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Potential Causal Relationship Between Chronic Obstructive Pulmonary Disease and Diabetes: A Bidirectional Two-Sample Mendelian Randomization Study

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Purpose: Diabetes, particularly type 2 diabetes (T2D), is a common comorbidity that occurs at a higher frequency in chronic obstructive pulmonary disease (COPD) patients compared to the general population. The COPD-diabetes association is documented epidemiologically and experimentally. Potential mechanisms, including systemic inflammation and metabolic dysregulation, are discussed as plausible pathways. However, their causal relationship still needs to be confirmed.

Methods: We conducted a comprehensive bidirectional two-sample Mendelian randomization (MR) analysis to evaluate the causal links between COPD and both type 1 diabetes (T1D) and T2D by using genome-wide association study (GWAS) summary statistics in European and Asian populations. By employing MR methods, the causal effect of diabetes on the risk of COPD as well as specific COPD-related clinical outcomes, including COPD with infections (COPD-I), pneumonia or pneumonia-derived septicaemia, chronic opportunistic infections, respiratory insufficiency, hospital admissions, and onset age (early or late) were explored.

Results: Forward MR analysis provided evidence consistent with a causal relationship between T2D and an increased risk of COPD in the European population (IVW odds ratio (OR): 1.002, 95% confidence interval (CI): 1.001–1.003, $P = 0.001$). This association appeared consistent with MR Egger analysis, yielding a similar result for European COPD patients (MR Egger OR: 1.108, 95% CI: 1.016 −1.208, $P = 0.021$). No statistically conclusive evidence of a causal relationship between diabetes and COPD was found in the Asian population. Besides, genetically determined T1D was identified as a risk factor for the incidence of COPD-I in the European-specific population (IVW OR: 1.017, 95% CI: 1.009–1.025, $P < 0.001$). The reverse MR analysis, exploring the effect of COPD on the risk of diabetes, did not achieve consistent results in either the European or Asian populations.

Conclusion: This study suggested a modest but statistically significant causal association between T2D and COPD in individuals of European ancestry. Further explorations are required to better understand the underlying mechanisms linking diabetes to COPD development.

Keywords: chronic obstructive pulmonary disease, type 1 diabetes mellitus, type 2 diabetes mellitus, Mendelian randomization, causal inference

Introduction

Comorbid conditions of chronic obstructive pulmonary disease (COPD) are associated with increased mortality, readmission, and healthcare utilization. Type 1 (T1D) and type 2 (T2D) diabetes mellitus are common comorbidities in patients with COPD, with higher prevalence rates compared to the general population, independent of body mass index (BMI), smoking, and other confounding factors.[1]

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A wealth of epidemiological studies and disease models have contributed to a primary understanding of their clinical associations. For example, comorbid diabetes is independently associated with reduced lung function and frequently reported respiratory symptoms.[2] Even in individuals without established pulmonary diseases or who are nonsmokers, diabetes often leads to reduced total lung capacity (TLC), diffusing capacity carbon monoxide (DLCO), lung elastic recoil, pulmonary capillary volume, and 6-minute walk distance.[3] Among COPD patients, the presence of diabetes is linked to more severe lung function impairment (GOLD 3–4)[4] as well as worse clinical outcomes, including higher short-term and long-term mortality and increased hospitalization.[5,6] Baseline hyperglycemia in COPD patients experiencing acute respiratory failure is also a reliable predictor of poor clinical outcomes.[7] Reciprocally, impaired lung function is associated with elevated glycated hemoglobin (HbA1c) levels and an increased risk of diabetes development.[8] Correction of hyperglycemia has been shown to mitigate some lung function abnormalities.[9]

Mechanistic evidence from disease models further supports the notion that comorbid diabetes and COPD mutually influence the progression of each other.[10] Notably, the association between diabetes and chronic pulmonary diseases seems specific to COPD but does not extend to asthma, as suggested by a prospective cohort study,[11] which implies a specific interplay between COPD and diabetes.

The underlying mechanisms driving the COPD-diabetes association are not yet fully understood. Several potential mechanisms have been documented, mainly associated with shared lifestyle risks, systemic inflammation, metabolic disorders, immune responses, and genetic factors. It is strongly suggested that enhanced inflammatory state observed in COPD may affect peripheral energy utilization, contributing to the development of diabetes. A recent large-scale genome-wide association study (GWAS) not only identified novel loci linking lung function to obesity, but also suggested a negative effect of BMI on lung function over an eight-year follow-up period.[12] Lifestyle risk factors, such as cigarette smoke (CS) and dietary intake, play significant roles in the development of both diabetes and COPD. Especially CS exposure, a substantial contributing factor to COPD, disrupts insulin signaling, impairs β-cell insulin production, and influences methylation patterns in genes associated with T2D.[13] Additionally, chronic hyperglycemia contributes to alveolar capillary microangiopathy, leading to restrictive and obstructive lung function impairments. Chronic hyperglycemia also leads to the formation of advanced glycation end products (AGEs) through non-specific glycation, which bind to their receptor named the receptor for advanced glycation end-products (RAGE) and induce signal induced chronic airway and vascular inflammation. Overexpression of AGEs-RAGE signaling pathway has been observed in the airway epithelium and smooth muscle of COPD patients.[14] Moreover, hyperglycemia may lead to COPD exacerbation (ECOPD) by creating a favorable environment for microbial colonization in the airways, thus increasing the risk of respiratory infections.[15]

Considering the shared pathophysiological mechanisms between two conditions, some pharmacological approaches have been explored for their potential to benefit both diabetes and COPD.[16] For example, metformin has been investigated as a potential treatment in smoke-induced lung injury, the development and progression emphysema, and osteoporosis in COPD patients.[17] It may also improve health outcomes in patients with both COPD and T2D, including symptoms and the transitional dyspnea index.[18] However, metformin does not improve physiological or clinical outcomes in non-diabetic COPD patients and may increase the risk of pneumonia, hospitalization, and invasive mechanical ventilation use in COPD patients with T2D.[19] Other oral hyperglycemic drugs like thiazolidines and peroxisome proliferator-activated receptor gamma agonists also show potential benefits in managing inflammation and reducing COPD exacerbations.[20]

Despite the strong correlation between COPD and diabetes, most evidence comes from observational studies, which are prone to bias due to confounding variables, even after adjusting for demographics, socioeconomic status, and comorbidities. Notably, a study indicated that presence of diabetes, in isolation, may not be a direct risk factor for COPD, and its role in COPD pathogenesis remains uncertain.[21] Changes in the glycation of lung collagen and alveolar microangiopathy may contribute to altered pulmonary dysfunctions, but the causal relationship between COPD and diabetes requires further exploration.

