International Journal of Chronic Obstructive Pulmonary Disease

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

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

Jiadong Ji[1], Qian Zhao[1], Jie Yuan[2], Zhongshang Yuan[2], Nannan Gao[3]

[1]Institute for Financial Studies, Shandong University, Jinan, Shandong, People's Republic of China; [2]Department of Biostatistics, School of Public Health, Cheeloo College of Medicine, Shandong University, Jinan, Shandong, People's Republic of China; [3]Department of Respiratory and Critical Care Medicine, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, People's Republic of China

Correspondence: Nannan Gao, Department of Respiratory and Critical Care Medicine, Shandong Provincial Hospital Affiliated to Shandong First Medical University, No. 324, Jingwu Weiqi Road, Jinan, Shandong, 250021, People's Republic of China, Tel +86 531 68773269, Email gaonan0570@163.com

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.[1] 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.[2,3] 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.[4] The interplay that exists between genetic factors and environmental exposures combine to influence the risk of COPD.[5] 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.[6,7]

Received: 29 September 2024
Accepted: 3 March 2025
Published: 8 March 2025

COPD patients often coexist with other chronic comorbid diseases[8,9] which have significant impact on disease prognosis.[10] 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.[11,12] 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.[13] Similar findings are supported by results from a meta-analysis including 29 datasets.[14] 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.[15] 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.[16] 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]).[17,18] MR corroborates causal associations between exposures and outcomes by excluding the interference from unobserved confounding factors and overcoming the reverse causation.[19] 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.[17] 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,[20] 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.[21]

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,[22] 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.[23]

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 ($P<5\times10^{-8}$). With regard to the GWAS summary data for COPD in our study, a more lenient threshold of 5×10^{-6} was chosen due to the limited number of SNPs falling below the threshold of 5×10^{-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),[24] 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.[25] 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.[26] (2) weighted mode-based method (MR-MBE): a consistent estimate can be obtained if valid instruments contribute the maximal weights in the k subsets.[27] (3) IVW method using robust regression (MR-Robust): a regression-based robust IVW method that assigns lower weights to outliers.[28] (4) MR-Lasso: the method applies Lasso penalization to identify the candidate instrumental SNPs.[28] (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.[29] (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.[30] (7) MR Robust Adjusted Profile Score (MR-RAPS): it is robust to both systematic and specific polymorphisms.[31] (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.[32]

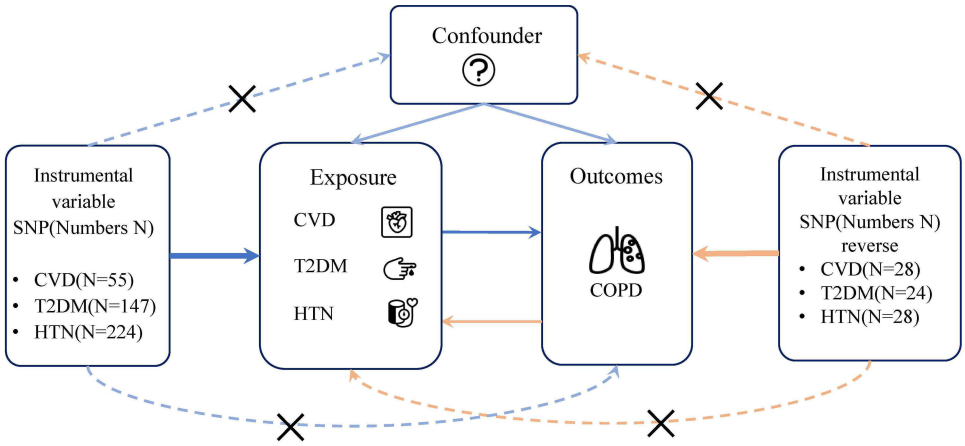

Figure 1 Illustrative diagram for the MR study design in our research. The instrumental variables (IVs) required in the analysis should satisfy three assumptions. Dotted lines represent possible ways that the assumptions could be violated.

https://doi.org/10.2147/COPD.S498513

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.[33] 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, 1.084–1.617; 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.

