

Original articles

New evidence for the effect of type 2 diabetes and glycemc traits on lung function: a Mendelian randomization and mediation analysis

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ABSTRACT

Background: Type 2 Diabetes Mellitus (T2DM) is common worldwide. Patients with T2DM often experience reduced lung function, but the relationship between the two conditions remains uncertain. This study employed Mendelian Randomization (MR) to explore the causal link between T2DM and lung function, and to identify the factors that mediate this relationship.**Methods:** Genome-wide association study data were obtained from public databases. Four glycemc traits were considered exposures, whereas lung function was considered an outcome. Inverse Variance Weighting (IVW) was used to investigate causality, supplemented by MR-Egger and weighted medians methods. Multivariable MR (MVMR) analysis investigated whether T2DM had an independent impact on lung function. Mediation analysis was employed to examine potential mediating impacts.**Results:** IVW revealed that T2DM was associated with decreased forced expiratory volume in 1s (FEV1) ($p = 0.012$) and Forced Vital Capacity (FVC) ($p = 0.004$). After adjusting for potential confounders, the effects of T2DM on FEV1 and FVC remained significant. Mediation analysis demonstrated that smoking and Systolic Blood Pressure (SBP) partially mediated the causal relationship between T2DM, and FEV1 and FVC. The proportions mediated by smoking, SBP, and both factors on FEV1 were 0.302, 0.412, and 0.418, respectively, while the proportion mediated by SBP on FVC was 0.594.**Conclusions:** This study validated the causal relationship between T2DM and decreased lung function, with smoking and SBP acting as mediators. This study provides a novel perspective on the occurrence and development mechanisms of reduced lung function as well as potential new targets for metabolic intervention in treatment.

Introduction

Diabetes mellitus is one of the most prevalent global epidemics, classified as a group of diseases characterized by chronic hyperglycemia.¹ The most common forms are Type 2 Diabetes Mellitus (T2DM), type 1 Diabetes Mellitus (T1DM), and gestational diabetes mellitus,² with T2DM being the predominant contributor to the current global epidemic.³ Between 1980 and 2014, the number of adults diagnosed with diabetes increased from 108 million to 422 million,⁴ with type 2 diabetes accounting for more than 90% of these cases.⁵ The global prevalence of diabetes is estimated to reach 700 million by 2045.⁶ Diabetes ranks among the top three diseases worldwide, and its prevalence is increasing.⁷ Furthermore, diabetes is linked to an increased cost

of healthcare, which is estimated to be \$850 billion worldwide.⁸ It is an ideal target for prevention owing to its enormous cost.

Genetic and environmental factors are associated with decreased lung function. Numerous epidemiological studies have indicated that individuals with T2DM tend to exhibit reduced lung function compared with those without diabetes.^{9,10} The variations in findings in previous studies could be attributed to biases or confounding factors present in observational epidemiological studies, including limited sample sizes, differences in demographic characteristics, reverse causation, and selection bias. T2DM is a persistent metabolic condition that progresses slowly and initially has hidden symptoms, making the connection between T2DM and lung function unclear.¹¹

Mendelian Randomization (MR) is an analytical method used to

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estimate the causal impact of outcomes of interest by utilizing genetic variants associated with exposure.¹² MR is more effective than traditional observational methods for preventing confounders and reverse causality.¹³ An MR study was conducted to gain new insights into the pathogenesis of lung function impairment. Multivariable MR (MVMR) was used to adjust for potential confounders that might affect causal estimation, whereas mediation analysis was used to explore the potential mediating role of smoking and Systolic Blood Pressure (SBP) in the causal link between T2DM and lung function. The present study offers a new outlook for investigating the mechanisms underlying the onset and progression of lung dysfunction and identifying new targets for metabolic therapy interventions.

Materials and methods

Reporting guidance

This study was conducted following the Strengthening the Reporting of Observational Studies in Epidemiology using the MR (STROBE-MR) guideline.¹⁴

Study design

MR and mediation analyses were used to determine the causal connection between glycemic characteristics and lung function and to explore potential mediators of this relationship. As shown in Fig. 1 MR analysis relies on three important assumptions. The overall causative association between glycemic traits and lung function was first investigated, followed by consideration of the ratio of mediating factors to causation. The MR investigation used publicly available Genome-Wide Association Study (GWAS) datasets. For the original GWAS, each participant had provided written informed consent.