Mendelian Randomization (MR) is an emerging analytical approach that leverages genetic variants as instrumental variables to infer causality between exposures and outcomes.[22] A recent MR study by Wang et al sought to investigate the causal relationship between COPD and T2D.[23] However, their study focused exclusively on T2D and COPD, without

considering the potential causal links between T1D and COPD. While T1D and T2D differ pathophysiologically, both share systemic complications that may impair pulmonary function, justifying the inclusion of T1D in this analysis. Besides, their analysis primarily examined the effect of COPD on T2D, while the reverse causal relationship – the impact of diabetes on COPD – has not been fully explored. Furthermore, given the differences in the prevalence and pathophysiological conditions of diabetes between European and Asian populations, it is crucial to explore the causal relationship between COPD and diabetes in both ancestries,[24] a gap not fully addressed in the existing literature. In response to these gaps, we conducted a more comprehensive bidirectional two-sample MR study leveraging a broader set of GWAS summary statistics across both European and Asian populations to determine whether diabetes is causally correlated with COPD risk and also COPD-related characteristics.

Materials and Methods

MR uses genetic variants such as single-nucleotide polymorphisms (SNPs) as instrumental variables (IVs) to investigate the relationship between an exposure and an outcome. This is achieved by comparing the effect size of the SNPs on the outcome to their impact on the exposure. In our study, we performed a bidirectional two-sample MR analysis using publicly available summary data. This study adhered to ethical guidelines for secondary data analysis. Ethical approval was waived under national legislation (Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects dated February 18, 2023, China). The study methods adhered to the guidelines outlined in STROBE-MR checklist.[25]

The MR approach relies on three crucial assumptions: (1) the genetic variants are linked to the exposure under investigation; (2) there are no unmeasured confounders influencing the associations of genetic variants with the outcome; and (3) the genetic variants exclusively influence the outcome through the exposure of interest (Figure 1). A comprehensive and methodical bidirectional MR analysis with prudent validation was performed in this study. Firstly, we reviewed and selected available GWAS data from European or Asian populations for individual clinical conditions. Secondly, we chose valid IVs based on a pre-defined selection criteria. Thirdly, we performed forward analyses to estimate population-specific causal effect of diabetes on the risk of COPD as well as COPD characteristics and outcomes by using five established conventional MR methods. Fourthly, we performed backward analyses to reveal the causal effect of COPD on the frequency of diabetes by conducting conventional MR methods. Fifthly, we replicated the associations by utilizing independent GWAS summary statistics of COPD. Finally, we confirmed the validated causal effects yielded from conventional MR methods by using optional CAUSE method, which modeled correlated and uncorrelated horizontal pleiotropy in order to avoid false positives through including a maximum number of SNPs. The overall study design is shown in Figure 2.

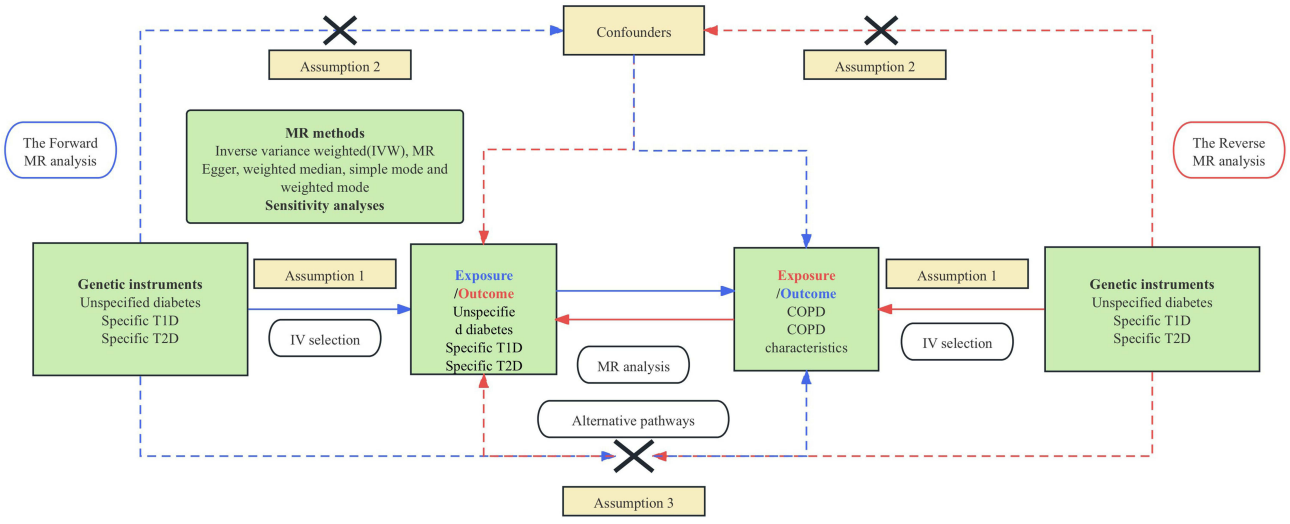

Figure 1 Flowchart of SNP selection assumptions and MR analysis framework.

