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ORIGINAL RESEARCH

Effects of Diabetes Mellitus and Glycemic Traits on COPD and Pulmonary Function Traits: Insights From Mendelian Randomization and NHANES

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Purpose: This two-sample Mendelian randomization (MR) analysis and study based on the National Health and Nutrition Examination Survey (NHANES) aimed to evaluate the effects of diabetes mellitus and glycemic traits on chronic obstructive pulmonary disease (COPD) and pulmonary function traits.

Patients and Methods: Utilizing a two-sample MR analysis and NHANES data (2007–2012), this study investigated the associations of diabetes and glycemic traits with COPD and pulmonary function traits. Exposures included type 1 (T1DM) and type 2 diabetes (T2DM), fasting glucose (FGlu), fasting insulin (FIns), glycated hemoglobin (HbA1c), and 2-hour glucose (2hGlu). Outcomes included COPD, forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), the FEV1/FVC ratio, and peak expiratory flow (PEF). The MR analysis employed inverse variance weighted (IVW) and weighted median methods. Multivariate logistic regression and linear regression were used to evaluate the associations, adjusting for age, gender, race, body mass index (BMI), and blood cholesterol in the NHANES database.

Results: MR analyses (IVW results) indicated significant causal relationships between T1DM and COPD, and FEV1/FVC ratio (OR = 1.023, 95% CI = 1.012 to 1.034, P < 0.0001; beta = −0.0075, 95% CI = −0.0122 to −0.0028, P = 0.0018, respectively). T2DM also exhibited significant causal associations with FVC and FEV1/FVC ratio (beta = −0.0330, 95% CI = −0.0448 to −0.0212, P < 0.0001; beta = 0.0172, 95% CI = 0.0065 to 0.0279, P = 0.0016). 2hGlu showed a significant causal relationship with FEV1/FVC ratio (beta = 0.0472, 95% CI = 0.0089 to 0.0856, P = 0.0159). A total of 389 participants were enrolled in this study (unweighted), with a weighted sample size of 6324845, based on the NHANES database. Multivariate logistic regression revealed no statistically significant association between diabetes, glycemic traits, and COPD. Multivariate linear regression indicated that a 2.7-fold increase in HbA1c levels was negatively correlated with declines in FEV1 (42.56%), FVC (34.92%), and PEF (37.77%).

Conclusion: This study demonstrated the impact of diabetes and glycemic traits on COPD and lung function traits, highlighting important clinical implications.

Keywords: Mendelian randomization, NHANES, mellitus, glycemic, COPD, pulmonary function

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Introduction

Chronic obstructive pulmonary disease (COPD) is a prevalent and severe chronic respiratory condition characterized by persistent airway inflammation leading to mucus overproduction, destruction of alveolar walls, and resultant narrowing and deformation of the small airways. These pathological changes result in airway obstruction and progressive respiratory difficulties,[1–3] significantly impacting health status of patients and bringing a huge economic burden globally.[4] Central to COPD is airflow limitation,[5] which is defined by a reduced post-bronchodilator forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) ratio.[6] This is typically accompanied by decreases in FEV1[7] and FVC.[8] Peak expiratory flow (PEF) is also a commonly employed measure for assessing lung function and overall health

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status in COPD patients.[9] Timely identification and intervention regarding risk factors that influence COPD and pulmonary function are essential for both COPD prevention and the preservation of pulmonary function.

Diabetes, a global metabolic disease, was observed at a higher frequency in COPD patients than in the general population.[10] Type 1 diabetes (T1DM) and type 2 diabetes (T2DM), especially T2DM, is a leading comorbidity in COPD.[10] Observational studies found that diabetes, poor glycemic control, duration, higher glycated hemoglobin (HbA1c) were associated with decreased worsening FVC, FEV1, and PEF.[11–14] However, the effects of diabetes and glycemic phenotypes on COPD and lung function have not been fully explored. Moreover, observational studies frequently encounter biases stemming from residual confounding, misclassification, and reverse causation, presenting challenges in establishing causality.[15] Causal effects of diabetes mellitus and glycemic traits on COPD and pulmonary function traits remain unclear.

Mendelian randomization (MR) is a method that leverages genetic variation as an instrumental variable (IV) to assess evidence for potential causal relationships between exposure factors and outcomes,[16] while helping to overcome some biases inherent in conventional observational studies.[17] By capitalizing on the random allocation of genetic variants during gametogenesis, MR can provide evidence that is less susceptible to confounding, analogous to the principles of randomized controlled trials, thus facilitating the investigation of causal hypotheses that may be impractical or ethically challenging to test directly. With the growing prominence of genome-wide association studies (GWAS), MR has become a widely used tool for evaluating putative disease risk factors and biomarkers.[18]

Based on extensive observational evidence and plausible biological mechanisms linking hyperglycemia to lung dysfunction, We hypothesized that diabetes mellitus and glycemic traits affect COPD and pulmonary function traits. We designed this two-sample MR study to evaluate the causal effects of diabetes mellitus and four glycemic traits (T1DM, T2DM, fasting glucose (FGlu), fasting insulin (FIns), HbA1c, and 2 h-glucose post-challenge (2hGlu)) on COPD and four pulmonary function traits (FEV1, FVC, FEV1/FVC ratio, and PEF). Additionally, we extracted data from the National Health and Nutrition Examination Survey (NHANES) database to evaluate the effects of diabetes mellitus and glycemic traits on COPD and pulmonary function traits. Clarifying these links is crucial for the assessment and management of impaired glycemic homeostasis and diabetes in patients with COPD, providing a higher level of evidence and deepening our understanding of how diabetes and blood glucose levels contribute to the occurrence and progression of COPD and decline pulmonary function.

Material and Methods

Study Design

This two-sample MR study and analysis based on the NHANES database aimed to assess the relationships between exposures (T1DM, T2DM, FGlu, FIns, HbA1c, and 2hGlu) and outcomes (COPD, FEV1, FVC, FEV1/FVC ratio, and PEF). The MR study adhered to three core assumptions of MR analysis: (1) the association assumption, (2) the independence assumption, and (3) the exclusion-restriction assumption, MR analysis is detailed in Figure 1.

Our data were obtained from the GWAS Catalog, published literature, and the NHANES website, which do have their own ethical approvals and informed consent processes. Approval from the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University was secured (Approval number: XJTU1AF2025LSYY-845).

Sources and Selection of Instrumental Variables for the MR Study

The genetic instrumental variables (IVs) linked to T1DM, T2DM, FGlu, FIns, HbA1c, and 2hGlu were obtained from studies conducted by Zhao et al.[15] The original IVs for T1DM and T2DM were obtained from existing research. The genetic instruments related to T1DM and T2DM were curated from studies by Forgetta et al and the DIAbetes Genetics Replication and Meta-analysis Consortium respectively.[18,19] The glycemic traits sourced from other studies,[20] in these studies, only data from European populations were utilized from trans-ancestral datasets related to T2DM and glycemic traits for exposure assessment to mitigate bias stemming from population structure.[15] Zhao et al summarized the IVs for diabetes mellitus and glycemic traits from the aforementioned studies based on specific selection criteria:[21] (1) single nucleotide polymorphism (SNP) associated with exposures at the genome-wide significance level ($P < 5 \times 10^{-8}$). (2) No

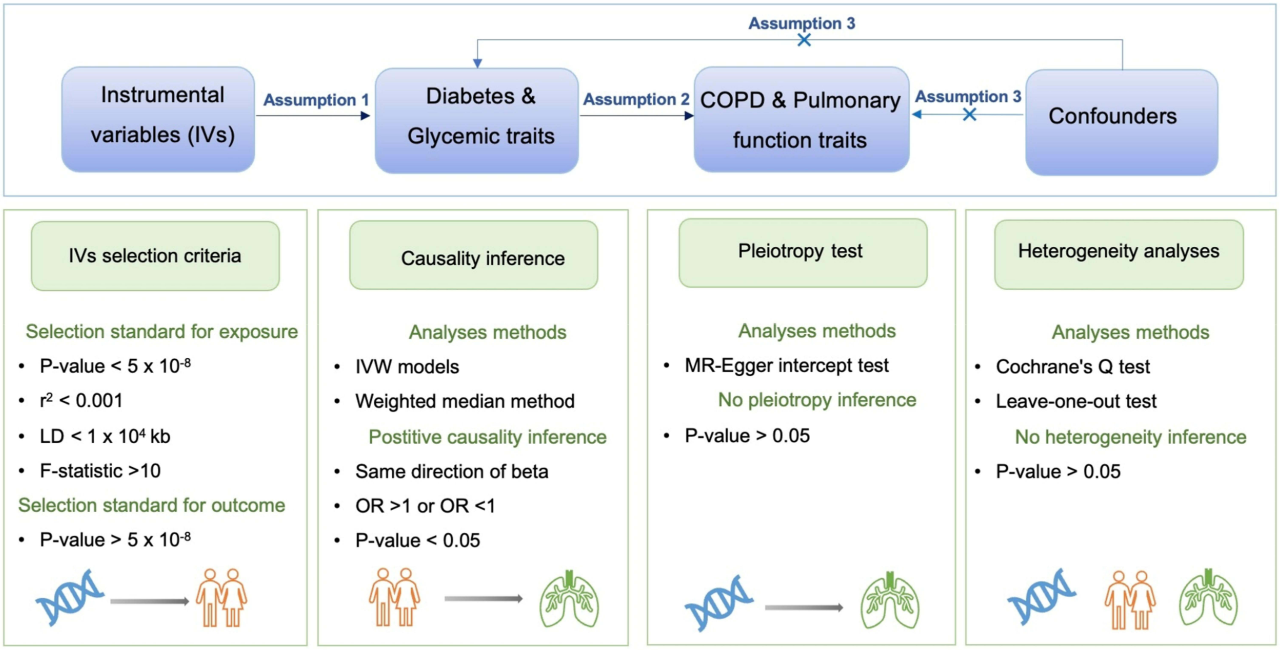


Figure 1 Study design and analyses methods of MR analysis.
Abbreviations: COPD, chronic obstructive pulmonary disease; LD, linkage disequilibrium; IVW, inverse variance weighted; OR, odds ratio.

linkage disequilibrium (LD) ($r^2 < 0.001$, genetic distance $= 10000$ kb). (3) the F-statistic was used to assess the strength of the IVs, with IVs having an F-statistic lower than 10 being excluded as weak instruments, and (4) exclusion of SNPs in LD. Eventually, Zhao et al identified 45, 185, 68, 38, 75, and 14 SNPs in T1DM, T2DM, FGlu, FIns, HbA1c, and 2hGlu, respectively. Detailed SNP information was provided in Supplementary Table 1.