Exposure	Outcome	Method	OR (95% CI)	P
		IVW	0.978(0.905,1.057)	0.5792
		MR−WME	0.953(0.876,1.037)	0.2641
		MR−MBE	0.877(0.687,1.119)	0.2903
		MR−Robust	0.986(0.909,1.069)	0.7283
CVD	COPD	MR−Lasso	0.984(0.923,1.048)	0.6108
		MR−PRESSO	0.986(0.913,1.064)	0.7101
		MR−Egger	0.581(0.254,1.325)	0.1964
		MR−RAPS	0.986(0.906,1.074)	0.7495
		MR−CONMIX	0.794(0.733,1.209)	0.0058
		IVW	1.111(1.063,1.160)	<0.0001
		MR−WME	1.130(1.071,1.193)	<0.0001
		MR−MBE	1.216(1.083,1.366)	0.0009
		MR−Robust	1.074(1.021,1.131)	0.0062
T2DM	COPD	MR−Lasso	1.103(1.063,1.145)	<0.0001
		MR−PRESSO	1.067(1.019,1.117)	0.0061
		MR−Egger	1.148(0.893,1.476)	0.2804
		MR−RAPS	1.075(1.022,1.130)	0.0054
		MR−CONMIX	1.301(1.250,1.354)	<0.0001
		IVW	1.125(1.084,1.167)	<0.0001
		MR−WME	1.144(1.094,1.197)	<0.0001
		MR−MBE	1.202(1.090,1.326)	0.0002
		MR−Robust	1.095(1.050,1.142)	<0.0001
HTN	COPD	MR−Lasso	1.165(1.131,1.201)	<0.0001
		MR−PRESSO	1.089(1.048,1.130)	<0.0001
		MR−Egger	1.085(0.950,1.240)	0.2283
		MR−RAPS	1.096(1.051,1.144)	<0.0001
		MR− CONMIX	1.316(1.277,1.356)	<0.0001

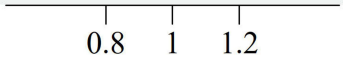

Figure 2 Estimations of causal effect of CVD, T2DM and HTN exposures on COPD outcome from various Mendelian randomization methods.

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

Exposure	Outcome	Method	OR (95% CI)	P
		IVW	1.077(0.985,1.177)	0.1019
		MR−WME	1.077(0.969,1.197)	0.1670
		MR−MBE	1.021(0.778,1.340)	0.8793
		MR−Robust	1.079(0.976,1.193)	0.1358
COPD	CVD	MR−Lasso	1.077(0.985,1.177)	0.1019
		MR−PRESSO	1.077(0.985,1.177)	0.1136
		MR−Egger	1.962(1.055,3.648)	0.0332
		MR−RAPS	1.085(0.985,1.194)	0.0976
		MR−CONMIX	1.131(1.017,1.414)	0.0707
		IVW	1.152(1.064,1.246)	0.0005
		MR−WME	1.191(1.063,1.334)	0.0026
		MR−MBE	1.245(0.994,1.560)	0.0569
		MR−Robust	1.127(1.012,1.255)	0.0289
COPD	T2DM	MR−Lasso	1.103(1.003,1.214)	0.0433
		MR−PRESSO	1.103(1.003,1.214)	0.0551
		MR−Egger	1.762(0.106,29.238)	0.6925
		MR−RAPS	1.132(1.027,1.249)	0.0128
		MR−CONMIX	1.269(1.103,1.417)	0.0024
		IVW	0.997(0.906,1.096)	0.9484
		MR−WME	1.001(0.899,1.114)	0.9865
		MR−MBE	1.130(0.891,1.434)	0.3130
		MR−Robust	1.000(0.906,1.105)	0.9973
COPD	HTN	MR−Lasso	0.996(0.914,1.086)	0.9361
		MR−PRESSO	0.997(0.906,1.096)	0.9488
		MR−Egger	0.559(0.031,9.994)	0.6925
		MR−RAPS	1.000(0.902,1.109)	0.9973
		MR−CONMIX	1.131(0.907,1.314)	0.1224

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.[34,35] Published study indicated that arterial stiffness is associated with the exacerbations of COPD, which would further contribute to systemic hypertension.[36] The shared risk factors such as lifestyle, smoking and environmental factors may predispose the patients to suffer from HTN and COPD.[37] 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,[38] as well as autonomic dysfunction.[39–41] 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.[42,43] 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.[44] 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,[45] and airflow limitation was linked with atherosclerosis irrespective of smoking history.[46] In addition, the intertwined genetic underpinnings of the comorbid conditions may also contribute to the causal association.[47]