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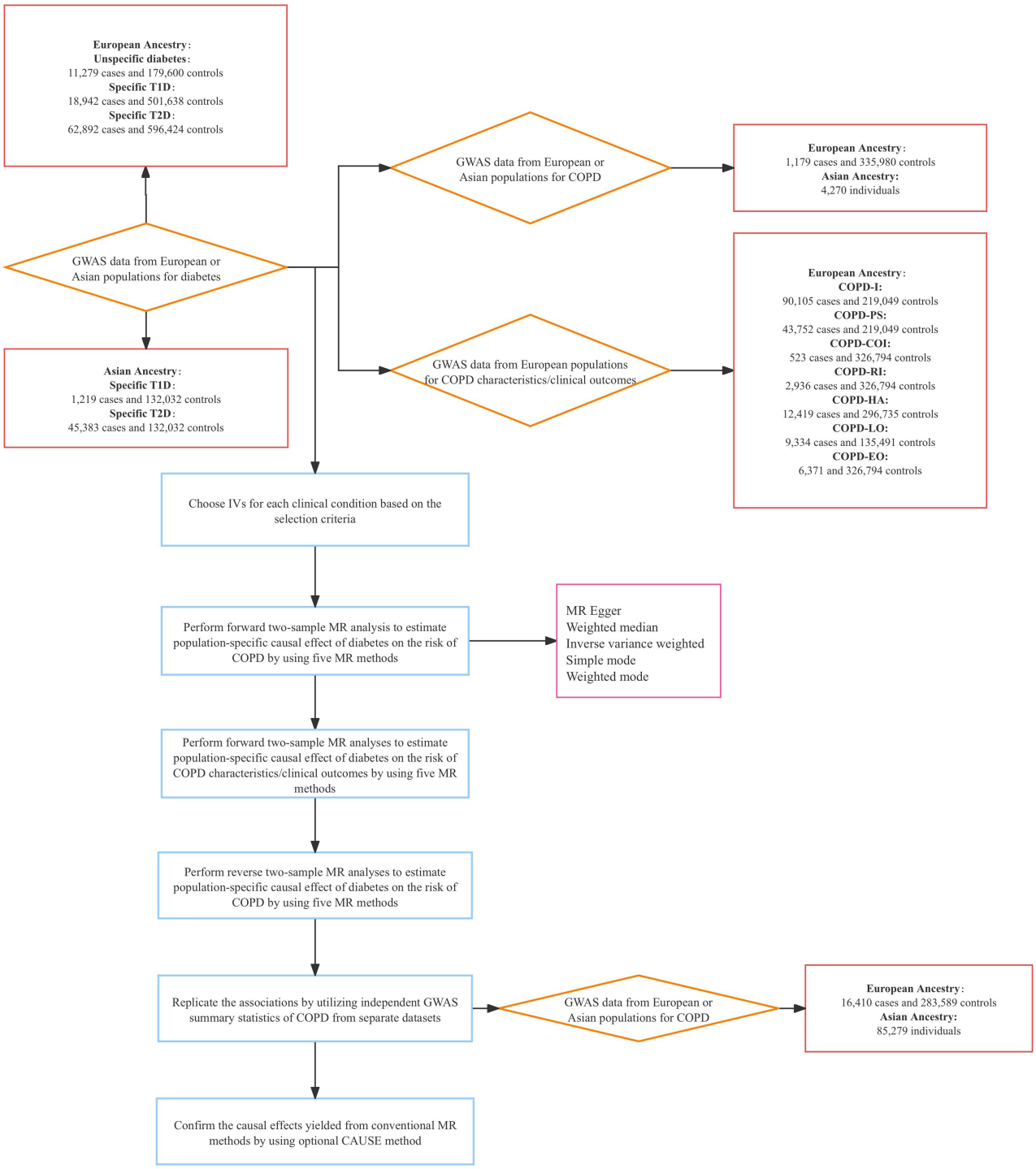

Figure 2 Schematic overview of the bidirectional two-sample MR study design.

GWAS Datasets

To conduct MR analysis, we collected GWAS summary statistics for diabetes, COPD, as well as clinical outcomes of COPD from publicly available datasets encompassing European populations and Asian populations.

Diabetes GWAS Datasets

For individuals of European ancestry, we analyzed GWAS summary statistics for unspecific diabetes, specific T1D, and specific T2D obtained from various sources. The FinnGen study provided data on diabetes (11,279 cases and 179,600 controls).[26] A meta-analysis based on 9 cohorts contributed data for T1D statistics (18,942 cases and 501,638 controls)[27] and a meta-analysis combined information from 3 GWAS datasets provided T2D statistics (62,892 cases and 596,424 controls).[28] The FinnGen research initiative harmonizes genomic information from Finnish biobanks with health-related data from the country's healthcare databases. Research endpoints in this research were defined using International Classification of Diseases (ICD) codes.[26] The GWAS data of T1D underwent quality control measures, including the application of uniform quality control for cohort-level variants and imputed genotypes based on the TOPMed reference panel.[29] Subsequently, the data were tested for T1D association, resulting in the identification of 81 loci reaching genome-wide significance ($P < 5\times10^{-8}$), including 48 of 59 known loci and 33 previously unreported loci.[27] The T2D GWAS data involved 5,053,015 genotyped or imputed autosomal SNPs (MAF ≥ 0.01) in T2D cases and controls from the DIAGRAM (Diabetes Genetics Replication and Meta-analysis) (12,171 cases vs 56,862 controls in stage 1 and 22,669 cases vs 58,119 controls in stage 2), GERA (Genetic Epidemiology Research on Aging) (6905 cases and 46,983 controls) and UKB (UK Biobank) (21,147 cases and 434,460 controls) data sets after quality controls.[28] Summary statistics in DIAGRAM were imputed to the 1000 Genomes Project Phase 1 using a summary data-based imputation approach. A meta-analysis was then conducted using an inverse-variance method (IVW) to combine the imputed DIAGRAM data with the summary data from GWAS analyses of GERA and UKB.[30]

For individuals of Asian ancestry, we obtained summary data of specific T1D and specific T2D GWAS summary statistics from the GWAS report measured in East Asian participants in Biobank Japan by searching for the GWAS catalog (https://www.ebi.ac.uk/gwas/), which comprised a total of 1,219 T1D cases (132,032 controls) (accession number: GCST90018705) and 45,383 cases (132,032 controls) (accession number: GCST90018706).[31]

COPD GWAS Datasets

For individuals of European ancestry, we utilized publicly available summary-level data of COPD extracted directly or indirectly from UK biobank by the IEU open GWAS project (https://gwas.mrcieu.ac.uk/). The summary data included 337,159 individuals of European ancestry (1,179 cases and 335,980 controls).