Data sources

Glycemic traits include T2DM, hyperinsulinemia, and hyperglycemia.¹⁵ Data on glycemic traits (T2DM, fasting insulin, fasting glucose, and two-hour glucose) from GWAS summary datasets were acquired from the Medical Research Council Integrative Epidemiology Unit OpenGWAS database at <https://gwas.mrcieu.ac.uk/>. This study examined four factors from various GWAS; T2DM (dataset finn-b-E4_DM2; n=215,654), fasting insulin (ieu-b-116; n = 108,557), fasting glucose (ieu-b-114; n=133,010), and two-hour glucose (ebi-a-GCST90002227; n = 63,396). Additional details of each characteristic are provided in Supplemental Table 1.

Data on lung function, specifically Forced Expiratory Volume in 1s (FEV1) (ukb-b-19657) and Forced Vital Capacity (FVC) (ukb-b-7953), collected by the Medical Research Council Integrative Epidemiology Unit were utilized as primary measures, involving a cohort of 421,986 individuals of European descent. For the MR analysis, genetic variants were chosen that met the criteria for genome-wide significance ($p < 5 \times 10^{-8}$).

Informed consent statement and ethics approval statement

Analyses were conducted using publicly accessible datasets from published GWAS or consortia without the need for additional consent or ethical approval for the current study.

Genetic instrumental variable (IV) selection

To identify Single Nucleotide Polymorphisms (SNPs) that were strongly associated with exposure or outcome, a threshold for genome-wide significance of $p < 5 \times 10^{-8}$ was established. To avoid bias caused by Linkage Disequilibrium (LD), SNPs with $R^2 < 0.001$ and