Observational studies have identified a higher risk of DM among COPD patients after adjusting for BMI, smoking, and other confounding factors.[48] In addition, published studies suggested diabetes was a risk factor for exacerbation of COPD and had negative impact on COPD patients.[49] 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.[50,51] Available evidence indicated that the inflammation markers were correlated with insulin resistance among COPD patients and subsequently promoted the glucose intolerance.[52] Oxidative stress decreased the insulin sensitivity and disrupted insulin signaling, which also contributed to the pulmonary damage.[53] 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.[54] 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.[55] COPD patients companied 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.[56] 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.[57] Additionally, genetic interplay may partly unveil the causal correlation between COPD and DM.[58]

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.[59,60] A weak association between poor glycemic control and increased risk of COPD in T2DM patients was observed.[61] On the other hand, researches indicated antihyperglycemic

medications may improve lung function index in DM patients.[62] Observational study found systolic blood pressure level was correlated with severity of airflow limitation.[63] 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.finngen.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.

Acknowledgment

We want to acknowledge the participants and investigators from the UKBB and FinnGen study.

Funding

This work has been supported by grants from the National Natural Science Foundation of China (82473738), the National Statistical Scientific Research Project (2022LY031), and the Young Scholars Program of Shandong University.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Celli B, Fabbri L, Criner G. et al. Definition and nomenclature of chronic obstructive pulmonary disease: time for its revision. *Am J Respir Crit Care Med*. 2022;206(11):1317–1325. doi:10.1164/rccm.202204-0671PP
2. Chen S, Kuhn M, Prettner K, et al. The global economic burden of chronic obstructive pulmonary disease for 204 countries and territories in 2020–50: a health-augmented macroeconomic modelling study. *Lancet Glob Health*. 2023;11(8):e1183–e1193. doi:10.1016/S2214-109X(23)00217-6
3. Meghji J, Mortimer K, Agusti A, et al. Improving lung health in low-income and middle-income countries: from challenges to solutions. *Lancet*. 2021;397(10277):928–940. doi:10.1016/S0140-6736(21)00458-X