For individuals of Asian ancestry, the summary statistics were obtained from the GWAS dataset available in the GWAS catalog (https://www.ebi.ac.uk/gwas/). The dataset specifically included 4,270 individuals of Asian ancestry (accession number: GCST90292627).[32]

COPD cases in the database cohorts were defined using ICD-10 codes and spirometry-confirmed airflow obstruction (FEV1/FVC < 0.70).

COPD Clinical Outcomes GWAS Datasets

The GWAS summary-level statistics reported ICD-10-based clinical traits that associated to the outcomes of COPD were gathered from publicly available FinnGen biobank database, including COPD with infections (COPD-I) (90,105 cases and 219,049 controls), COPD with pneumonia or pneumonia derived septicaemia (COPD-PS) (43,752 cases and 219,049 controls), COPD with chronic opportunist infection (COPD-COI) (523 cases and 326,794 controls), COPD with respiratory insufficiency (COPD-RI) (2,936 cases and 326,794 controls), COPD with hospital admission (COPD-HA) (12,419 cases and 296,735 controls), COPD with late onset (COPD-LO) (9,334 cases and 135,491 controls), and COPD with early onset (COPD-EO) (6,371 and 326,794 controls). All of the participants were of European ancestries.

IV Selection

To ensure the robustness and reliability of our MR analysis, we implemented stringent quality controls in the selection of IVs that fulfilled the three key assumptions of this analytical method. Firstly, we selected SNPs that were significantly associated with the exposure of interest ($r^2 < 0.001$, $P < 1\times10^{-5}$), which were commonly considered instrumental variables. While these SNPs exhibited strong statistical associations with the exposures, their exact biological functions

might not be fully understood. The *P*-value threshold ($P < 1\times10^{-5}$) was chosen based on the context of the study, acknowledging that it was less stringent than the typical stricter threshold (eg, $P < 5\times10^{-8}$). These SNPs were required to be present in both the exposure and outcome datasets. In cases where SNPs were unavailable in the outcome summary statistics, proxy SNPs were defined as being in linkage disequilibrium (LD) ($r^2 > 0.9$) and were generated using LDlink (http://analysistools.nci.nih.gov/LDlink/) and LD proxy, with the candidate SNP from the 1000 Genomes Phase 3 CEU/JPT populations serving as the reference.[33] Secondly, we employed LD-clumping ($r^2 < 0.001$ within a clumping window size of 1,000 KB) to select a set of independent instruments for the exposure trait. Thirdly, we excluded palindromic SNPs, which were SNPs whose alleles were represented by the same pair of letters on the forward and reverse strands. The inclusion of such SNPs could introduce ambiguity into determining the identity of the effect allele in the exposure and outcome GWASs. Fourthly, we conservatively queried each instrument SNP in the PhenoScanner database (http://www.phenoscanner.medschl.cam.ac.uk/phenoscanner, accessed on 18 October 2023) to identify SNPs with significant association to GWAS traits that potentially confounded the outcomes ($P < 1\times10^{-5}$).[34] SNPs considered to be correlated with the confounders were subsequently removed from the following MR estimates to eliminate potential pleiotropic effects. Fifthly, we excluded selected SNPs with a MAF $\leq$ 0.01. Sixthly, we quantified the instrument strength by calculating F-statistic for each SNP individually and cumulatively using the formula $F = R^2 (N - 2)/(1 - R^2)$, where R^2 is the proportion of the variability of exposure explained by each instrument and N is sample size. To calculate R^2, we use the following formula: $(2\times EAF\times(1-EAF)\times beta^2)/[(2\times EAF\times(1-EAF)\times beta^2) + (2\times EAF\times(1-EAF)\times N\times SE(beta)^2)]$, where EAF is the effect allele frequency, beta is the estimated genetic effect on exposure, and SE (beta) is the standard error of the genetic effect.[35] SNPs with an F statistic > 10 were selected as strong IVs to provide substantial evidence for the exposures under investigation.

Discovery MR Analyses

We performed bidirectional two-sample MR analyses using GWAS statistics from discovery datasets. In forward MR analyses, we investigated the causal effects of genetically predicted unspecified diabetes, specific T1D, and specific T2D on the risk of COPD, in both European and Asian ancestries. The impact of specific T1D and specific T2D on certain clinical outcomes of COPD was also explored, specifically in the European individuals. In reverse MR analyses, we examined the effect of COPD on the risk of unspecified diabetes, T1D, and T2D, based on the discovery GWASs summary data from both European and Asian populations.

The random-effects IVW was performed as the main basis of our study, which incorporates SNP-specific Wald ratios to assess causal connections while assuming balanced pleiotropy.[36] However, directional pleiotropy occurs when the net effect of horizontal pleiotropy across all SNPs is non-zero and introduces bias into the IVW estimates. Therefore, alternative MR methods, including MR-Egger, weighted median, simple mode, and weighted mode that were more robust to directional pleiotropy, were employed to calculate estimates for comparison with the IVW estimates. MR Egger allows for the detection of horizontal pleiotropy, which arises when genetic variants affect both the exposure and outcome through different pathways. It provides unbiased estimates of causal effects even when there is directional pleiotropy.[37] The weighted median method estimates the causal effect by taking the median of the individual IV ratio estimates and is resilient to up to 50% of the instruments being invalid.[38] The simple mode method estimates the causal effect by taking the mode of the individual IV ratio estimates. It is non-parametric and computationally efficient.[39] The weighted mode groups SNPs into clusters and calculates an estimate based on the cluster with the most SNPs, combining the advantages of the simple mode and weighted median approaches in handling heterogeneity between instruments.[39] The TwoSample MR package (version 0.5.6) was used to conduct these analyses in R (version 4.2.3).