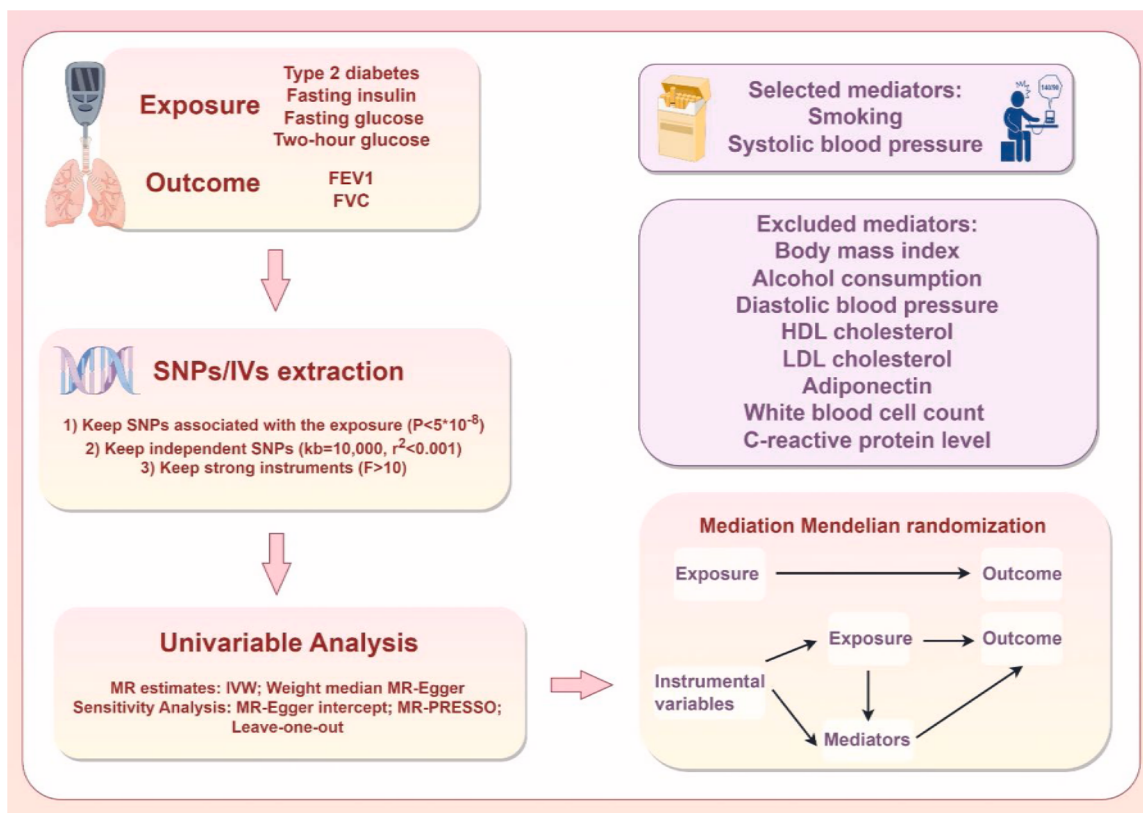


Fig. 1. Study overview. FEV1, Forced Expiratory Volume in 1s; FVC, Forced Vital Capacity; SNPs, Single Nucleotide Polymorphisms; MR, Mendelian Randomization; IVW, Inverse Variance Weighting; IV, Instrumental Variable.

kb>10,000 which were strongly associated with exposure were selected.¹⁶ Palindromic SNPs with mid-range allele frequencies were excluded. Furthermore, the F-statistic was calculated as $F = \beta^2 \text{exposure} / \text{SE}^2 \text{exposure}$ to measure the effectiveness of the genetic instrument for all SNPs, with SNPs having an F-value <10 being classified as weak instruments.^{17,18}

To avoid possible pleiotropic effects, SNPs were additionally examined using PhenoScanner V2 (<http://www.phenoscaner.medschl.cam.ac.uk/>) to determine whether instrumental variables were linked to confounders or risk factors.^{19,20}

Mendelian randomization analysis

The main method used in MR to estimate the causal relationship between T2DM and glycemic traits with lung function was Inverse-Variance Weighting (IVW).²¹ Due to the variability in the databases utilized, a random-effects model was used for all MR analyses. Concurrently, MR-Egger and MR-PRESSO were used to conduct sensitivity tests to assess the reliability of the findings and confirm the presence of horizontal pleiotropy. The MR-Egger regression analysis utilized the embedded intercept to identify horizontal pleiotropy and generated accurate estimates following adjustment for pleiotropy effects. The MR-PRESSO global test can estimate the level of pleiotropy caused by SNP heterogeneity after using MR-PRESSO to identify and adjust for potential outliers.¹⁷

FEV1 and FVC were considered outcomes, with β being utilized to evaluate the impact of T2DM and associated glycemic indicators on lung function. All evaluations were conducted considering both possibilities. For this analysis, the R packages TwoSampleMR and MR-PRESSO in R 4.3.2 were used.²²

Mediation analysis

MR was performed on two samples to assess the overall impact of T2DM on lung function. The total influence of a given exposure on an outcome can be analyzed by considering both indirect and direct consequences.²³ MVMR was used to determine the direct impact of exposure on outcomes, including T2DM, fasting insulin, fasting glucose, and two-hour glucose while accounting for the mediators. The mediated effect, known as the indirect effect, was calculated by multiplying β_1 and β_2 . Here, β_1 represents the effect of exposure on mediators, while β_2 represents the effect of mediator k on outcome after adjusting for genetically determined glycemic traits. The proportion of the mediation Effect (E%) was estimated using the following equation^{24,25}: $E(\%) = \frac{\sum_{k=1}^t \beta_1 \times \beta_2 k}{\sum_{k=1}^t \beta_3 + \beta_1 \times \beta_2 k}$; β_3 represents the impact of glycemic characteristics on lung function after accounting for potential mediators determined by genetics.

Results

Selection of IVs

Independent SNPs were identified by screening for SNPs with LD using thresholds of $p < 5 \times 10^{-8}$. Next, palindromic SNPs were excluded, and outlier SNPs were removed via MR-PRESSO analysis.