Subsequently, we eliminated SNPs associated with COPD and pulmonary function traits at the genome-wide significance level ($P < 5 \times 10^{-8}$) and excluded SNPs with palindromic and intermediate allele frequencies.

Outcome Data Sources for MR Study

Outcome data for COPD, FEV1, FVC, FEV1/FVC, and PEF were extracted from the GWAS Catalog, sourced from published Meta-analyses studies (https://www.ebi.ac.uk/gwas/), all of which focused on European cohorts. The details of the data sources are listed in Table 1. For FEV1, FVC, FEV1/FVC, and PEF data from the GWAS Catalog, our variables included SNPs, effect alleles, other alleles, effect allele frequency (EAF), Z-scores, P-value, and sample sizes. Notably, standard errors (SE) and beta coefficients are pivotal for MR analysis but are not directly provided. To address this, we calculated SE and beta using the following formulas:[22]

Table 1 Data Source and Information of Outcomes From the GWAS Catalog

Traits	GWAS ID	Gender	People	Sample Size	Year
COPD	GCST90399694	Both	European	995917	2024
FEV1	GCST90292609	Both	European	320656	2023
FVC	GCST90292610	Both	European	320656	2023
FEV1/FVC ratio	GCST90292611	Both	European	320656	2023
PEF	GCST90292612	Both	European	320656	2023

Notes: Data sources and information of the outcomes of COPD, FEV1, FVC, FEV1/FVC ratio, and PEF.
Abbreviations: GWAS, genome-wide association studies; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow.

$$\mathrm{SE} = \frac{1}{\sqrt{2\mathrm{MAF}(1 - (\mathrm{MAF})(\mathrm{N} + (\mathrm{Z} - \mathrm{scores}^2)}}$$

$$\mathrm{Beta} = \frac{\mathrm{Z} - \mathrm{scores}}{\sqrt{2\mathrm{MAF}(1 - (\mathrm{MAF})(\mathrm{N} + (\mathrm{Z} - \mathrm{scores}^2)}}$$

The minor allele frequency (MAF) was computed using EAF. Specifically, if EAF is greater than 0.5, then MAF is calculated as 1 - EAF, whereas if EAF is less than 0.5, MAF = EAF.

Study Population Based on the NHANES

We obtained datasets from the NHANES website from the years 2007 to 2012 (2007–2008, 2009–2010, and 2011–2012) (https://wwwn.cdc.gov/nchs/nhanes/Default.aspx). Demographic information, smoking history, medical conditions (including diabetes, COPD, asthma, congestive heart failure, hypertension, coronary heart disease, and chronic kidney disease), glycemic traits, pulmonary function measures, liver function, and other relevant examination data were extracted. Individuals under 18 years of age and those with missing information on diseases, glycemic traits, pulmonary function measures, and other experimental variables were excluded. The diagnosis of COPD was based on post-bronchodilator spirometry data, which was consistent with a previous study in.[23] We defined a FEV1/FVC ratio of less than 0.7 as meeting the criteria for COPD as outlined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD).[24] Consistent with previous study,[25] The diagnosis of diabetes was based on the most recent 2025 diabetes guideline consensus published by the American Diabetes Association (ADA) that FGlu ≥ 126mg/dL (≥ 7.0mmol/L), HbA1c ≥ 6.5%, or 2hGlu ≥ 200mg/dL (≥ 11.1mmol/L).[26] For cigarette use status, we assessed two questions: "Have you smoked at least 100 cigarettes in your lifetime?" and "Are you currently smoking?". Current smokers were defined as individuals who had smoked at least 100 cigarettes in their lifetime and who were still smokers. Former smokers had smoked at least 100 cigarettes but had not smoked at the time of the survey. Never smokers were defined as individuals who had not smoked 100 or more cigarettes in their lifetime. Appropriate weighting procedures were applied to account for the multiple years of NHANES data included in this study (a total of 6 years).

Statistical Analysis

This study was conducted using R software (version 4.3.2). We used the R packages of TwoSampleMR (version 0.6.5), forestploter (version 1.1.2), data.table (version 1.15.4), cowplot (version 1.1.3), survey (version 4.4–2) and related functions for the analysis.

For the two-sample MR analysis, multiplicative random effects inverse variance weighted (IVW-MRE), fixed effects inverse variance weighted (IVW-FE), and weighted median methods were used to evaluate the causal links between exposures to diabetes mellitus and glycemic traits and outcomes for COPD and pulmonary function traits according to the heterogeneity test.[27,28] MR Egger regression was conducted as an additional analysis. IVW was determined as the main outcome due to its ability to yield the most resilient and accurate estimates.[29] IVW methods offer reliable estimates of exposure effects on outcomes, provided that each variant satisfies instrumental variable assumptions.[30] Subsequently, weighted median methods and MR Egger regression were applied, which ensure consistent causal estimates across multiple genetic variants, leveraging pooled data under milder assumptions.[30] Even with to 50% of data derived from invalid IVs, weighted median methods maintain consistent causal effect estimates. Overall, the weighted median method offers more precise estimations compared to MR-Egger analysis.[28] If heterogeneity test for Cochrane's Q test (mainly IVW method, additional MR Egger) showed $P < 0.05$, the IVW-MRE method should be used for assessing the causal effect, if not, using IVW-FE. For the outcome of COPD, all results from the IVW and weighted median methods showed odds ratio (OR) > 1 or OR < 1, and P-value < 0.05, which were regarded as causal links. For the outcome of FEV1, FVC, FEV1/FVC ratio, and PEF, at least the IVW and weighted median methods were statistically significant ($P < 0.05$), and three MR analyses (IVW, MR Egger, and weighted median) results showed that the same direction of beta was regarded as causal link. Regarding sensitivity analyses, in addition to the heterogeneity test (Cochran's Q test), the pleiotropy test (MR-Egger intercept test) and the leave-one-out test were used to verify the stability of the results.

In the study utilizing the NHANES database, continuous variables were summarized using the mean and standard deviation (SD). Categorical variables were presented as frequencies and percentages (%). Continuous variables were analyzed using either the Student's *t* test or the Mann–Whitney *U*-test, while categorical variables were assessed using the Chi-square test or Fisher's exact test. Multivariate logistic regression was used to analyze the relationship between COPD, diabetes, and glycemic traits, adjusting for age, gender, race, body mass index (BMI), and blood cholesterol level. For this specific analysis, we restricted our study population to participants aged 40 years and older to ensure clinical consistency with diagnostic criteria for COPD according to GOLD. This approach resulted in the inclusion of 254 patients, and all analyses were conducted using appropriate weighting methods to account for the complex survey design. Additionally, multivariate linear regression was applied to investigate the association between glycemic traits, COPD, and pulmonary function traits after adjusting for age, gender, race, BMI, and blood cholesterol. To conduct linear regression of glycemic trait and pulmonary function traits, we applied a logarithmic transformation to the glycemic traits and pulmonary function traits, which helped reduce data skewness and enhance the accuracy of the results.

Results

Genetic Instrumental Variables for Diabetes and Glycemic Traits on COPD and Pulmonary Function Traits of MR Study

We excluded 12 SNPs for MR analysis, among them, 2 SNPs (rs116141873 and rs11727676) associated with outcomes at the genome-wide significance level ($P < 5 \times 10^{-8}$), while 10 SNPs characterized by palindromic and intermediate allele frequencies (rs1131017, rs34954, rs10908278, rs703972, rs34341, rs1999536, rs648795, rs10487796, rs10231021, and rs118164457). Finally, 413 SNPs were included, with F-statistic ranging from 22.44 to 1999.37. We extracted 36, 39, 40, 40, and 41 SNPs for T1DM related to COPD, FEV1, FVC, the FEV1/FVC ratio, and PEF, respectively. For T2DM, 141, 168, 167, 168, and 171 SNPs were selected for COPD and pulmonary function traits. The selection process continued for FGlu (52, 64, 63, 64, and 63 SNPs), FIns (24, 35, 36, 35, and 37 SNPs), HbA1c (57, 70, 71, 70, and 70 SNPs), and 2hGlu (9, 13, 12, 13, and 13 SNPs) in relation to COPD, FEV1, FVC, FEV1/FVC ratio, and PEF. Comprehensive information on the IVs is provided in the Supplementary Tables 2–7.