Sensitivity Analyses

To assess the robustness of the findings and evaluate the potential impact of different assumptions or methodological choices on the results, sensitivity analyses using MR-Egger and Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) were conducted. Although both methods address issues of confounding and pleiotropy bias, they differ in statistical power, assumptions, methods, sample size, data quality, and types of pleiotropy presented in the analyzed dataset. For example, MR-Egger regression has higher statistical power compared to the MR-PRESSO global

test in detecting horizontal pleiotropy,[37,40] making it more likely to identify potential pleiotropic effects even when they are weak or subtle. Besides, MR-Egger regression and MR-PRESSO global test rely on different assumptions and employ different methods to detect and correct for pleiotropy. MR-Egger regression assumes the InSIDE assumption, which allows for the detection of directional pleiotropy, while MR-PRESSO global test assumes the absence of pleiotropy and detects outliers that may indicate the presence of pleiotropic effects. The differences can lead to divergent results, and the size and quality of the dataset used in the analysis can also influence the presence or absence of pleiotropy. In this study, we used MR-Egger regression and then MR-PRESSO as sensitivity analyses to detect violations of the instrumental variable assumptions. The distortion test of MR-PRESSO analysis was used to detect outliers in our MR analysis that were excluded to reassess the causal estimates. The "leave-one-out" analysis was used to investigate whether the causal relationship was influenced by a single SNP. $P > 0.05$ indicated no horizontal pleiotropy in intercept test of MR Egger and global test of MR-PRESSO analysis. The Cochran's Q statistic (MR-IVW) was used to detect the heterogeneity of our MR analysis, and $P > 0.05$ indicated no heterogeneity. The MRPRESSO R package (version 1.0) was used to perform MR-PRESSO. A significance threshold of Bonferroni correction test accounting for multiple comparisons was used (0.05/3 = 0.017 for the analysis in the European ancestry and 0.05/2 = 0.025 for the analysis in the Asian ancestry) to reduce the Type 1 Error rate.

Validation MR Analyses

To validate the associations found in the discovery process, we performed a validation analysis by collecting GWAS summary statistics of COPD from independent datasets. For European ancestry, we obtained summary statistics data from the R8 release of the FinnGen consortium, encompassing 16,410 cases and 283,589 controls. COPD was defined using ICD codes retrieved from nationwide registries in Finland.[26] The analyses in FinnGen were adjusted for age, sex, 10 principal components and genotype batch using mixed-model logistic regression by the investigators. For Asian ancestry, we collected the validation genetic association estimates of SNPs associated with COPD from a GWAS report measured in East Asian participants. This data was retrieved from the GWAS catalog (https://www.ebi.ac.uk/gwas/), which comprised 85,279 East Asian ancestry individuals (accession number: GCST90292631).[32]

As an additional validation approach, we also conducted an optional MR analysis method namely CAUSE to confirm the associations observed in both discovery and validation datasets.[41] CAUSE models correlated and uncorrelated horizontal pleiotropy in order to avoid false positives that may occur in other methods. To include a maximum number of IVs, we performed LD pruning using a threshold of $r^2 < 0.01$ and $P < 1\times10^{-3}$. CAUSE R package (version 1.2.0) was utilized to conduct the analysis.

Results

Causal Effect of Diabetes on COPD

SNPs were preliminarily selected based on the European-specific diabetes/T1D/T2D GWAS statistics, and detailed information were summarized in Supplementary Table S1. A total of 483 SNPS were retained as IVs for subsequent analyses (Supplementary Table S2) after comprehensive exclusions due to reasons including potential associations with the outcomes, outcome-related confounders, and palindromes (Supplementary Table S3). The summary F-statistics of the IVs was presented in Supplementary Table S4. The F-statistics ranged from 26.885 to 185.205 (larger than 10), indicating a strong instrumental strength.

By using the discovery COPD GWAS dataset, results of IVW method showed that genetically predicted T2D was causally associated with an increased risk of COPD [odds ratio (OR): 1.002, 95% confidence interval (CI): 1.001–1.003, $P < 0.001$] (Table 1, Supplementary Table S5). For this identified association, Cochran's Q test detected no significant heterogeneity among all these IVs (Q = 369.834, $P = 0.075$) (Supplementary Table S6). Regarding the potential presence of horizontal pleiotropy, MR-Egger regression and MR-PRESSO global test were utilized to calculate it. The results indicated no evidence of potential horizontal pleiotropy that might distort the influence of T2D on COPD (MR-Egger regression $P = 0.064$; MR-PRESSO global test $P = 0.076$) (Supplementary Tables S6 and S7). Furthermore, the leave-one-out analysis was conducted to assess whether the causality observed was dependent on or biased by any single SNPs,

which revealed none capability of individual SNPs in influencing the result (Supplementary Figure S1). Overall, the results of MR analyses illustrated no causal effect of unspecific diabetes and T1D on the development of COPD in European population (Supplementary Table S5).