Causal association of glycemic traits with lung function via univariable MR

A negative association between genetically predicted T2DM and FEV1 (IVW: Beta -0.017 [-0.031, -0.004], $p = 0.012$) and FVC (IVW: -0.020 [-0.035, -0.006], $p = 0.004$) was observed. These findings are consistent with those of previous studies. However, based on the IVW evaluation, genetically estimated fasting insulin, fasting glucose, and two-hour glucose did not show significant associations with lung

function. Fig. 2, Supplemental Table 2 displays the outcomes achieved using the various methods. Consistent results were obtained using the MR-PRESSO method.

Causal association of confounders with lung function via univariable MR

The study revealed that predicted Body Mass Index (BMI), smoking status, Systolic Blood Pressure (SBP), white blood cell count, and C-Reactive Protein (CRP) levels were all associated with reduced FEV1. Furthermore, genetic predictions of BMI, SBP, white blood cell count, and CRP levels were linked to a reduction of FVC. Conversely, IVW estimation indicated that genetically forecasted alcohol intake, diastolic blood pressure, triglyceride, High-Density Lipoprotein (HDL) cholesterol, Low-Density Lipoprotein (LDL) cholesterol, and adiponectin levels were not linked to pulmonary function. Fig. 3 and Supplementary Table 3 show the outcomes achieved using the various methods.

Causal association of type 2 diabetes with confounders via univariable MR

The findings indicated a positive correlation between the genetically predicted risk of T2DM and higher rates of smoking (IVW Beta = 0.009 [0.001, 0.017], $p = 0.024$) and elevated SBP (IVW Beta = 0.508 [0.195, 0.820], $p = 0.001$). The results of the various methods are shown in Fig. 4 and Table 1. The results of MR-PRESSO were similar.

Mediating effect and proportion by smoking status and systolic blood pressure

The direct effects in the multivariable MR analysis of T2DM-smoking-FEV1, T2DM-SBP-FEV1, and T2DM-SBP-FVC were reduced to Beta -0.012 (95% CI -0.026, -0.002; $p = 0.100$), Beta -0.025 (95% CI -0.041, -0.008, $p = 0.003$), and Beta -0.003 (95% CI -0.049, -0.016, $p < 0.001$), respectively (Table 2). The proportions mediated by these mediators were 0.302, 0.412, and 0.418, respectively, and the proportion mediated by SBP was 0.504. After adjusting for both smoking and SBP, the direct effect was Beta -0.025. The proportion mediated by smoking and SBP was 0.43.

Discussion

In this study, a genetic predisposition to T2DM, smoking status, and high SBP were associated with lung function reduction. The individual proportions mediated by smoking and SBP on FEV1 were 0.302 and 0.412, respectively, whereas the proportion mediated by SBP on FVC was 0.594. The proportion that was mediated by smoking and SBP together was 0.418. The MR study demonstrated that those diagnosed with T2DM are more likely to have reduced lung function.

Glycemic traits refer to a range of measurable biological markers associated with blood glucose levels and how the body processes glucose. The Meta-Analyses of Glucose and Insulin-related Traits Consortium (MAGIC) previously analyzed GWAS data on glycemic traits in non-diabetic individuals, identifying 16 loci associated with fasting glucose, two with fasting insulin, and five with post-challenge Glucose (2hGlu) concentrations.²⁶ Fasting glucose and two-hour glucose represent blood glucose levels. The authors also used the fasting insulin level as an exposure factor, which provides a proxy for the degree of insulin resistance.²⁷ Lung function typically refers to a set of physiological measurements that assess respiratory health and the efficiency of the lungs. It is commonly assessed by FEV1 and FVC.²⁸

The present findings align with previous research showing reduced FVC and FEV1 in adults with diabetes compared with those without diabetes.^{29,30} Nevertheless, these results were largely derived from observational research, with the potential for numerous confounding factors, such as data collection methods, genetics specific to certain populations, and exposure to environmental factors. Hence, in this study, MR was performed to investigate the relationship between lung