The MR Analysis

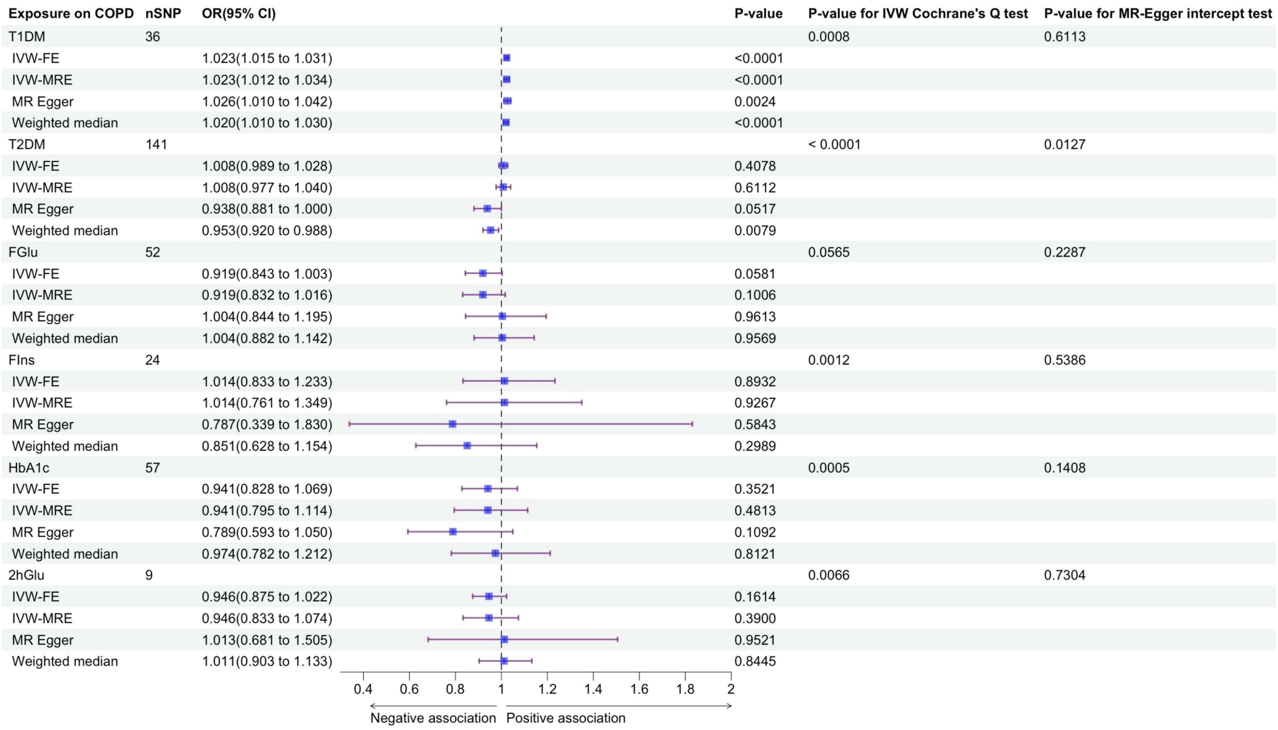
The primary outcomes of the MR analysis, Cochrane's Q test, and pleiotropy test of MR-Egger intercept test are shown in Figures 2–6. Sensitivity analysis revealed heterogeneity in all results except for FGlu on COPD. Moreover, pleiotropy of T2DM on COPD was observed. Considering the presence of heterogeneity, IVW-MRE (mainly) and weighted median methods were used to assess the causal effect of diabetes and glycemic traits on COPD and pulmonary function traits.

We observed significant negative causal links (Results of IVW-MRE) between T1DM and COPD and FEV1/FVC ratio (OR = 1.023, 95% CI = 1.012 to 1.034, $P < 0.0001$; beta = −0.0075, 95% CI = −0.0122 to −0.0028, P = 0.0018). Additionally, T2DM exhibited significant negative causal association with FVC (beta = −0.0330, 95% CI = −0.0448 to −0.0212, $P < 0.0001$), but a positive causal associations with FEV1/FVC ratio (beta = 0.0172, 95% CI = 0.0065 to 0.0279, P = 0.0016). Furthermore, 2hGlu showed a significant positive causality with FEV1/FVC ratio (beta = 0.0472, 95% CI = 0.0089 to 0.0856, P = 0.0159).

Sensitivity Analyses of MR Study

As shown in Figures 2–6, the MR-Egger intercept test (IVW method) observed no pleiotropy (all $P > 0.05$) (Supplementary Figures 1–5), excepting for T2DM in COPD (MR-Egger intercept = 0.057, P = 0.0127). Cochrane's Q test showed heterogeneity in all results except for FGlu in COPD (all $P < 0.05$), details are shown in Supplementary Table 8, and Funnel plot of diabetes mellitus and glycemic traits in COPD and pulmonary function traits are shown in Supplementary Figures 6–10.

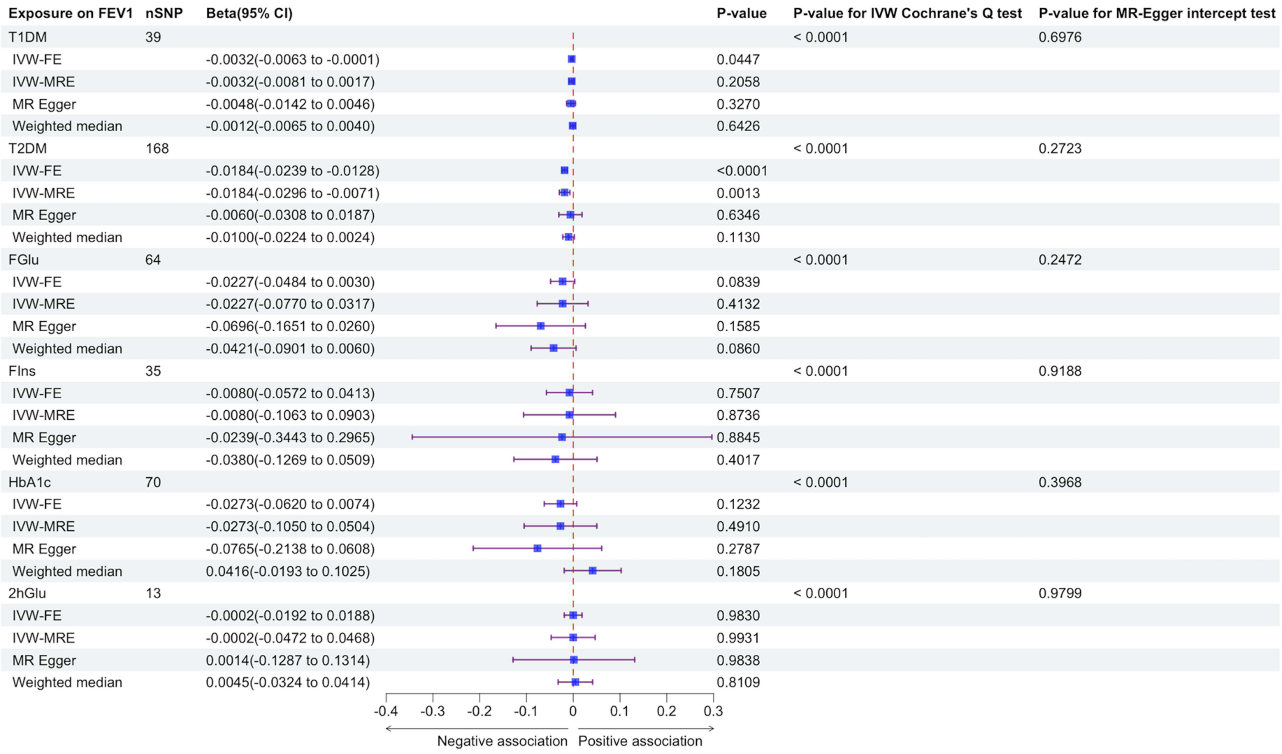
We also used a leave-one-out test to verify the stability of the results (Supplementary Figures 11–16). We found that SNPs linked to T1DM significantly affected MR outcomes for FVC (rs9273364), the FEV1/FVC ratio (rs506770), and PEF (rs567302488 and rs506770). We further removed these SNPs and performed the MR analysis again. The updated



Exposure on COPD	nSNP	OR(95% CI)	P-value	P-value for IVW Cochrane's Q test	P-value for MR-Egger intercept test
T1DM	36			0.0008	0.6113
IVW-FE		1.023(1.015 to 1.031)	<0.0001		
IVW-MRE		1.023(1.012 to 1.034)	<0.0001		
MR Egger		1.026(1.010 to 1.042)	0.0024		
Weighted median		1.020(1.010 to 1.030)	<0.0001		
T2DM	141			< 0.0001	0.0127
IVW-FE		1.008(0.989 to 1.028)	0.4078		
IVW-MRE		1.008(0.977 to 1.040)	0.6112		
MR Egger		0.938(0.881 to 1.000)	0.0517		
Weighted median		0.953(0.920 to 0.988)	0.0079		
FGlu	52			0.0565	0.2287
IVW-FE		0.919(0.843 to 1.003)	0.0581		
IVW-MRE		0.919(0.832 to 1.016)	0.1006		
MR Egger		1.004(0.844 to 1.195)	0.9613		
Weighted median		1.004(0.882 to 1.142)	0.9569		
FIns	24			0.0012	0.5386
IVW-FE		1.014(0.833 to 1.233)	0.8932		
IVW-MRE		1.014(0.761 to 1.349)	0.9267		
MR Egger		0.787(0.339 to 1.830)	0.5843		
Weighted median		0.851(0.628 to 1.154)	0.2989		
HbA1c	57			0.0005	0.1408
IVW-FE		0.941(0.828 to 1.069)	0.3521		
IVW-MRE		0.941(0.795 to 1.114)	0.4813		
MR Egger		0.789(0.593 to 1.050)	0.1092		
Weighted median		0.974(0.782 to 1.212)	0.8121		
2hGlu	9			0.0066	0.7304
IVW-FE		0.946(0.875 to 1.022)	0.1614		
IVW-MRE		0.946(0.833 to 1.074)	0.3900		
MR Egger		1.013(0.681 to 1.505)	0.9521		
Weighted median		1.011(0.903 to 1.133)	0.8445		

Figure 2 MR analysis of diabetes and glycemic traits on COPD.