To confirm the causal relationship identified in the discovery sample set in European populations, summary-level data from an independent COPD GWAS was used to repeat the analyses. Selected SNPs were shown in Supplementary Table S8. The F-statistic of SNPs used as the IVs of unspecified diabetes, T1D, and T2D were all greater than 10, indicating that weak instrument was unlikely to bias the results (Supplementary Table S9). The MR Egger approach [OR: 1.108, 95% CI: 1.016 −1.208, $P = 0.021$] in the replication process yielded a causal effect of T2D on the risk of COPD (Table 1, Supplementary Table S10), which was consistent with the observation found in the discovery process. However, the Bonferroni correction did not adjust the significance level ($P = 0.021$). Meanwhile, the Cochran's Q test detected significant heterogeneity among selected IVs ($P < 0.001$) (Table 1, Supplementary Table S11). And an evidence of horizontal pleiotropy was revealed by MR-Egger regression ($P = 0.002$) and MR-PRESSO global test ($P < 0.001$) (Supplementary Tables S11 and S12). The result of leave-one-out analysis showed that no single SNP was driving the whole effect (Supplementary Figure S2). Moreover, the weighted median [OR: 1.021, 95% CI: 1.002 −1.040, $P = 0.032$] and weighted mode [OR: 1.022, 95% CI: 1.005 −1.040, $P = 0.016$] showed a role of T1D in increasing the risk of COPD in the validation process (Supplementary Table S10). Notably, the result obtained from the weighted mode method reached the threshold of Bonferroni correction.

The causal effect of T1D and T2D on the risk of COPD was also explored in Asian ancestry individuals. The detailed information of selected SNPs and summary F-statistics of the IVs were summarized in Supplementary Tables S13–S15. F statistics quantified the strength of the selected SNPs (Supplementary Table S15). Based on the IVW method, no causal link was detected between genetically determined T1D [IVW OR: 0.969, 95% CI: 0.903–1.040, $P = 0.386$] or T2D [IVW OR: 1.009, 95% CI: 0.953–1.068, $P = 0.760$] on the risk of COPD in Asian ancestry (Table 1, Supplementary Table S16). MR-Egger regression or MR-PRESSO test did not suggest any directional pleiotropy for the IVs (Supplementary Tables S16 and S17). Similarly, none significant association was discovered by using an independent COPD GWAS sample set in the validation process (Supplementary Tables S18–S21).

Table 1 MR Estimates of the Causal Association Between T2D and the Risk of COPD in Forward Analysis (Both Populations)

Datasets	Nsnp	Methods	F Statistic	Beta	SE	*P*	OR (95% CI)	Horizontal Pleiotropy *P*	Heterogeneity *P*
European-discovery process	333	MR Egger	40.854	<0.001	<0.001	0.355	1.000 (0.999, 1.000)	0.064	0.075
		Weighted median		<0.001	<0.001	0.310	1.000 (1.000, 1.001)		
		IVW		<0.001	<0.001	**<0.001**	1.002 (1.001, 1.003)		
		Simple mode		<0.001	<0.001	0.416	1.001 (0.999, 1.002)		
		Weighted mode		<0.001	<0.001	0.403	1.000 (0.999, 1.001)		
European-validation process	325	MR Egger	41.067	0.102	0.044	**0.021**	1.108 (1.016, 1.208)	0.002	<0.001
		Weighted median		0.024	0.027	0.382	1.024 (0.971, 1.081)		
		IVW		<0.001	0.017	0.114	0.973 (0.941, 1.007)		
		Simple mode		0.047	0.070	0.504	1.048 (0.913, 1.203)		
		Weighted mode		0.036	0.038	0.353	1.036 (0.961, 1.118)		
Asian-discovery process	131	MR Egger	44.342	0.040	0.059	0.495	1.041 (0.927, 1.169)	0.540	0.396
		Weighted median		<0.001	0.057	0.813	0.987 (0.882, 1.104)		
		IVW		0.009	0.029	0.760	1.009 (0.953, 1.068)		
		Simple mode		0.032	0.111	0.772	1.033 (0.830, 1.285)		
		Weighted mode		<0.001	0.059	0.845	0.988 (0.880, 1.111)		
Asian-validation process	131	MR Egger	44.670	0.170	0.146	0.246	1.185 (0.891, 1.578)	0.097	0.065
		Weighted median		<0.001	0.087	0.899	0.989 (0.834, 1.173)		
		IVW		<0.001	0.059	0.359	0.948 (0.845, 1.063)		
		Simple mode		<0.001	0.227	0.637	0.898 (0.575, 1.402)		
		Weighted mode		0.006	0.127	0.963	1.006 (0.784, 1.290)		

Notes: Bold values indicate statistical significance ($P < 0.05$).
Abbreviations: Nsnp, number of single-nucleotide polymorphisms; IVW, inverse-variance-weighted; SE, standard error; OR, odds ratio.

As the conventional MR methods potentially indicated a European-specific causal association between T2D and the risk of COPD, an alternative MR method called CAUSE was employed to confirm this causality. The CAUSE analysis consistently suggested the potential causality between T2D and COPD in European population (Supplementary Table S22). However, no statistically significant difference was found ($P = 0.450$).

Causal Effect of Diabetes on COPD-Associated Outcomes

The causal effect of T1D and T2D on COPD-associated characteristics and outcomes was further investigated in European ancestry. Detailed information of IVs for T1D and T2D was listed in Supplementary Table S23. The F statistics of IVs used in the analyses ranged from 38.679 to 278.426 (Supplementary Table S24), showing valid strength of these IVs. As the GWAS statistics for interested outcomes were limited to individuals of European ancestry, the causality between diabetes and COPD-related characteristics and outcomes was solely discovered in this population. A Bonferroni correction test (0.05/2 = 0.025) was applied in order to account for the increased likelihood of chance findings when conducting multiple statistical tests.