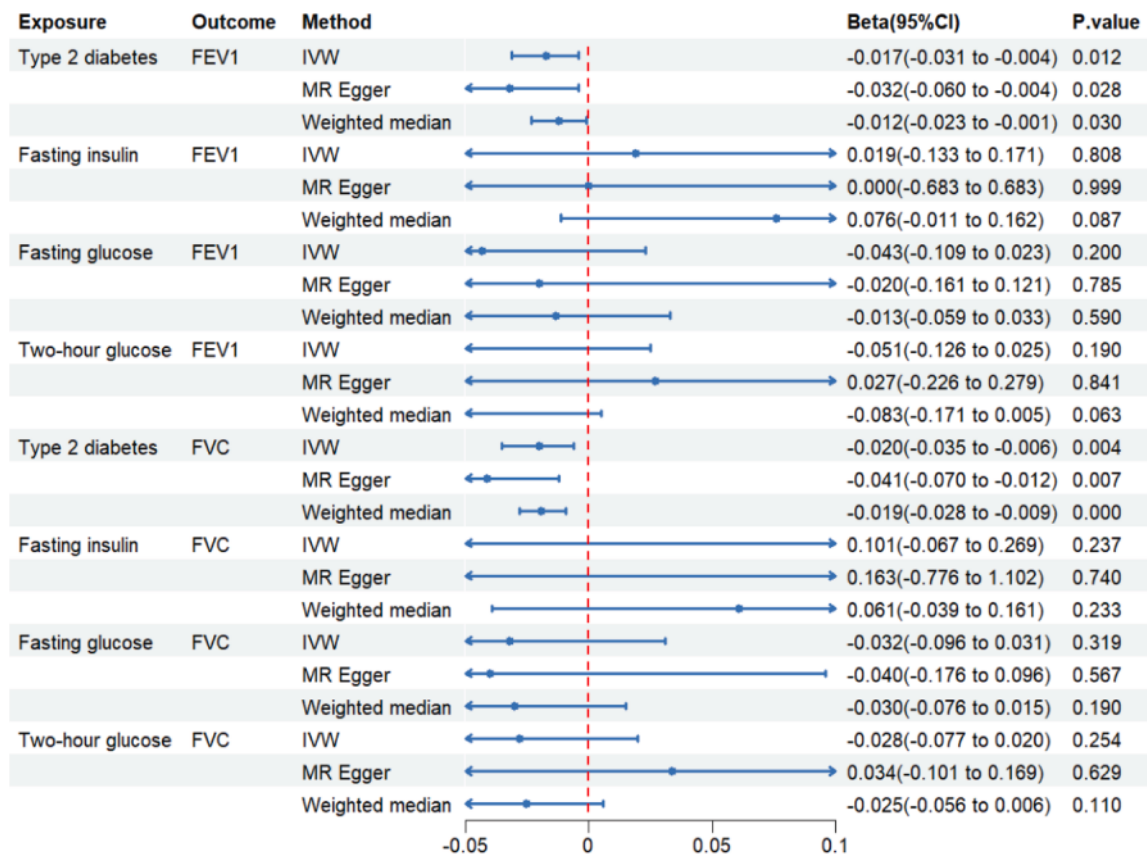


Fig 2. Causal effect of glycemic traits on lung function. The blue point indicates the effect (Beta). FEV1, Forced Expiratory Volume in 1s; FVC, Forced Vital Capacity; IVW, Inverse Variance Weighting; MD, Mendelian Randomization.