4. Rabe KF, Watz H. Chronic obstructive pulmonary disease. *Lancet*. 2017;389(10082):1931–1940. doi:10.1016/S0140-6736(17)31222-9
5. Agustí A, Melén E, DeMeo DL, Breyer-Kohansal R, Faner R. Pathogenesis of chronic obstructive pulmonary disease: understanding the contributions of gene–environment interactions across the lifespan. *Lancet Respir Med*. 2022;10(5):512–524. doi:10.1016/S2213-2600(21)00555-5
6. She J, Yang P, Wang Y, et al. Chinese water-pipe smoking and the risk of COPD. *Chest*. 2014;146(4):924–931. doi:10.1378/chest.13-1499
7. Cho MH, McDonald MLN, Zhou X, et al. Risk loci for chronic obstructive pulmonary disease: a genome-wide association study and meta-analysis. *Lancet Respir Med*. 2014;2(3):214–225. doi:10.1016/S2213-2600(14)70002-5
8. Vanfleteren LEGW, Spruit MA, Groenen M, et al. Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2013;187(7):728–735. doi:10.1164/rccm.201209-1665OC
9. Dal negro RW, Bonadiman L, Turco P. Prevalence of different comorbidities in COPD patients by gender and GOLD stage. *Multidisciplinary Respiratory Med*. 2015;10(1):24. doi:10.1186/s40248-015-0023-2
10. Corlateanu A, Covantev S, Mathioudakis AG, Botnaru V, Siafakas N. Prevalence and burden of comorbidities in chronic obstructive pulmonary disease. *Respir Investig*. 2016;54(6):387–396. doi:10.1016/j.resinv.2016.07.001
11. Schnell K, Weiss CO, Lee T, et al. The prevalence of clinically-relevant comorbid conditions in patients with physician-diagnosed COPD: a cross-sectional study using data from NHANES 1999–2008. *BMC Pulm Med*. 2012;12(1):26. doi:10.1186/1471-2466-12-26
12. Fabbri LM, Celli BR, Agustí A, et al. COPD and multimorbidity: recognising and addressing a syndemic occurrence. *Lancet Respir Med*. 2023;11(11):1020–1034. doi:10.1016/S2213-2600(23)00261-8
13. Maclagan LC, Croxford R, Chu A, et al. Quantifying COPD as a risk factor for cardiac disease in a primary prevention cohort. *Eur Respir J*. 2023;62(2):2202364. doi:10.1183/13993003.02364-2022
14. Chen W, Thomas J, Sadatsafavi M, FitzGerald JM. Risk of cardiovascular comorbidity in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Lancet Respir Med*. 2015;3(8):631–639. doi:10.1016/S2213-2600(15)00241-6
15. Burgess S, Foley CN, Zuber V. Inferring causal relationships between risk factors and outcomes from genome-wide association study data. *Annu Rev Genomics Hum Genet*. 2018;19(1):303–327. doi:10.1146/annurev-genom-083117-021731
16. Jones DS, Podolsky SH. The history and fate of the gold standard. *Lancet*. 2015;385(9977):1502–1503. doi:10.1016/S0140-6736(15)60742-5
17. Smith GD, Ebrahim S. Mendelian randomization": can genetic epidemiology contribute to understanding environmental determinants of disease? *Int J Epidemiol*. 2003;32(1):1–22. doi:10.1093/ije/dyg070
18. Sanderson E, Glymour MM, Holmes MV, et al. Mendelian randomization. *Nat Rev Meth Primers*. 2022;2(1):1–21. doi:10.1038/s43586-021-00092-5
19. Emdin CA, Khera AV, Kathiresan S. Mendelian Randomization. *JAMA*. 2017;318(19):1925–1926. doi:10.1001/jama.2017.17219
20. Cano-Gamez E, Trynka G. From GWAS to function: using functional genomics to identify the mechanisms underlying complex diseases. *Front Genetics*. 2020;11:424. doi:10.3389/fgene.2020.00424
