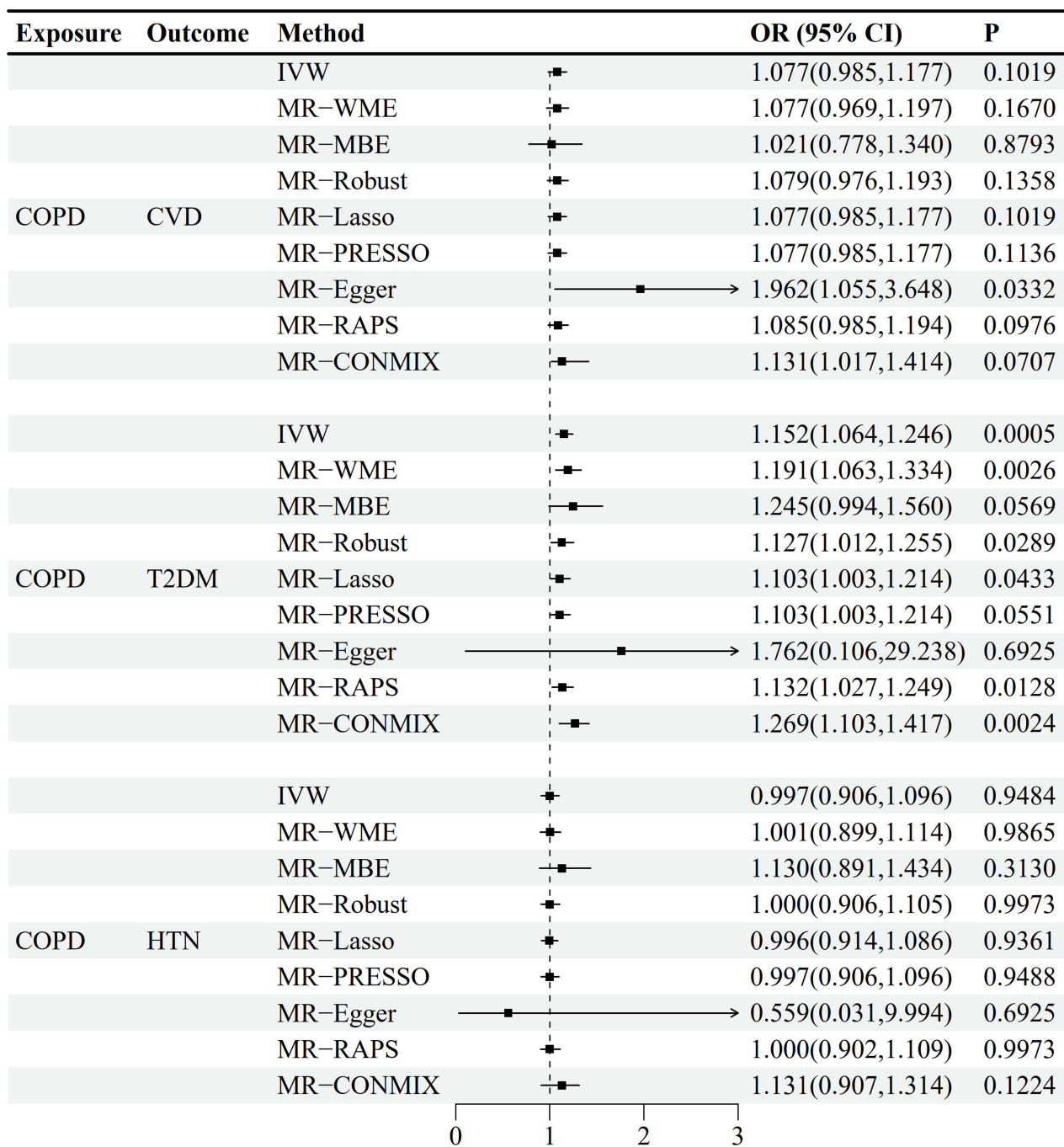


Figure 2 Estimations of causal effect of CVD, T2DM and HTN exposures on COPD outcome from various Mendelian randomization methods.