According to the IVW MR approach, genetically predicted T1D was positively associated with the increased risk of COPD-I [OR: 1.017, 95% CI: 1.009–1.025, $P < 0.001$] in European population (Table 2, Supplementary Table S25). While the methods of MR Egger [OR: 1.023, 95% CI: 1.011–1.036, $P < 0.001$] and weighted mode [OR: 1.011, 95% CI: 1.002–1.020, $P = 0.015$] also yielded significant association between T1D and COPD-I with the same direction (Table 2, Supplementary Table S25). However, Cochran's Q statistics revealed potential heterogeneity between IVs ($P < 0.001$) (Table 2). And the results of MR-PRESSO global test indicated evidence of potential horizontal pleiotropy that distorted the influence of T1D on COPD ($P < 0.001$) (Supplementary Table S26). The leave-one-out plot showed that the overall estimated effect was not driven by any individual SNPs (Supplementary Figure S3). The IVW method also indicated a potential causal role of T2D on an increased risk of COPD-I ($P = 0.025$), with a P value being found to be on the borderline of Bonferroni corrected statistical significance (Supplementary Table S25). Besides, the role of T2D in increasing the risk of COPD-related infection was also indicated by IVW method [OR: 1.102, 95% CI: 1.002–1.037, $P = 0.025$] but not by other approaches (Table 2 and Supplementary Table S25).

Causal Effect of COPD on Diabetes

To evaluate any reverse causation effects, we conducted reverse MR approaches where COPD was analysed as the exposure and diabetes was analysed as the outcomes. The detailed information of the IVs in the reverse MR analysis from European and Asian ancestries was presented in Supplementary Tables S27 and S28, respectively. F-statistics of IVs that used in the reverse MR analysis for both populations were larger than 10, indicating that all instruments had a strong potential to predict exposure and could be used for the MR analysis (Supplementary Tables S29 and S30).

Table 2 MR Estimates of the Causal Association Between Diabetes and the Risk of COPD with Infections in Forward Analysis (European Population)

Exposure	Outcome	Nsnp	Methods	F Statistic	Beta	SE	*P*	OR (95% CI)	Horizontal Pleiotropy *P*	Heterogeneity *P*
T1D	COPD-I	78	MR Egger	220.149	0.023	0.006	**<0.001**	1.023 (1.011, 1.036)	0.209	<0.001
		78	Weighted median		0.008	0.005	0.096	1.008 (0.999, 1.018)		
		78	IVW		0.017	0.004	**<0.001**	1.017 (1.009, 1.025)		
		78	Simple mode		0.014	0.008	0.088	1.015 (0.998, 1.031)		
		78	Weighted mode		0.011	0.004	**0.015**	1.011 (1.002, 1.020)		
T2D	COPD-I	274	MR Egger	42.058	<0.001	0.022	0.366	0.980 (0.939, 1.023)	0.050	0.002
		274	Weighted median		0.006	0.012	0.609	1.006 (0.982, 1.031)		
		274	IVW		0.020	0.009	**0.025**	1.020 (1.002, 1.037)		
		274	Simple mode		0.035	0.040	0.374	1.036 (0.959, 1.119)		
		274	Weighted mode		<0.001	0.022	0.104	0.964 (0.923, 1.007)		

Notes: Bold values indicate statistical significance ($P < 0.05$).

Abbreviations: T1D, type 1 diabetes mellitus; COPD-I, COPD with infections; Nsnp, number of single-nucleotide polymorphisms; IVW, inverse-variance-weighted; SE, standard error; OR, odds ratio.

For both ancestry populations, no consistent causal associations between COPD and the risk of T1D or T2D were observed through comprehensive discovery and validation processes (Supplementary Tables S31–S34). The MR-Egger intercept analysis found no evidence of directional pleiotropy in selected SNPs (Supplementary Tables S31–S34).

Discussion

As one of the leading causes of death worldwide, COPD frequently coexists with various comorbidities which result in significant health and economic burdens for patients. Diabetes mellitus is a common comorbidity in the context of COPD.[42] Observational studies have reported an increased prevalence of diabetes in COPD patients, and vice versa.[43] Despite the growing body of evidence highlighting common environmental, lifestyle, and genetic factors linking COPD and diabetes, the causal relationship between the two remains uncertain due to the inherent limitations of observational studies, which can establish correlation but not causation.[10] A recent MR study attempted to explore the causal relationship between COPD and diabetes; however, several key points relevant to clinical practice were not adequately addressed.[24] Our current study provided clinicians with more robust evidence in terms of the causal relationship between those conditions, which might help to define the strategies in assessing and managing the comorbid condition in clinical care of multi-diseased COPD patients.

In our analysis, we evaluated the causal association between genetically predicted diabetes and the risk of COPD using two-sample MR with GWAS summary data from both European and Asian ancestries. Our findings suggested that T2D may represent was a potential risk factor for the development of COPD in individuals of European ancestry, which brought into correspondence with findings from previous cohort studies.[44] In contrast, no robust causal association was observed between T1D and COPD. Although T1D has been shown to be associated with impaired pulmonary function, including reduced lung elastic recoil, DLCO, and pulmonary capillary volume,[45] it is important to note that the decline in lung function in T1D patients may be less pronounced compared to T2D patients, especially since individuals with T1D are generally younger.[46] Additionally, no causal effect of genetically predicted T1D or T2D on the risk of COPD was found in the Asian ancestry. This lack of association might be partially explained by the significant variations in diabetes prevalence, pathophysiology, and phenotypes between European and Asian populations, as well as differences in diabetes management and drug responses across ethnic groups.[47–49] For instance, sodium-glucose cotransporter 2 inhibitors are more effective in lowering blood glucose in Asians compared to Europeans,[50] and α-glucosidase inhibitors are better tolerated in East Asians.[51] These ethnic differences underscore the need for further studies to investigate the potential impact of ethnicity on the relationship between diabetes and COPD.