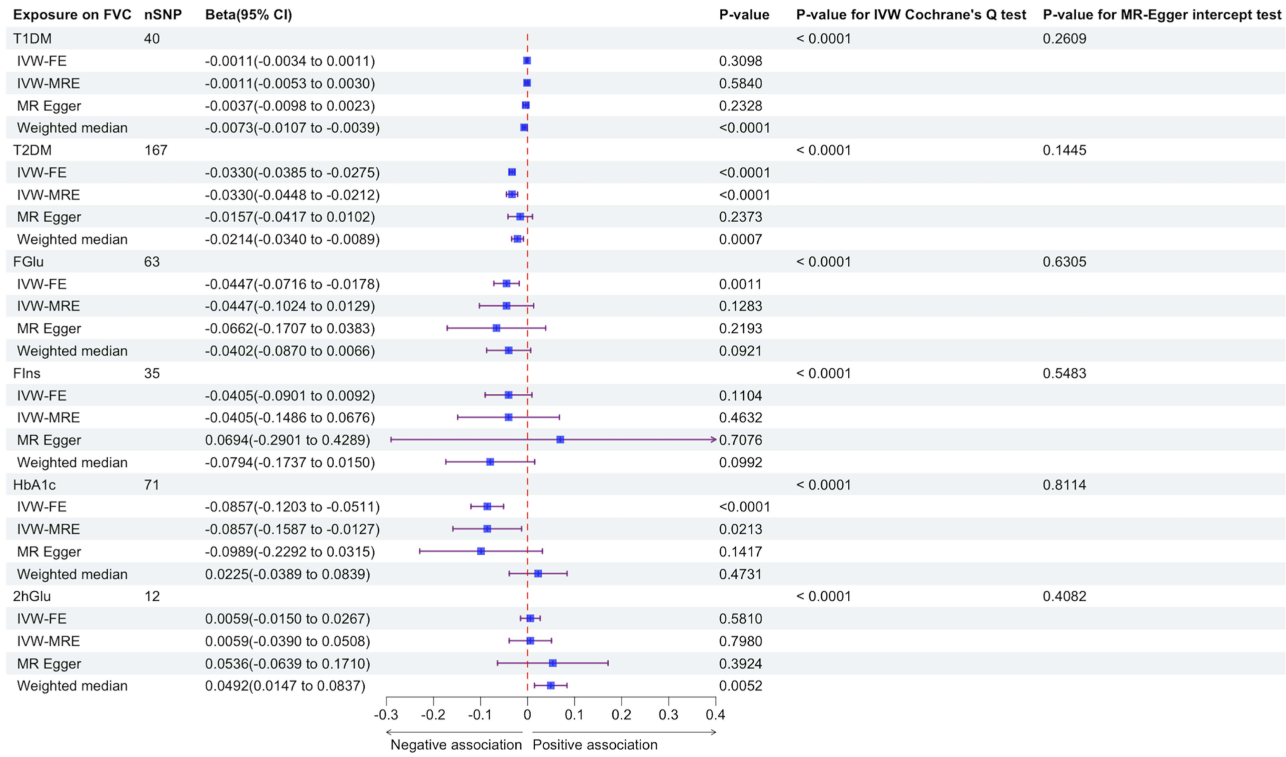
Abbreviations: COPD, chronic obstructive pulmonary disease; T1DM, type 1 diabetes; T2DM, type 2 diabetes; FGlu, fasting glucose; FIns, fasting insulin; HbA1c, glycated hemoglobin; 2hGlu, 2h-glucose post-challenge; IVW-MRE, inverse variance weighted (multiplicative random effects); IVW-FE, inverse variance weighted (fixed effects); OR, odds ratio.



Exposure on FEV1	nSNP	Beta(95% CI)	P-value	P-value for IVW Cochrane's Q test	P-value for MR-Egger intercept test
T1DM	39			< 0.0001	0.6976
IVW-FE		-0.0032(-0.0063 to -0.0001)	0.0447		
IVW-MRE		-0.0032(-0.0081 to 0.0017)	0.2058		
MR Egger		-0.0048(-0.0142 to 0.0046)	0.3270		
Weighted median		-0.0012(-0.0065 to 0.0040)	0.6426		
T2DM	168			< 0.0001	0.2723
IVW-FE		-0.0184(-0.0239 to -0.0128)	<0.0001		
IVW-MRE		-0.0184(-0.0296 to -0.0071)	0.0013		
MR Egger		-0.0060(-0.0308 to 0.0187)	0.6346		
Weighted median		-0.0100(-0.0224 to 0.0024)	0.1130		
FGlu	64			< 0.0001	0.2472
IVW-FE		-0.0227(-0.0484 to 0.0030)	0.0839		
IVW-MRE		-0.0227(-0.0770 to 0.0317)	0.4132		
MR Egger		-0.0696(-0.1651 to 0.0260)	0.1585		
Weighted median		-0.0421(-0.0901 to 0.0060)	0.0860		
FIns	35			< 0.0001	0.9188
IVW-FE		-0.0080(-0.0572 to 0.0413)	0.7507		
IVW-MRE		-0.0080(-0.1063 to 0.0903)	0.8736		
MR Egger		-0.0239(-0.3443 to 0.2965)	0.8845		
Weighted median		-0.0380(-0.1269 to 0.0509)	0.4017		
HbA1c	70			< 0.0001	0.3968
IVW-FE		-0.0273(-0.0620 to 0.0074)	0.1232		
IVW-MRE		-0.0273(-0.1050 to 0.0504)	0.4910		
MR Egger		-0.0765(-0.2138 to 0.0608)	0.2787		
Weighted median		0.0416(-0.0193 to 0.1025)	0.1805		
2hGlu	13			< 0.0001	0.9799
IVW-FE		-0.0002(-0.0192 to 0.0188)	0.9830		
IVW-MRE		-0.0002(-0.0472 to 0.0468)	0.9931		
MR Egger		0.0014(-0.1287 to 0.1314)	0.9838		
Weighted median		0.0045(-0.0324 to 0.0414)	0.8109		

Figure 3 MR analysis of diabetes and glycemic traits on FEV1.

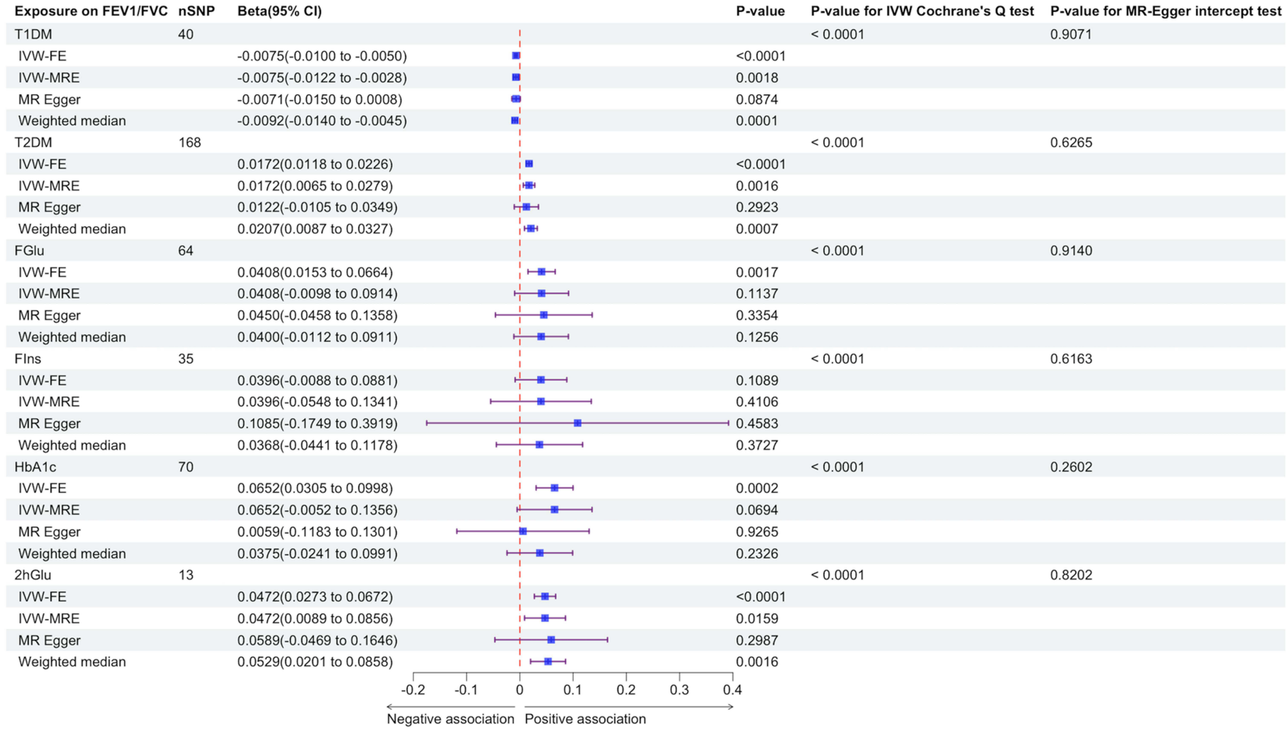
Abbreviations: T1DM, type 1 diabetes; T2DM, type 2 diabetes; FGlu, fasting glucose; FIns, fasting insulin; HbA1c, glycated hemoglobin; 2hGlu, 2h-glucose post-challenge; IVW-MRE, inverse variance weighted (multiplicative random effects); IVW-FE, inverse variance weighted (fixed effects); FEV1, forced expiratory volume in 1 second.