21. Swerdlow DI, Kuchenbaecker KB, Shah S, et al. Selecting instruments for Mendelian randomization in the wake of genome-wide association studies. *Int J Epidemiol*. 2016;45(5):1600–1616. doi:10.1093/ije/dyw088
22. Burgess S, Davies NM, Thompson SG. Bias due to participant overlap in two-sample Mendelian randomization. *Genetic Epidemiol*. 2016;40(7):597–608. doi:10.1002/gepi.21998
23. Bulik-Sullivan B, Finucane HK, Anttila V, et al. An atlas of genetic correlations across human diseases and traits. *Nat Genet*. 2015;47(11):1236–1241. doi:10.1038/ng.3406
24. Purcell S, Neale B, Todd-Brown K, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet*. 2007;81(3):559–575. doi:10.1086/519795
25. Bowden J, Del Greco MF, Minelli C, Davey Smith G, Sheehan N, Thompson J. A framework for the investigation of pleiotropy in two-sample summary data Mendelian randomization. *Stat Med*. 2017;36(11):1783–1802. doi:10.1002/sim.7221
26. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. *Genet Epidemiol*. 2016;40(4):304–314. doi:10.1002/gepi.21965
27. Hartwig FP, Davey Smith G, Bowden J. Robust inference in summary data Mendelian randomization via the zero modal pleiotropy assumption. *Int J Epidemiol*. 2017;46(6):1985–1998. doi:10.1093/ije/dyx102
28. Slob EAW, Burgess S. A comparison of robust Mendelian randomization methods using summary data. *Genet Epidemiol*. 2020;44(4):313–329. doi:10.1002/gepi.22295
29. Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nat Genet*. 2018;50(5):693–698. doi:10.1038/s41588-018-0099-7
30. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Epidemiol*. 2015;44(2):512–525. doi:10.1093/ije/dyv080
31. Zhao Q, Wang J, Hemani G, Bowden J, Small DS. Statistical inference in two-sample summary-data Mendelian randomization using robust adjusted profile score. *Ann Stat*. 2020;48:1742–1769. doi:10.1214/19-aos1866
32. Burgess S, Foley CN, Allara E, Staley JR, Howson JMM. A robust and efficient method for Mendelian randomization with hundreds of genetic variants. *Nat Commun*. 2020;11(1):376. doi:10.1038/s41467-019-14156-4
33. Zeng P, Zhou X. Causal effects of blood lipids on amyotrophic lateral sclerosis: a Mendelian randomization study. *Human Molecular Genetics*. 2019;28(4):688–697. doi:10.1093/hmg/ddy384
34. Westerik JAM, Metting EI, Van Boven JFM, Tiersma W, Kocks JWH, Schermer TR. Associations between chronic comorbidity and exacerbation risk in primary care patients with COPD. *Respir Res*. 2017;18(1):31. doi:10.1186/s12931-017-0512-2
35. Almagro P, Soler-Cataluña JJ, Huerta A, González-Segura D, Cosío BG. CLAVE Study Investigators. Impact of comorbidities in COPD clinical control criteria. The CLAVE study. *BMC Pulm Med*. 2024;24(1):6. doi:10.1186/s12890-023-02758-0
36. Finks SW, Rumbak MJ, Self TH. Treating hypertension in chronic obstructive pulmonary disease. Ingelfinger JR, ed. *N Engl J Med*. 2020;382(4):353–363. doi:10.1056/NEJMra1805377
37. Balbirsingh V, Mohammed AS, Turner AM, Newnham M. Cardiovascular disease in chronic obstructive pulmonary disease: a narrative review. *Thorax*. 2022;77(9):939–945. doi:10.1136/thoraxjnl-2021-218333
38. Gaisl T, Schlatzer C, Schwarz EI, et al. Coronary artery calcification, epicardial fat burden, and cardiovascular events in chronic obstructive pulmonary disease. *PLoS One*. 2015;10(5):e0126613. doi:10.1371/journal.pone.0126613