### Causal Effect of COPD on T2DM

We selected 24 SNPs as valid instrumental variables with overall F statistic of 22.63 (Supplementary Table S5). After robust regression correction, IVW effects model showed that the OR value was estimated to be 1.152 (95% CI, 1.064–1.246; P=0.0005), indicating that COPD patients had an increased risk of T2DM. In addition, results from other MR methods suggested the causal effect of COPD for T2DM was convincing (Figure 3). Specifically, it was estimated to be 1.191 (95% CI, 1.063–1.334; P=0.0026) by MR-WME, 1.127 (95% CI, 1.102–1.255; P=0.0289) by MR-Robust, 1.103 (95% CI, 1.003–1.214; P=0.0433) by MR-Lasso, 1.103 (95% CI, 1.003–1.214; P=0.0551) by MR-PRESSO, 1.132 (95% CI, 1.027–1.249; P=0.0128) by MR-RAPS and 1.269 (95% CI, 1.103–1.417; P=0.0024) by MR-CONMIX. No



**Figure 3** Estimations of causal effect of COPD exposure on CVD, T2DM and HTN outcomes from various Mendelian randomization methods.

horizontal pleiotropy existed ( $P=0.207$ ). Scatter plot, funnel plot, and LOO plot were listed in [Figure S2B](#), [S2D](#) and [S2F](#), which indicated no obvious outliers and no potential outlier.

### Causal Effect of COPD on HTN

For the causal analysis of COPD on HTN, 28 SNPs were obtained and the overall F statistic was 22.86 ([Supplementary Table S6](#)). The causal effect of COPD on HTN was insignificant with different MR models ([Figure 2](#)). MR-Egger intercept term ( $P=0.694$ ) shown no horizontal pleiotropy.

## Discussion

This study mainly investigated the causal associations between COPD and common comorbidities (CVD, T2DM and HTN) by the two-sample MR method from the perspective of statistics and genetics. The MR method distinguished from traditional observational research by diminishing the impact of confounding factors. Our study suggested that HTN and T2DM had positive causal effects on COPD, increasing the risks of suffering from COPD. On the other hand, our investigation found that COPD had a positive causal effect on T2DM, with COPD patients having an increased risk of T2DM compared to those without COPD. Benefiting from the Mendelian randomization, our research mitigated the confounding affects stemming from observational studies and contributed to robust evidentiary causal associations between COPD and its comorbidities.

It has been extensively depicted that COPD patients often comorbid with chronic diseases, with hypertension highly prevalent in COPD patients.<sup>34,35</sup> Published study indicated that arterial stiffness is associated with the exacerbations of COPD, which would further contribute to systemic hypertension.<sup>36</sup> The shared risk factors such as lifestyle, smoking and environmental factors may predispose the patients to suffer from HTN and COPD.<sup>37</sup> Our study demonstrated positive causal association of HTN exposure on COPD outcome, which suggested a novel insight unreported in the previous literature.

There are several underlying mechanisms contributed to this association including oxidative stress, systemic inflammation, enhanced platelet activation, endothelial dysfunction,<sup>38</sup> as well as autonomic dysfunction.<sup>39–41</sup> Published studies had shown strong evidence that COPD patients are known to exhibit high systemic inflammation which acted as major pathobiological role connecting COPD and HTN.<sup>42,43</sup> Studies had shown that higher inflammatory markers such as C-reactive protein and interleukin-6 are associated with lower forced expiratory volume in 1 second (FEV1) level.<sup>44</sup> Besides the above mechanisms, some studies have speculated that the association between HTN and COPD could be explained by the destruction of elastic fibers and increased deposition of collagen fibers. Research indicated that arterial stiffness is associated with decreased FEV1 and increased emphysema,<sup>45</sup> and airflow limitation was linked with atherosclerosis irrespective of smoking history.<sup>46</sup> In addition, the intertwined genetic underpinnings of the comorbid conditions may also contribute to the causal association.<sup>47</sup>