Exposure on FVC	nSNP	Beta(95% CI)	P-value	P-value for IVW Cochrane's Q test	P-value for MR-Egger intercept test
T1DM	40			< 0.0001	0.2609
IVW-FE		-0.0011(-0.0034 to 0.0011)	0.3098		
IVW-MRE		-0.0011(-0.0053 to 0.0030)	0.5840		
MR Egger		-0.0037(-0.0098 to 0.0023)	0.2328		
Weighted median		-0.0073(-0.0107 to -0.0039)	<0.0001		
T2DM	167			< 0.0001	0.1445
IVW-FE		-0.0330(-0.0385 to -0.0275)	<0.0001		
IVW-MRE		-0.0330(-0.0448 to -0.0212)	<0.0001		
MR Egger		-0.0157(-0.0417 to 0.0102)	0.2373		
Weighted median		-0.0214(-0.0340 to -0.0089)	0.0007		
FGlu	63			< 0.0001	0.6305
IVW-FE		-0.0447(-0.0716 to -0.0178)	0.0011		
IVW-MRE		-0.0447(-0.1024 to 0.0129)	0.1283		
MR Egger		-0.0662(-0.1707 to 0.0383)	0.2193		
Weighted median		-0.0402(-0.0870 to 0.0066)	0.0921		
FIns	35			< 0.0001	0.5483
IVW-FE		-0.0405(-0.0901 to 0.0092)	0.1104		
IVW-MRE		-0.0405(-0.1486 to 0.0676)	0.4632		
MR Egger		0.0694(-0.2901 to 0.4289)	0.7076		
Weighted median		-0.0794(-0.1737 to 0.0150)	0.0992		
HbA1c	71			< 0.0001	0.8114
IVW-FE		-0.0857(-0.1203 to -0.0511)	<0.0001		
IVW-MRE		-0.0857(-0.1587 to -0.0127)	0.0213		
MR Egger		-0.0989(-0.2292 to 0.0315)	0.1417		
Weighted median		0.0225(-0.0389 to 0.0839)	0.4731		
2hGlu	12			< 0.0001	0.4082
IVW-FE		0.0059(-0.0150 to 0.0267)	0.5810		
IVW-MRE		0.0059(-0.0390 to 0.0508)	0.7980		
MR Egger		0.0536(-0.0639 to 0.1710)	0.3924		
Weighted median		0.0492(0.0147 to 0.0837)	0.0052		

Figure 4 MR analysis of diabetes and glycemic traits on FVC.

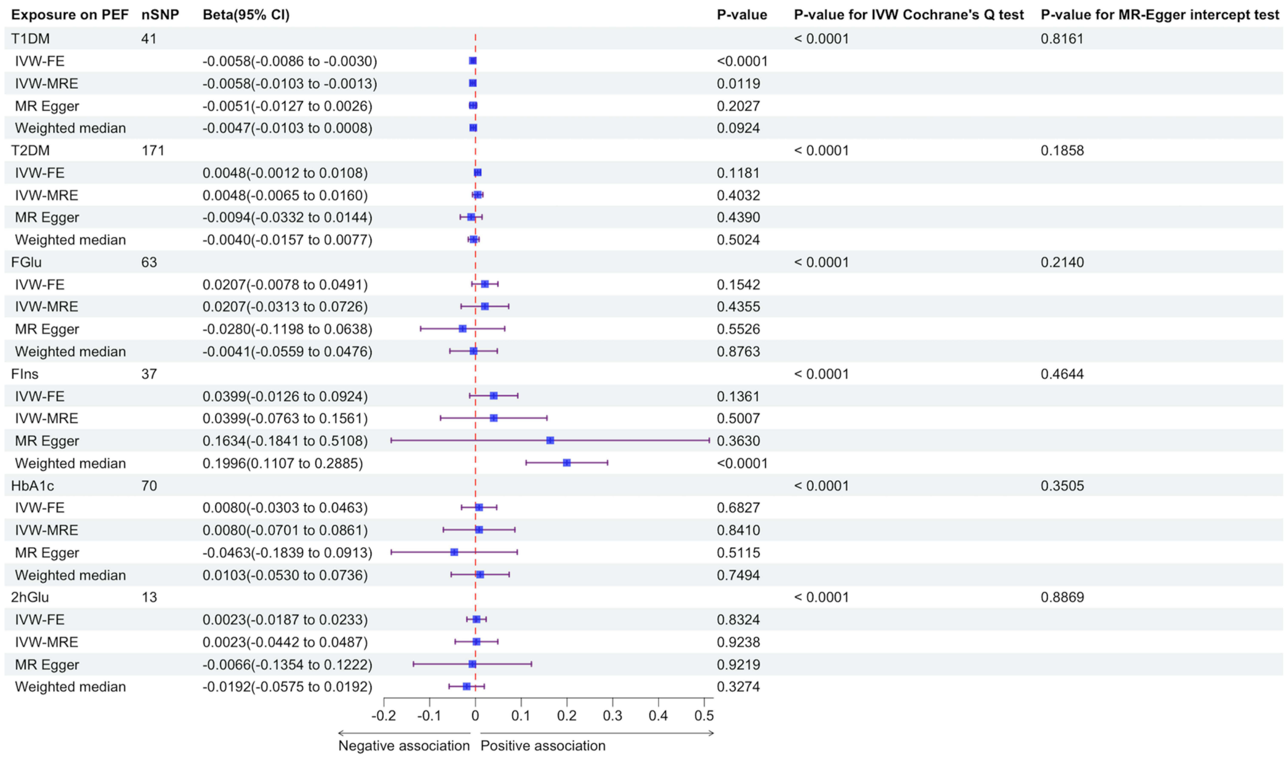
Abbreviations: T1DM, type 1 diabetes; T2DM, type 2 diabetes; FGlu, fasting glucose; FIns, fasting insulin; HbA1c, glycated hemoglobin; 2hGlu, 2h-glucose post-challenge; IVW-MRE, inverse variance weighted (multiplicative random effects); IVW-FE, inverse variance weighted (fixed effects); FVC, forced vital capacity.



Exposure on FEV1/FVC	nSNP	Beta(95% CI)	P-value	P-value for IVW Cochrane's Q test	P-value for MR-Egger intercept test
T1DM	40			< 0.0001	0.9071
IVW-FE		-0.0075(-0.0100 to -0.0050)	<0.0001		
IVW-MRE		-0.0075(-0.0122 to -0.0028)	0.0018		
MR Egger		-0.0071(-0.0150 to 0.0008)	0.0874		
Weighted median		-0.0092(-0.0140 to -0.0045)	0.0001		
T2DM	168			< 0.0001	0.6265
IVW-FE		0.0172(0.0118 to 0.0226)	<0.0001		
IVW-MRE		0.0172(0.0065 to 0.0279)	0.0016		
MR Egger		0.0122(-0.0105 to 0.0349)	0.2923		
Weighted median		0.0207(0.0087 to 0.0327)	0.0007		
FGlu	64			< 0.0001	0.9140
IVW-FE		0.0408(0.0153 to 0.0664)	0.0017		
IVW-MRE		0.0408(-0.0098 to 0.0914)	0.1137		
MR Egger		0.0450(-0.0458 to 0.1358)	0.3354		
Weighted median		0.0400(-0.0112 to 0.0911)	0.1256		
FIns	35			< 0.0001	0.6163
IVW-FE		0.0396(-0.0088 to 0.0881)	0.1089		
IVW-MRE		0.0396(-0.0548 to 0.1341)	0.4106		
MR Egger		0.1085(-0.1749 to 0.3919)	0.4583		
Weighted median		0.0368(-0.0441 to 0.1178)	0.3727		
HbA1c	70			< 0.0001	0.2602
IVW-FE		0.0652(0.0305 to 0.0998)	0.0002		
IVW-MRE		0.0652(-0.0052 to 0.1356)	0.0694		
MR Egger		0.0059(-0.1183 to 0.1301)	0.9265		
Weighted median		0.0375(-0.0241 to 0.0991)	0.2326		
2hGlu	13			< 0.0001	0.8202
IVW-FE		0.0472(0.0273 to 0.0672)	<0.0001		
IVW-MRE		0.0472(0.0089 to 0.0856)	0.0159		
MR Egger		0.0589(-0.0469 to 0.1646)	0.2987		
Weighted median		0.0529(0.0201 to 0.0858)	0.0016		

Figure 5 MR of diabetes and glycemic traits on FEV1/FVC ratio.

Abbreviations: T1DM, type 1 diabetes; T2DM, type 2 diabetes; FGlu, fasting glucose; FIns, fasting insulin; HbA1c, glycated hemoglobin; 2hGlu, 2h-glucose post-challenge; IVW-MRE, inverse variance weighted (multiplicative random effects); IVW-FE, inverse variance weighted (fixed effects).