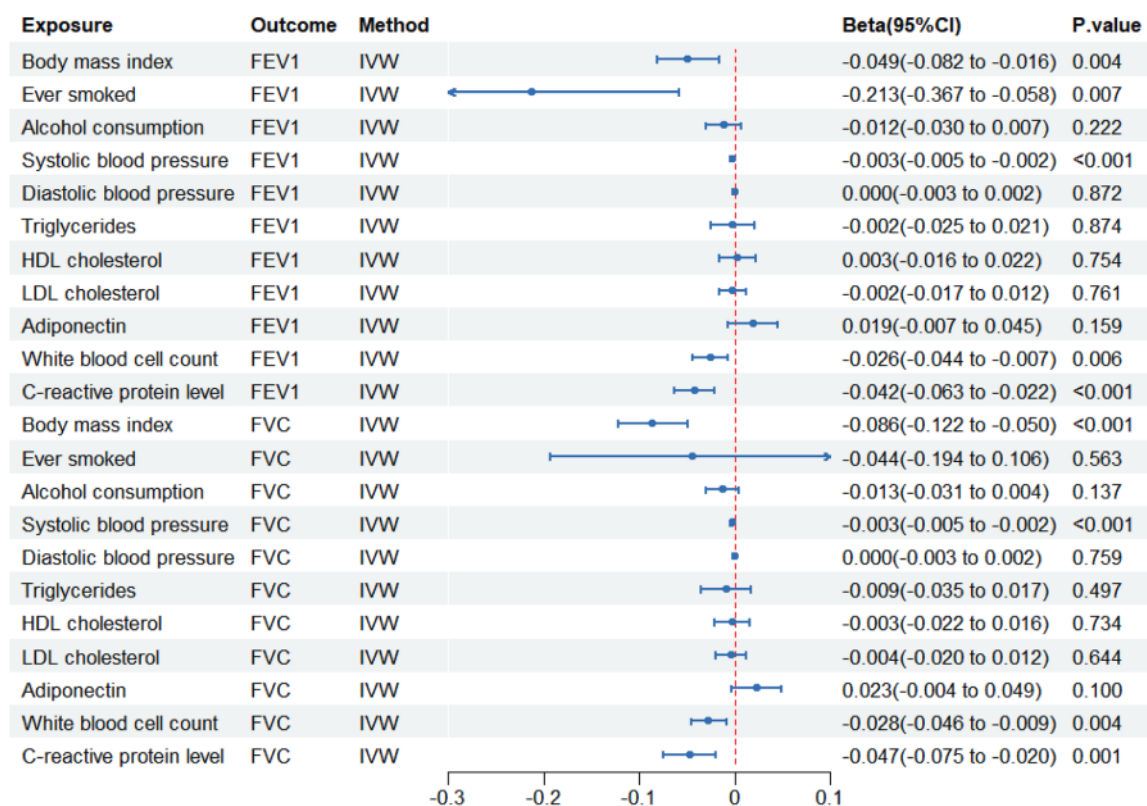


Fig 3. Causal effect of confounders on lung function. The blue point indicates the effect (Beta). LDL, Low-Density Lipoprotein; HDL, High-Density Lipoprotein; FEV1, Forced Expiratory Volume in 1s; FVC, Forced Vital Capacity; IVW, Inverse Variance Weighting.

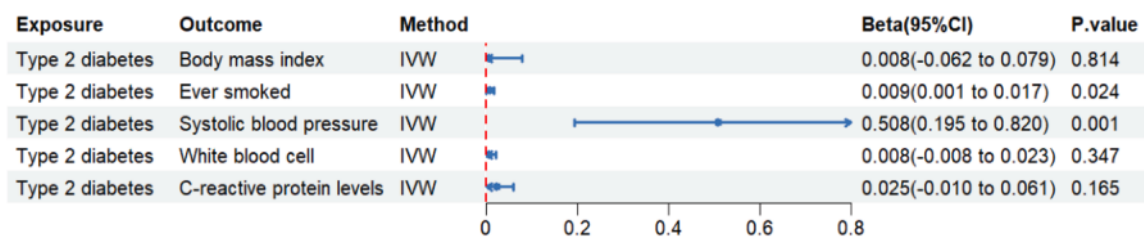


Fig 4. Casual effect of T2DM on body mass index, smoking status, systolic blood pressure, white blood cell count, and C-reactive protein level. The blue point indicates the effect (Beta). IVW, Inverse Variance Weighting.

Table 1
Result and sensitivity analyses for the associations of genetically predicted factors with mediators.