COPD exacerbations are clinically and socioeconomically significant events that have far-reaching consequences on patient health and functional capacity.[52,53] Previous studies have indicated that increased blood glucose level exhibits an impact on the outcomes of COPD through common pathological pathways,[54] particularly exacerbation-related outcomes.[5,43] In patients with COPD, pneumonia is associated with more severe airflow obstruction and exacerbations that lead to hospitalizations.[55] Glucose levels rise in the body may directly stimulate bacterial growth or promote interaction between bacteria and the airway epithelium.[56] Furthermore, immune function is impaired in diabetes, increasing susceptibility to pathogens and enhancing infections in COPD patients.[57] In our study, we found that T1D and T2D were positively related to the risk of infections in COPD patients of European ancestry. This causal association aligns with previous studies showing diabetes-related increases in the risk of lower respiratory tract, urinary tract, and skin infections,[58,59] as well as lung infections resulting from impaired immune function.[60]

Given the increased prevalence of diabetes in COPD patients, we also performed the reverse MR analysis in both European and Asian ancestries to discover the causal effect of COPD on the risk of diabetes. This approach helped mitigate potential reverse causality in the forward association. The results showed no consistent causal association between genetically predicted COPD and the risk of diabetes. Since higher doses of corticosteroids, key maintenance therapy for COPD, are associated with a greater risk of diabetes,[61] the increased incidence of diabetes in COPD patients might be related to the use of corticosteroids, though the risk of developing new-onset diabetes with inhaled corticosteroid remains debated.[62]

From a biological perspective, the small MR estimates may arise from several factors, including weak direct effects of the exposure on the outcome, complex mediating mechanisms, individual differences, and interference from other environmental factors. First, the exposure (eg, genetic susceptibility to diabetes) may influence the outcome (eg, COPD) indirectly through mediating mechanisms such as chronic inflammation, oxidative stress, or metabolic dysregulation,[63] which are not directly captured by MR analyses. Additionally, the biological effects of the exposure

on the outcome may vary among subgroups or individuals,[64] such as differences in COPD severity or diabetes control, diluting the overall effect size. Moreover, the complex etiology of COPD and diabetes, involving factors like smoking, environmental pollution, and genetic background, could mask the direct impact of a single exposure, further reducing the MR estimate.[65] Pleiotropy interference may also occur, where certain SNPs influence the outcome through pathways unrelated to the exposure, leading to an underestimation of the true causal effect.[37]

While our MR analysis primarily focused on genetic instruments to infer causality, the role of non-genetic factors, particularly physical inactivity, warrants further discussion. Patients with COPD frequently experience dyspnea and exercise intolerance, leading to reduced physical activity levels. This sedentary behavior may independently contribute to insulin resistance and impaired glucose metabolism, exacerbating diabetes risk through pathways such as diminished skeletal muscle glucose uptake, adipose tissue dysfunction, and chronic low-grade inflammation.[66,67] Beyond physical inactivity, other modifiable factors may confound or mediate the COPD-diabetes relationship. Cigarette smoking, a shared risk factor for both conditions, induces systemic oxidative stress and β-cell dysfunction, potentially amplifying diabetes susceptibility in COPD patients.[68] Dietary patterns high in saturated fats, common in populations with chronic respiratory symptoms,[69] may dysregulate glucose homeostasis. Notably, corticosteroid therapy, a mainstay of COPD management, may transiently elevate blood glucose levels, though its long-term contribution to diabetes pathogenesis remains debated.

Our study shares several methodological similarities with the MR study by Wang et al;[24] however, there are key differences in research objective, methods, and findings. Regarding the study objective, our work focused more on exploring the causal effect of both T1D and T2D on the risk of COPD, with an emphasis on how diabetes influences COPD risk and associated clinical outcomes. In terms of methodology, we incorporated multiple MR approaches and sensitivity analyses to explore the bidirectional causal relationship, whereas Wang et al used a unidirectional MR method. Moreover, our study utilized GWAS data from European and Asian populations respectively for both exposures and outcomes, while Wang et al's study elected European cohorts for COPD exposure and Asian cohorts for T2D outcomes. We also specifically examined the association between diabetes and COPD-related clinical characteristics, such as infections, which was not addressed in Wang's study. Moreover, we used multiple GWAS datasets to apply discovery analysis and validation analysis, which would give more robust results. Regarding the findings, we identified no consistent causal effect of COPD on the risk of T1D or T2D, whereas Wang et al found that COPD was a risk factor for T2D. This discrepancy might be attributed to differences in the genetic instruments used, sample sizes, and population characteristics. These differences highlight the unique contribution of our work, which offers new insights into this specific field and enriches the current understanding of the correlations between these conditions. More importantly, the divergence in results highlights the importance of further research to better understand the complex interplay between COPD and diabetes.

Although our study utilized a robust and validated methodology, we acknowledged several limitations. First, MR analysis was performed only using existing genetic data; non-genetic factors that might influence the association were not explored. Second, although we covered GWAS data from East Asian populations, the generalizability of our findings to other racial and ethnic groups was still limited as the available GWAS statistics pertaining to COPD characteristics and outcomes in public databases predominantly derived from individuals of European ancestry. Thirdly, the COPD GWAS datasets utilized in our analysis contained samples from patients with asthma, which could introduce a potential bias in the causal relationships examined, as the selected SNPs might also be associated with asthma. Consequently, caution should be exercised when interpreting and generalizing the findings, considering the potential confounding effect of asthma on the observed causal relationships. Finally, the heterogeneity obtained by the Cochran's Q test in our MR analyses suggested that further research is needed to verify these relationships.

Conclusion

This bidirectional two-sample MR study provides tentative evidence for a potential causal role of T2D in increasing the risk of developing COPD within the European population. However, caution is warranted, and further validation of this association is necessary to enhance our understanding and facilitate the identification of new therapeutic targets and interventions aimed at effectively managing the burden of COPD, particularly in individuals with comorbidities such as diabetes. Ongoing research in this area will be crucial for improving patient care and clinical outcomes.

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Author Contributions

XYW and XC were co-first authors and contributed equally to this study. WL and HLJ conceived and designed the study. XYW and WL drafted the manuscript. XYW, XC, and RZF performed the MR statistical analyses and sensitivity analyses. WL and XYW contributed to drafting and revising the article. 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 report no conflicts of interest in this work.

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