Exposure on PEF	nSNP	Beta(95% CI)	P-value	P-value for IVW Cochrane's Q test	P-value for MR-Egger intercept test
T1DM	41			< 0.0001	0.8161
IVW-FE		-0.0058(-0.0086 to -0.0030)	<0.0001		
IVW-MRE		-0.0058(-0.0103 to -0.0013)	0.0119		
MR Egger		-0.0051(-0.0127 to 0.0026)	0.2027		
Weighted median		-0.0047(-0.0103 to 0.0008)	0.0924		
T2DM	171			< 0.0001	0.1858
IVW-FE		0.0048(-0.0012 to 0.0108)	0.1181		
IVW-MRE		0.0048(-0.0065 to 0.0160)	0.4032		
MR Egger		-0.0094(-0.0332 to 0.0144)	0.4390		
Weighted median		-0.0040(-0.0157 to 0.0077)	0.5024		
FGlu	63			< 0.0001	0.2140
IVW-FE		0.0207(-0.0078 to 0.0491)	0.1542		
IVW-MRE		0.0207(-0.0313 to 0.0726)	0.4355		
MR Egger		-0.0280(-0.1198 to 0.0638)	0.5526		
Weighted median		-0.0041(-0.0559 to 0.0476)	0.8763		
FIns	37			< 0.0001	0.4644
IVW-FE		0.0399(-0.0126 to 0.0924)	0.1361		
IVW-MRE		0.0399(-0.0763 to 0.1561)	0.5007		
MR Egger		0.1634(-0.1841 to 0.5108)	0.3630		
Weighted median		0.1996(0.1107 to 0.2885)	<0.0001		
HbA1c	70			< 0.0001	0.3505
IVW-FE		0.0080(-0.0303 to 0.0463)	0.6827		
IVW-MRE		0.0080(-0.0701 to 0.0861)	0.8410		
MR Egger		-0.0463(-0.1839 to 0.0913)	0.5115		
Weighted median		0.0103(-0.0530 to 0.0736)	0.7494		
2hGlu	13			< 0.0001	0.8869
IVW-FE		0.0023(-0.0187 to 0.0233)	0.8324		
IVW-MRE		0.0023(-0.0442 to 0.0487)	0.9238		
MR Egger		-0.0066(-0.1354 to 0.1222)	0.9219		
Weighted median		-0.0192(-0.0575 to 0.0192)	0.3274		

Figure 6 MR analysis of diabetes and glycemic traits on PEF.

Abbreviations: T1DM, type 1 diabetes; T2DM, type 2 diabetes; FGlu, fasting glucose; FIns, fasting insulin; HbA1c, glycated hemoglobin; 2hGlu, 2h-glucose post-challenge; IVW-MRE, inverse variance weighted (multiplicative random effects); IVW-FE, inverse variance weighted (fixed effects); PEF, peak expiratory flow.

MR analysis revealed no causal relationship between T1DM and FVC (beta = 0.0050, 95% CI = −0.0001 to 0.0101, P = 0.0553. IVW-MRE result). However, T1DM remains associated with decreased FEV1/FVC ratio (beta = −0.0106, 95% CI = −0.0158 to −0.0053, P < 0.0001; beta = −0.0102, 95% CI = −0.0148 to −0.0055, P < 0.0001). IVW-MRE and the weighted median method). Furthermore, we observed a correlation between T1DM and reduced PEF (beta = −0.01057453, 95% CI = −0.0158 to −0.0053, P < 0.0001; beta = −0.0102, 95% CI = −0.0148 to −0.0055, P < 0.0001. IVW-MRE and the weighted median methods).

Baseline Characteristics of the Population and Comparison Between COPD and Non-COPD Groups

As shown in Table 2, this study enrolled 389 participants (Figure 7), with a weighted sample size of 6324845. A total of 254 (weighted n = 4,250,878.5) participants aged 40 years and older met the spirometric criteria for COPD diagnosis. Among COPD patients, The population had a higher proportion of males (62.1%) and an average age of 56.77 years, with a mean BMI of 27.08 kg/m^2.

Compared with the non-COPD group, the COPD group exhibited a higher proportion of males (70.0%), an advanced age profile, a greater prevalence of smoking, and a higher percentage of former smokers. Comorbidities were more common in the COPD group, with increased incidence of coronary heart disease. Examination results revealed that direct HDL cholesterol were lower in the COPD group. Pulmonary function tests indicated that the COPD group had markedly FEV1/FVC ratio, and PEF than the non-COPD group (all P < 0.05). Furthermore, levels of FGlu, FIns, HbA1c, and 2hGlu were higher in the COPD group but not significantly (P > 0.05).

Table 2 Baseline Characteristics of the Population and Comparisons Between the COPD and Non-COPD Groups After Weighting

Characteristics (Mean (SD))	**Total (Unweighted n = 254; Weighted n = 4250878.5)**	**COPD (Unweighted n = 150; Weighted n = 2531214.8)**	**Non-COPD (Unweighted n= 104; Weighted n = 1719663.6)**	**P-Value[a]**
Male, n (%)	2639333.9 (62.1)	1772356.5 (70.0)	866977.4 (50.4)	0.049
Age, years	56.77 (9.23)	59.26 (8.68)	53.10 (8.81)	<0.001
Race, n (%)				0.155
Mexican American	56552.1 (1.3)	14550.3 (0.6)	42001.9 (2.4)	
Non-Hispanic Black	92090.8 (2.2)	48200.1 (1.9)	43890.7 (2.6)	
Non-Hispanic White	3729107.6 (87.7)	2250107.0 (88.9)	1479000.6 (86.0)	
Other Hispanic	227993.9 (5.4)	113757.7 (4.5)	114236.2 (6.6)	
Other Race - Including Multi-Racial	145134.1 (3.4)	104599.8 (4.1)	40534.2 (2.4)	
Year, n (%)				0.555
2007–2008	1708663.4 (40.2)	1037602.7 (41.0)	671060.8 (39.0)	
2009–2010	1373524.0 (32.3)	752498.4 (29.7)	621025.5 (36.1)	
2011–2012	1168691.1 (27.5)	741113.8 (29.3)	427577.3 (24.9)	
BMI, kg/m^2	27.08 (4.87)	27.66 (4.96)	26.23 (4.64)	0.081
Smoking status, n (%)				0.039
Current	1235070.1 (29.1)	825625.3 (32.6)	409444.8 (23.8)	
Former	1391566.9 (32.7)	950687.4 (37.6)	440879.5 (25.6)	
Never	1624241.5 (38.2)	754902.2 (29.8)	869339.3 (50.6)	
Comorbidities, n (%)				
Asthma	803994.5 (18.9)	553594.9 (21.9)	250399.7 (14.6)	0.305
Congestive Heart Failure	72163.5 (1.7)	56879.9 (2.2)	15283.6 (0.9)	0.439
Coronary heart disease	176215.1 (4.1)	160931.5 (6.4)	15283.6 (0.9)	0.041
Hypertension	1463989.5 (34.4)	1024231.2 (40.5)	439758.3 (25.6)	0.061
Chronic kidney disease	78560.0 (1.8)	65636.8 (2.6)	12923.3 (0.8)	0.327
Diabetes	165220.3 (3.9)	116976.0 (4.6)	48244.3 (2.8)	0.581
Examination				
Red blood cell, (10^{12}/L)	4.68 (0.44)	4.72 (0.45)	4.64 (0.42)	0.336
Platelet, (10^9/L)	254.57 (65.66)	251.04 (63.49)	259.76 (68.70)	0.432
Hemoglobin, (g/dL)	14.64 (1.27)	14.68 (1.33)	14.59 (1.18)	0.646
Leukocyte, (10^9/L)	6.54 (1.88)	6.72 (1.91)	6.27 (1.81)	0.161
Neutrophil, (10^9/L)	3.91 (1.47)	4.09 (1.53)	3.65 (1.33)	0.085
Lymphocyte, (10^9/L)	1.85 (0.60)	1.85 (0.60)	1.86 (0.59)	0.909
Monocyte, (10^9/L)	0.52 (0.16)	0.53 (0.17)	0.50 (0.16)	0.196
Basophil, (10^9/L)	0.04 (0.06)	0.04 (0.05)	0.05 (0.07)	0.428
Eosinophil, (10^9/L)	0.21 (0.14)	0.21 (0.13)	0.21 (0.15)	0.818
ALT, (U/L)	23.58 (10.86)	23.92 (10.41)	23.06 (11.52)	0.523
AST, (U/L)	24.91 (7.97)	24.64 (7.11)	25.30 (9.10)	0.545
Total Protein, (g/L)	70.19 (3.96)	70.23 (4.05)	70.14 (3.84)	0.864
Albumin, (g/L)	42.36 (2.64)	42.24 (2.75)	42.54 (2.47)	0.413
Total Bilirubin, (umol/L)	14.66 (6.34)	14.52 (6.77)	14.85 (5.66)	0.791
Creatinine, (umol/L)	81.08 (32.55)	83.59 (40.11)	77.39 (15.34)	0.068
Blood Urea Nitrogen, (mmol/L)	4.93 (1.63)	4.91 (1.74)	4.95 (1.46)	0.866
Uric Acid, (umol/L)	332.63 (70.21)	338.13 (63.13)	324.54 (79.12)	0.231
Lactate Dehydrogenase, (U/L)	131.34 (22.27)	131.62 (20.93)	130.91 (24.20)	0.841
Total Calcium, (mmol/L)	2.33 (0.08)	2.34 (0.08)	2.32 (0.08)	0.272
Total Cholesterol, (mmol/L)	5.24 (1.05)	5.23 (1.08)	5.25 (1.01)	0.893
Triglyceride, (mmol/L)	1.37 (0.77)	1.41 (0.79)	1.31 (0.74)	0.458
LDL Cholesterol, (mmol/L)	3.18 (0.93)	3.23 (0.98)	3.11 (0.85)	0.397
Direct HDL Cholesterol, (mmol/L)	1.43 (0.43)	1.35 (0.42)	1.55 (0.42)	0.007
FGlu, (mmol/L)	5.68 (0.69)	5.70 (0.61)	5.66 (0.80)	0.703
FIns, (pmol/L)	62.77 (45.75)	68.01 (39.95)	55.06 (52.40)	0.059
HbA1c, (%)	5.50 (0.44)	5.54 (0.38)	5.44 (0.52)	0.216
2hGlu, (mmol/L)	6.51 (2.52)	6.62 (2.38)	6.35 (2.72)	0.549

(*Continued*)

https://doi.org/10.2147/COPD.S551945

Table 2 (Continued).