Exposure	Outcome	MR					Heterogeneity			Pleiotropy	
		Method	Beta	(95%CI)	SE	p-value	Method	Cochran's Q	p-value	MR-Egger intercept	p-value
Type 2 diabetes	Body mass index	IVW	0.008	(-0.062, 0.079)	0.036	0.814	IVW	1312.510	<0.001	0.007	0.345
	Ever smoked	IVW	0.009	(0.001, 0.017)	0.004	0.024	IVW	209.973	<0.001	-0.001	0.893
	Systolic blood pressure	IVW	0.508	(0.195, 0.820)	0.159	0.001	IVW	474.929	<0.001	0.963	0.963
	White blood cell count	IVW	0.008	(-0.008, 0.023)	0.008	0.347	IVW	44.045	0.554	0.000	0.825
	C-reactive protein levels	IVW	0.025	(-0.010, 0.061)	0.018	0.165	IVW	379.089	<0.001	-0.002	0.397

CI, Confidence Interval; SE, Standard Error; MR, Mendelian Randomization.

Table 2
Multivariate MR analysis of the direct effect of Systolic blood pressure and smoking on lung function.

Exposure/ Outcome	Adjusted Factors	Beta	(95%CI)	p-value	Mediation Effect
Type 2 diabetes/ FEV1	None	-0.017	(-0.031, -0.004)	0.012	
Type 2 diabetes/ FEV1	Smoking	-0.012	(-0.026, -0.002)	0.100	0.302
Type 2 diabetes/ FEV1	Systolic blood pressure	-0.025	(-0.041, -0.008)	0.003	0.412
Type 2 diabetes/ FEV1	Smoking, Systolic blood pressure	-0.025	(-0.071, 0.102)	0.003	0.418
Type 2 diabetes/ FVC	None	-0.020	(-0.035, -0.006)	0.004	
Type 2 diabetes/ FVC	Systolic blood pressure	-0.033	(-0.049, -0.016)	<0.001	0.594

CI, Confidence Interval.

function and glycemic traits. MR-Egger regression was used to assess the potential pleiotropic effects of SNPs chosen as IVs, offering insights into whether horizontal pleiotropy affects the analysis. Horizontal pleiotropy was not observed in any of the analyses.

This finding is consistent with that of a previous study that was less susceptible to confusion bias. Autopsies of individuals with diabetes revealed an increase in the thickness of the alveolar walls and minor blood vessels.³¹ These changes could be the cause of restriction in lung expansion and a decrease in ventilatory capacity. Klein et al. demonstrated that the lungs in individuals with diabetes could experience microangiopathy.³² Individuals with diabetes experience reduced lung capacity compared with those without diabetes, irrespective of additional risk factors. Glycemic control and the length of time a person has diabetes are the primary factors that pose the greatest risk.⁷

The present study showed that smoking was associated with impaired lung function, as indicated by decreased FEV1. Smoking is a harmful agent that contributes to many health problems worldwide,

including lung disease.³³ Smoking during adulthood is classically associated with an accelerated decrease in FEV1.³⁴ A previous study demonstrated that, between the ages of 43- and 60-64 years, the decrease in FEV1 was accelerated by smoking; however, smoking did not influence the decrease in FVC.³⁵ Another study indicated that the annual rate of FEV1 loss was greater in continuing smokers, by more than 10 mL/year, than in non-smokers.³⁶ In summary, smokers exhibit changes in lung morphology, inflammation, and function.³⁷ Smoking control is a pivotal health concern, and there is an urgent need to correct alterations in the risk perception of smoking and to cease smoking early.

This study revealed an inverse relationship between SBP and lung function. Previous research found that decreased FVC was linked to hypertension, and this connection remained consistent regardless of weight and age.³⁸ Another study³⁹ reported a robust negative correlation between FVC and the likelihood of high blood pressure. Additionally, previous research found an inverse correlation between lung function and blood pressure among Chinese individuals, although the correlation was minimal.⁴⁰ In contrast, another study revealed a significant correlation among hypertension, beta-blocker use, and decreased pulmonary function in German adults.⁴¹ A recent study from Korea suggested a connection between high blood pressure and an increased decline in FVC and that medications for hypertension could slow this decline in asymptomatic individuals.⁴² However, the mechanism underlying the relationship between lung function and hypertension requires further investigation.