Observational studies have identified a higher risk of DM among COPD patients after adjusting for BMI, smoking, and other confounding factors.<sup>48</sup> In addition, published studies suggested diabetes was a risk factor for exacerbation of COPD and had negative impact on COPD patients.<sup>49</sup> Results from our study provided evidence to corroborate the bidirectional causal effects between COPD and T2DM, reinforcing conclusions drawn from observational studies. Chronic systemic inflammation and oxidative stress may contribute to the bidirectional causal relationship between COPD and DM.<sup>50,51</sup> Available evidence indicated that the inflammation markers were correlated with insulin resistance among COPD patients and subsequently promoted the glucose intolerance.<sup>52</sup> Oxidative stress decreased the insulin sensitivity and disrupted insulin signaling, which also contributed to the pulmonary damage.<sup>53</sup> Notably, different from other respiratory disease, it has been speculated that COPD and diabetes shared similar inflammatory state dominated by Th1 cells, neutrophils and macrophages.<sup>54</sup> Pro-inflammatory cytokines produced by adipose tissue and increased ectopic fat accumulation in COPD patients may inhibit insulin receptor signaling and lead to insulin resistance and cause an increased risk of DM.<sup>55</sup> COPD patients accompanied with lower activity level and the usage of corticosteroids may lead to higher risk of hyperglycemia which should be another potential mechanism. Conversely, evidence suggested that hyperglycemia had adverse effect on the lungs by increasing the pulmonary inflammation or susceptibility to bacterial infection.<sup>56</sup> Further, T2DM was associated with reduced lung volume and airflow limitation. A prospective study indicated that diabetes and prediabetes were related with higher risk of and worse survival for COPD.<sup>57</sup> Additionally, genetic interplay may partly unveil the causal correlation between COPD and DM.<sup>58</sup>

Finding the modifiable risk factors is vital for disease diagnosis and treatment. Our results suggested that hypertension and T2DM increased the risk of COPD and COPD patients had high risk of developing T2DM. Previous study also suggested that insulin network and sodium-glucose transporter-2 inhibitors may serve as potential targets to manage COPD patients and prevent incidence of COPD exacerbation.<sup>59,60</sup> A weak association between poor glycemic control and increased risk of COPD in T2DM patients was observed.<sup>61</sup> On the other hand, researches indicated antihyperglycemic

medications may improve lung function index in DM patients.<sup>62</sup> Observational study found systolic blood pressure level was correlated with severity of airflow limitation.<sup>63</sup> Therefore, we suggested that optimal control of blood pressure and glucose level may reduce the risk of COPD and beneficial for the prognosis of the COPD. Clinicians should put more attention on the regular check-ups among the high-risk patients. Considering their mutual increased risk and incorporating the research findings into public health campaigns, advocating for lifestyle changes and early intervention would be beneficial for COPD and T2DM prevention and management.

Our strength of this study was the bidirectional causal effects between exposures and outcomes were achieved by comprehensive and complementary genetic methods. Further, multiple-sensitivity analyses were employed to enhance the robustness of the conclusion. However, several limitations existed in our study. First, we were unable to explore the gender-specific effect on COPD due to the lack of gender-specific GWAS summary data. Second, participants included in this study were from European populations, so the conclusion drawn from this study may not be representative of the general population.

## Conclusion

Our study demonstrated the casual relationships between HTN, T2DM and COPD. Based on our findings, there are strong evidence that T2DM and HTN would increase the risk of COPD. And patients with COPD would have higher risk of T2DM. These results suggest that lung function tests should be incorporated into clinical evaluation among hypertension and diabetes patients. Meanwhile, blood glucose level should be frequently screened in COPD patients. Control of blood pressure and glucose may reduce the incidence of COPD. However, further studies are required to validate the mechanism and test whether interventions to control hypertension or diabetes may reduce the COPD risk.

## Data Sharing Statement

The GWAS summary data were acquired from the publicly accessible online platform (<https://gwas.mrcieu.ac.uk/> and <https://www.finnngen.fi/en>).

## Ethical Approval

Summary statistics for the studies used for analysis were composed and obtained from published studies. All studies have received prior approval from their respective institutional review boards (IRBs). The Institutional Review Board of Shandong Provincial Hospital Affiliated to Shandong First Medical University approved the protocol for this study, and 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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## Disclosure

The authors report no conflicts of interest in this work.

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