Characteristics (Mean (SD))	**Total (Unweighted n = 254; Weighted n = 4250878.5)**	**COPD (Unweighted n = 150; Weighted n = 2531214.8)**	**Non-COPD (Unweighted n= 104; Weighted n = 1719663.6)**	**P-Value[a]**
FEV1, (mL/s)	2841.71 (761.49)	2771.45 (792.58)	2945.12 (704.31)	0.161
FVC, (mL/s)	4379.68 (1117.59)	4410.16 (1171.19)	4334.82 (1037.65)	0.681
FEV1/FVC ratio	0.65 (0.05)	0.63 (0.06)	0.68 (0.02)	<0.001
PEF, (mL/s)	7598.21 (1939.06)	7353.78 (1963.82)	7957.99 (1853.27)	0.048

Notes: [a]Comparison between groups of COPD and non-COPD groups after weighting.

Abbreviations: SD, standard deviation; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDL, low density lipoprotein; HDL, high density lipoprotein; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow; FGlu, fasting glucose; FIns, fasting insulin; HbA1c, glycated hemoglobin; 2hGlu, 2h-glucose post-challenge.

Logistic Regression Analysis of COPD in Relation to Diabetes and Glycemic Traits Based on the NHANES Database

Multivariate logistic regression analysis was performed to evaluate the relationship between COPD, diabetes, and glycemic traits. The analysis revealed that diabetes had an OR of 1.133 (95% CI: 0.131 to 9.861, P = 0.906), indicating no significant association with COPD. Similarly, FGlu had an OR of 1.227 (95% CI: 0.768 to 1.958, P = 0.377), FIns had an OR of 0.993 (95% CI: 0.937 to 1.007, P = 0.337), HbA1c had an OR of 0.762 (95% CI: 0.208 to 2.792, P = 0.671), and 2hGlu had an OR of 1.036 (95% CI: 0.903 to 1.189, P = 0.595), suggesting that they were not significantly associated with the incidence of COPD. Collectively, none of the variables examined demonstrated a statistically significant association with COPD, suggesting that the glycemic control factors may not be critical in the development of COPD in this population (Figure 8). Further studies are warranted to investigate this relationship in larger and more heterogeneous populations.

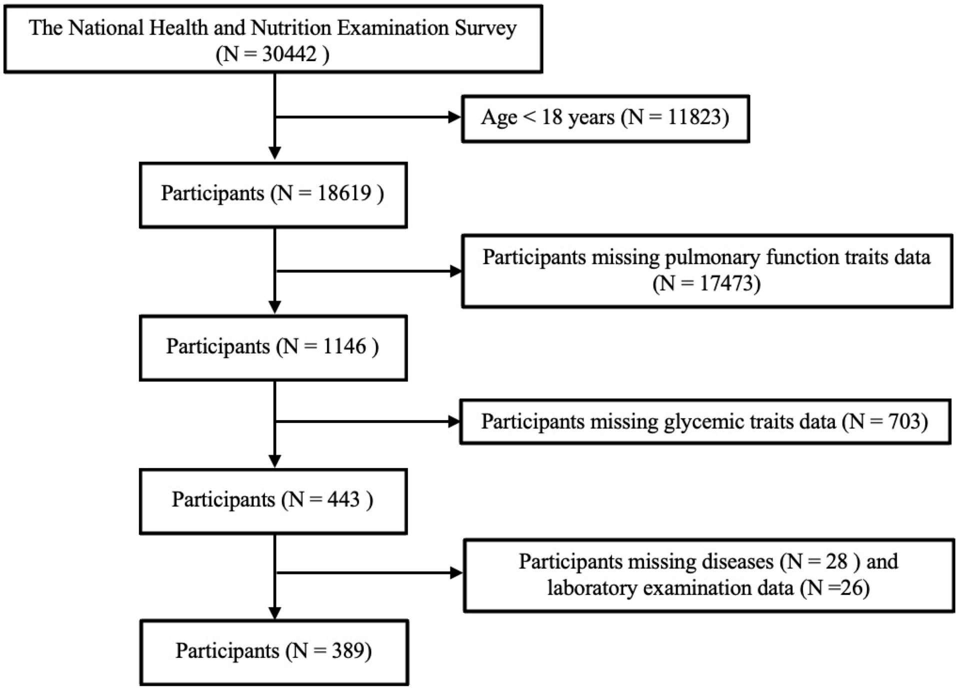


Figure 7 Step-by-step participants enrollment.

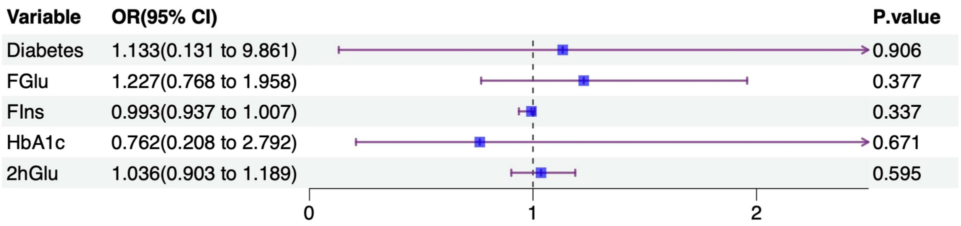


Figure 8 Logistic regression of COPD with diabetes and glycemic traits.
Notes: Adjusted for age, gender, race, BMI, and blood cholesterol level.
Abbreviations: FGlu, fasting glucose; FIns, fasting insulin; HbA1c, glycated hemoglobin; 2hGlu, 2h-glucose post-challenge; OR, odds ratio.

Linear Regression of Glycemic Traits with COPD and Pulmonary Function Traits

As shown in Table 3, after adjusting for age, gender, race, BMI, and blood cholesterol, linear regression results indicated that with each approximately 2.7-fold increase in HbA1c, FEV1 decreased by approximately 42.56% ($P = 0.0111$), FVC decreased by approximately 34.92% ($P = 0.0071$), and PEF decreased by approximately 37.77% ($P = 0.0394$), exhibiting a negative correlation. Multivariate linear regression also indicated no correlation between diabetes and pulmonary function traits (all $P > 0.05$) (Supplementary Figure 17).

Discussion

In this study, we utilized extensive GWAS data from summary databases and published literature to perform a two-sample MR analysis, along with an evaluation based on the NHANES data, to evaluate the impact of diabetes mellitus and glycemic traits on COPD and pulmonary function traits. This study was a comprehensive MR analysis and

Table 3 Multivariate Linear Regression of Glycemic Traits with Pulmonary Function Traits

Traits	Adjusted Change (95% CI)[a]	Adjusted Change (95% CI)[b]	P-Value
FEV1			
FGlu	−0.0250 (−0.1965 to 0.1464)	−2.47% (−17.84% to 15.77%)	0.7688
FIns	−0.0291 (−0.0739 to 0.0156)	−2.87% (−7.12% to 1.57%)	0.1946
HbA1c	−0.5545 (−0.9748 to −0.1342)	−42.56% (−62.27% to −12.56%)	0.0111
2hGlu	−0.0483 (−0.1324 to 0.0356)	−4.72% (−12.40% to 3.62%)	0.2509
FVC			
FGlu	−0.0218 (−0.1649 to 0.1212)	−2.16% (−15.20% to 12.89%)	0.7583
FIns	−0.0132 (−0.0557 to 0.0292)	−1.31% (−5.42% to 2.96%)	0.5305
HbA1c	−0.4296 (−0.7349 to −0.1242)	−34.92% (−52.04% to −13.23%)	0.0071
2hGlu	−0.0672 (−0.1457 to 0.0111)	−6.50% (−13.56% to 1.12%)	0.0905
FEV1/FVC ratio			
FGlu	−0.0031 (−0.1062 to 0.0999)	−0.31% (−10.08% to 10.51%)	0.9507
FIns	−0.0159 (−0.0363 to 0.0044)	−1.58% (−3.56% to 0.44%)	0.1224
HbA1c	−0.1249 (−0.3346 to 0.0847)	−11.74% (−28.44% to 8.84%)	0.2347
2hGlu	0.0189 (−0.0044 to 0.0422)	1.91% (−0.44% to 4.31%)	0.1089
PEF			
FGlu	0.0337 (−0.1776 to 0.2450)	3.84% (−16.27% to 27.76%)	0.7481
FIns	−0.0452 (−0.0993 to 0.0089)	−4.42% (−9.45% to 0.89%)	0.0990
HbA1c	−0.4743 (−0.9245 to −0.0242)	−37.77% (−60.33% to −2.39%)	0.0394
2hGlu	−0.0335 (−0.1126 to 0.0454)	−3.29% (−10.65% to 4.64%)	0.3950

Notes: [a] Results of multivariate linear regression of glycemic phenotypes and pulmonary function phenotypes were analyzed in their logarithmic form. Adjustments for age, gender, race, BMI, and blood cholesterol level. [b]An increase of 2.7 times in glycemic phenotypes corresponds to a percentage change in pulmonary function phenotypes. Adjustments for age, gender, race, BMI, and blood cholesterol levels.
Abbreviations: FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow; FGlu, fasting glucose; FIns, fasting insulin; HbA1c, glycated hemoglobin; 2hGlu, 2h-glucose post-challenge; CI, confidence interval.