39. MacDonald DM, Ji Y, Adabag S, et al. Cardiovascular autonomic function and incident chronic obstructive pulmonary disease hospitalizations in atherosclerosis risk in communities. *Ann ATS*. 2023;20(10):1435–1444. doi:10.1513/AnnalsATS.202211-964OC
40. Brassington K, Selemidis S, Bozinovski S, Vlahos R. Chronic obstructive pulmonary disease and atherosclerosis: common mechanisms and novel therapeutics. *Clin Sci*. 2022;136(6):405–423. doi:10.1042/CS20210835
41. Kim SH, Park JH, Lee JK, Heo EY, Kim DK, Chung HS. Chronic obstructive pulmonary disease is independently associated with hypertension in men: a survey design analysis using nationwide survey data. *Medicine*. 2017;96(19):e6826. doi:10.1097/MD.0000000000006826
42. Fuhr DP, Brotto AR, Rowe BH, Bhutani M, Rosychuk RJ, Stickland MK. Examining changes in vascular function, arterial stiffness and systemic inflammation during hospitalization and recovery from an acute exacerbation of chronic obstructive pulmonary disease. *Sci Rep*. 2023;13(1):12245. doi:10.1038/s41598-023-39001-z
43. Nussbaumer-Ochsner Y, Rabe KF. Systemic manifestations of COPD. *Chest*. 2011;139(1):165–173. doi:10.1378/chest.10-1252
44. Van Rooyen Y, Schutte AE, Huisman HW, et al. Inflammation as possible mediator for the relationship between lung and arterial function. *Lung*. 2016;194(1):107–115. doi:10.1007/s00408-015-9804-9
45. Böcskei RM, Benczúr B, Losonczy G, et al. Soluble urokinase-type plasminogen activator receptor and arterial stiffness in patients with COPD. *Lung*. 2019;197(2):189–197. doi:10.1007/s00408-019-00211-w
46. Sheen SS, Kim HJ, Singh D, et al. Airflow limitation as a risk factor for vascular stiffness. *Int J Tuberc Lung Dis*. 2020;24(6):577–584. doi:10.5588/ijtld.19.0457
47. Zhu Z, Wang X, Li X, et al.; International COPD Genetics Consortium. Genetic overlap of chronic obstructive pulmonary disease and cardiovascular disease-related traits: a large-scale genome-wide cross-trait analysis. *Respir Res*. 2019;20(1):64. doi:10.1186/s12931-019-1036-8.
48. Ctc. L, Mao I, Lin C, Lin S, Hsieh M. Chronic obstructive pulmonary disease: a risk factor for type 2 diabetes: a nationwide population-based study. *Eur J Clin Investigation*. 2013;43(11):1113–1119. doi:10.1111/eci.12147
49. Castañ-Abad MT, Montserrat-Capdevila J, Godoy P, et al. Diabetes as a risk factor for severe exacerbation and death in patients with COPD: a prospective cohort study. *European Journal of Public Health*. 2020;30(4):822–827. doi:10.1093/eurpub/ckz219
50. Visca D, Pignatti P, Spanevello A, Lucini E, La Rocca E. Relationship between diabetes and respiratory diseases—Clinical and therapeutic aspects. *Pharmacol Res*. 2018;137:230–235. doi:10.1016/j.phrs.2018.10.008
51. Machado FVC, Pitta F, Hernandes NA, Bertolini GL. Physiopathological relationship between chronic obstructive pulmonary disease and insulin resistance. *Endocrine*. 2018;61(1):17–22. doi:10.1007/s12020-018-1554-z
52. Peng Y, Zhong GC, Wang L, et al. Chronic obstructive pulmonary disease, lung function and risk of type 2 diabetes: a systematic review and meta-analysis of cohort studies. *BMC Pulm Med*. 2020;20(1):137. doi:10.1186/s12890-020-1178-y
53. Kirkham PA, Barnes PJ. Oxidative stress in COPD. *Chest*. 2013;144(1):266–273. doi:10.1378/chest.12-2664
54. Festa A, D'Agostino R Jr, Tracy RP, Haffner SM. Elevated levels of acute-phase proteins and plasminogen activator inhibitor-1 predict the development of type 2 diabetes: the insulin resistance atherosclerosis study. *Diabetes*. 2002;51(4):1131–1137. doi:10.2337/diabetes.51.4.1131
55. Park SS, Perez Perez JL, Perez Gandara B, et al. Mechanisms linking COPD to type 1 and 2 diabetes mellitus: is there a relationship between diabetes and COPD? *Medicina (Kaunas)*. 2022;58(8):1030. doi:10.3390/medicina58081030
56. Gläser S, Krüger S, Merkel M, Bramlage P, Herth FJ. Chronic obstructive pulmonary disease and diabetes mellitus: a systematic review of the literature. *Respiration*. 2015;89(3):253–264. doi:10.1159/000369863
57. Su J, Li M, Wan X, et al. Associations of diabetes, prediabetes and diabetes duration with the risk of chronic obstructive pulmonary disease: a prospective UK BIOBANK study. *Diabetes Obesity Metab*. 2023;25(9):2575–2585. doi:10.1111/dom.15142
58. Meteran H, Backer V, Kyvik KO, Skytthe A, Thomsen SF. Comorbidity between chronic obstructive pulmonary disease and type 2 diabetes: a nation-wide cohort twin study. *Respir Med*. 2015;109(8):1026–1030. doi:10.1016/j.rmed.2015.05.015
59. Ruan W, Yan C, Zhu H, et al. Downregulated level of insulin in COPD patients during AE; role beyond glucose control? *Int J Chron Obstruct Pulmon Dis*. 2019;14:1559–1566. doi:10.2147/COPD.S197164
60. Gupta S, Mohta A, Lauinger A, Thameem D. The role of Sodium-Glucose Transporter-2 Inhibitors (SGLT-2i) in preventing chronic obstructive disease exacerbation in patients with diabetes and COPD: an electronic health database analysis. *Heart Lung*. 2024;68:191–194. doi:10.1016/j.hrtlng.2024.07.003
61. Pino-Sedeno T D, Gonzalez de Leon B, Perez Martin EF, et al. Relationship between glycemic control and chronic obstructive pulmonary disease in patients with type 2 diabetes: a nested case-control study. *Prim Care Diabetes*. 2020;14(6):729–735. doi:10.1016/j.pcd.2020.05.007
62. Mirrakhimov AE. Chronic obstructive pulmonary disease and glucose metabolism: a bitter sweet symphony. *Cardiovasc Diabetol*. 2012;11:132. doi:10.1186/1475-2840-11-132
63. Arslan S, Yildiz G, Ozdemir L, Kaysoydu E, Ozdemir B. Association between blood pressure, inflammation and spirometry parameters in chronic obstructive pulmonary disease. *Korean J Intern Med*. 2019;34(1):108–115. doi:10.3904/kjim.2017.284