NHANES-based investigation of the effects of diabetes mellitus and glycemic traits on COPD and pulmonary function traits.

COPD and diabetes are significant global health issues,[1,10] which develop from decreased pulmonary function and impaired glucose homeostasis.[31] This MR analysis revealed a genetically negative association between T1DM and COPD, accompanied by a reduction in the FEV1/FVC ratio. T2DM was linked to a decrease in FVC but an increase in the FEV1/FVC ratio. Conversely, elevated 2hGlu levels were significantly associated with higher FEV1/FVC ratio. This MR study overcame the limitations of observational research by evaluating the causal links between diabetes and glycemic traits with COPD and pulmonary function traits. Additionally, based on the NHANES database, we found that a 2.7-fold increase in HbA1c levels was negatively correlated with a significant decline in FEV1 (42.56%), FVC (34.92%), and PEF (37.77%). These findings have critical clinical implications, emphasizing the importance of early clinical attention to impaired glucose status and diabetes in the development of declining lung function and COPD, ultimately benefiting a large population.

The progression of COPD and decline in pulmonary function involve intricate biological mechanisms, with hyperglycemia linked to diabetes potentially playing a role in the pathophysiology of lung diseases.[32] Impaired lung function is associated with worsening glycemic control and diabetes-related oxidative stress in individuals with long-standing T1DM and T2DM. Chronic hyperglycemia, a hallmark of T1DM, promotes the formation of advanced glycation end-products and sustained systemic inflammation.[33] This pro-inflammatory state could potentially exacerbate the pulmonary inflammation and tissue remodeling central to COPD pathogenesis.[34] Furthermore, patients with recent-onset T2DM demonstrate a decline in pulmonary function parameters, potentially attributable, at least partially, to glucotoxicity.[35] Observational studies have indicated that hyperglycemia can result in increased non-enzymatic glycosylation of tissue proteins, reflecting a decline in pulmonary function (FEV1 and FVC), particularly in individuals with T2DM, potentially impacting lung tissue physiology.[36] Additionally, a study involved 7055 participants without a history of T2DM and COPD observed that after an average follow-up period of 3.9 years, FEV1 and FVC exhibited a significant decline over time. Furthermore, baseline FVC and its longitudinal changes were found to have a negative correlation with baseline and longitudinal changes in HbA1c levels, which is consistent with the results of our observational study results. Longitudinal changes in FVC were negatively associated with the risk of newly diagnosed T2DM. Moreover, individuals who developed new-onset diabetes showed a more pronounced decline in FVC over time than those without incident diabetes.[37]

This study thoroughly accounted for obesity as a potential confounding factor and its influence on disease progression. The so-called “obesity paradox” — wherein a low BMI is often associated with increased mortality in COPD — highlights the complex role of adiposity. As a well-established risk factor for T2DM and altered lung mechanics, obesity merits particular attention in this context. In our analyses, we carefully adjusted for BMI to mitigate its potential confounding effect on the observed associations between diabetes, glycemic traits, and COPD or pulmonary function traits. Acute exacerbations of COPD (AECOPD), commonly triggered by infections and managed with high-dose systemic corticosteroids, represent a risk factor for transient hyperglycemia and even new-onset diabetes.[38] This suggests a potential vicious cycle wherein frequent exacerbators may be more susceptible to developing glucose metabolism disorders as a consequence of their treatment, which could in turn worsen long-term COPD outcomes and potentially increase the risk of future exacerbations. This pathway illustrates a clinically relevant mechanism by which the management of COPD itself may contribute to the development of the comorbidity identified in this study. Future longitudinal studies are warranted to disentangle the direct causal effects of dysglycemia on pulmonary function from the consequences of treatments related to acute exacerbations.

Nevertheless, the complex interplay of genetic and environmental factors, and comorbid conditions contributes to the accelerated decline in lung function and the development of COPD, posing challenges for identification and intervention. MR analysis, a tool leveraging genetic variation to deduce causality, presents a valuable approach for investigating causal relationships in this context.[27] A prior MR study highlighted the impact of anti-diabetic medications on enhancing COPD and lung function, specifically FEV1 and FEV1/FVC ratio.[39] Building upon these findings, our two-sample MR analysis revealed a significant negative association between T1DM and COPD, FEV1/FVC ratio, as well as PEF. Furthermore, T2DM is notably linked to a decline in FVC.

Unpredictably, we identified an association between T2DM and a decline in FVC, as well as an increase in the FEV1/FVC ratio, which is consistent with a previous MR study,[40] suggesting that T2DM may have differential effects on lung function. These differences may be linked to the increased susceptibility of T2DM patients to various respiratory infections and complications, which could contribute to the decline in lung function. Obesity, as a common comorbidity in T2DM[41] may contribute to restrictive lung physiology through mechanical impedance of diaphragm excursion and reduced chest wall compliance, potentially explaining the observed reduction in FVC. And reduced physical activity levels in T2DM patients (due to neuropathy or cardiovascular comorbidities) may lead to respiratory muscle deconditioning,[42] thereby compounding lung function decline and potentially masking the true causal relationship and the systemic inflammation[43,44] and muscle wasting characteristic of severe COPD might synergize with diabetic pathways to accelerate respiratory function deterioration. Conversely, elevated 2hGlu levels were significantly associated with higher FEV1/FVC ratio. This correlation may indicate a link between higher 2hGlu levels and improved lung function, although the underlying mechanisms remain unclear. One possible explanation is that maintaining high 2hGlu levels may be beneficial for the protection and repair of lung tissues, thereby enhancing lung function. Further research is needed to explore the distinct mechanisms by which T2DM and high blood glucose levels affect lung functions. Future investigations should consider other potential factors, such as inflammation, oxidative stress, and metabolic abnormalities, to gain a more comprehensive understanding of the influence of diabetes and blood glucose characteristics on COPD and lung function. By delving into these mechanisms, we can offer deeper insight into the development of more effective preventive and therapeutic strategies in the future, aiming to improve lung function and the overall quality of life of patients.

This study has several strengths. First, it draws upon extensive GWAS data from aggregated databases and published literature to conduct two-sample MR analysis, thereby ensuring robust statistical power and comprehensive coverage. Second, this study stands out as one of the most thorough MR investigations to date, delving into the causal links between diabetes, glycemic traits, COPD, and pulmonary function traits and illuminating potential interrelations among various diseases. Third, by utilizing MR methods to assess the causal links between diabetes, glycemic traits, COPD, and pulmonary function traits, this study successfully overcame the limitations inherent in observational research, underscoring the importance of distinguishing between correlations and causation. Furthermore, we utilized the NHANES database to assess the effects of diabetes and glycemic traits on COPD and pulmonary function traits. This database includes diverse populations and extensive demographic and health data, enabling researchers to explore a wide range of variables along with genetic information. By integrating genetic data from MR with the large sample size of the NHANES, we can enhance statistical power, facilitating the detection of subtle associations.

However, this study had certain limitations. First, despite the thorough analysis of a large dataset, the presence of biases and missing data confined to individuals of European descent may impede the interpretation and generalizability of the findings. Second, the reliance of MR methods on genetic variations to evaluate the relationship between exposure and disease introduces constraints, as factors such as gene-environment interactions could potentially compromise the accuracy of the results. Third, while MR analysis offers insights into causality, the need for further research and empirical evidence to confirm causal relationships underscores the potential influence of various other factors on the interpretation of the results. Finally, we investigated the effect of exposure on outcomes based on the NHANES database; however, we did not conduct a prospective study. A dynamic observation of the effects of diabetes and glycemic traits on COPD and pulmonary function traits would enhance the robustness of statistical results.

Conclusion

This study provides the effects of diabetes and glycemic traits on COPD and pulmonary function traits. MR analysis indicated a genetically negative association between T1DM and COPD, accompanied by a reduction in the FEV1/FVC ratio. T2DM was linked to a decrease in FVC but an increase in the FEV1/FVC ratio. Conversely, elevated 2hGlu levels were significantly associated with a higher FEV1/FVC ratio. Analysis of the NHANES database further revealed that increased HbA1c levels were negatively correlated with significant declines in FEV1, FVC, and PEF. Our results advocate for integrated care that combines optimal respiratory and glycemic management, highlighting the role of pulmonologists in screening for glucose intolerance and endocrinologists in considering pulmonary outcomes when treating diabetic patients.

Abbreviations

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; COPD, chronic obstructive pulmonary disease; EAF, effect allele frequency; FEV1, forced expiratory volume in 1 second; FGlu, fasting glucose; FIns, fasting insulin; FVC, forced vital capacity; GWAS, genome-wide association studies; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HbA1c, glycated hemoglobin; HDL, high density lipoprotein; IVW, inverse variance weighted; IV, instrumental variable; LD, linkage disequilibrium; LDL, low density lipoprotein; MR, Mendelian randomization; MAF, minor allele frequency; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio; PEF, peak expiratory flow; SNP, single nucleotide polymorphism; SE, standard errors; SD, standard deviation; T1DM, type 1 diabetes; T2DM, type 2 diabetes; 2hGlu, 2h-glucose post-challenge.

Data Sharing Statement

The datasets supporting the conclusions of this article are available in the following repositories: GWAS information of the genetic instrumental variables linked to exposures (T1DM, T2DM, FGlu, FIns, HbA1c, and 2hGlu) can be obtained from the study conducted by Zhao et al (DOI: 10.1186/s12933-023-02079-w); full GWAS summary statistics for the outcome data used in this study can be found at https://www.ebi.ac.uk/gwas/; and NHANES data (2007–2012) is available at https://wwwn.cdc.gov/nchs/nhanes/.

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Disclosure

The authors report no conflicts of interest in this work.

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