The present study benefited from the use of a stronger MR approach that enforces a more rigorous IV selection process as well as the implementation of strict criteria for IV selection to enhance statistical power. In addition, this study used GWAS datasets from large European populations for both exposure and outcomes, which enhanced the credibility of the results.

Nevertheless, this study has some limitations. First, while smoking status is a significant environmental factor and a possible confounding variable in the association between blood glucose levels and respiratory illnesses in individuals with compromised lung function, the results were not corrected for smoking habits. Second, due to GWAS limitations, the authors used fasting insulin levels as a proxy for insulin resistance. Although this indicator can indicate insulin resistance to some extent, it isn't the gold standard.⁴³ Furthermore, the association between glyce-mic traits and lung function was limited to the European population,

suggesting possible selection biases and further investigation is needed to determine whether the results can be generalized to populations of other races. In addition, in the analysis, there were some differences in composition. Due to the utilization of GWAS data, it was not feasible to explore potential nonlinear associations or stratification effects that are dependent on age, health condition, or sex.

Conclusions

The study found a connection between the predicted genetic risk of T2DM, smoking status, SBP, and reduction in FEV1 and FVC. Thus, strengthening blood pressure and blood sugar control, and changing unhealthy lifestyles may serve as potential intervention targets for preventing impaired lung function.

Ethics approval

As this study was based on a re-analysis of previously conducted and published GWASs data, there is no requirement for further ethical approval.

Consent to publish

Not applicable.

Consent to participate

Not applicable.

Availability of data and materials

All data relevant to the study are included in the article or uploaded as supplementary information.

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CRediT authorship contribution statement

Shuo Xie: Conceptualization, Methodology, Formal analysis, Writing – original draft. **Liping Yu:** Supervision. **Lulu Song:** Supervision. **Fei Chen:** Supervision. **Wanlu Ma:** Supervision. **Yifan He:** . **Xiaoping Chen:** Supervision. **Ying Yang:** Writing – review & editing. **Bo Zhang:** Conceptualization, Supervision, Funding acquisition.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.clinsp.2025.100693](https://doi.org/10.1016/j.clinsp.2025.100693).

References

- Zimmet P, Alberti KG, Magliano DJ, Bennett PH. Diabetes mellitus statistics on prevalence and mortality: facts and fallacies. *Nat Rev Endocrinol*. 2016;12(10):616–622.
- Tuomi T, Santoro N, Caprio S, Cai M, Weng J, Groop L. The many faces of diabetes: a disease with increasing heterogeneity. *Lancet*. 2014;383(9922):1084–1094.
- Zimmet PZ, Magliano DJ, Herman WH, Shaw JE. Diabetes: a 21st century challenge. *Lancet Diabetes Endocrinol*. 2014;2(1):56–64.
- Collaboration NCDRF. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. *Lancet*. 2016;387(10027):1513–1530.
- Howarth FC, Shafiqullah M, Qureshi MA. Chronic effects of type 2 diabetes mellitus on cardiac muscle contraction in the Goto-Kakizaki rat. *Exp Physiol*. 2007;92(6):1029–1036.
- Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the International Diabetes Federation Diabetes Atlas, 9(th) edition. *Diabetes Res Clin Pract*. 2019;157, 107843.
- Li G, Zhang P, Wang J, An Y, Gong Q, Gregg EW, et al. Cardiovascular mortality, all-cause mortality, and diabetes incidence after lifestyle intervention for people with impaired glucose tolerance in the Da Qing Diabetes Prevention Study: a 23-year follow-up study. *Lancet Diabetes Endocrinol*. 2014;2(6):474–480.
- Cho NH, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, Ohlrogge AW, et al. IDF Diabetes Atlas: global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Res Clin Pract*. 2018;138:271–281.
- Yeh H-C, Punjabi NM, Wang N-Y, Pankow JS, Duncan BB, Cox CE, et al. Cross-sectional and prospective study of lung function in adults with type 2 diabetes: the Atherosclerosis Risk in Communities (ARIC) study. *Diabetes Care*. 2008;31(4):741–746.
- Giovannelli J, Trouiller P, Hulo S, Chérot-Kornobis N, Ciuchete A, Edmé J-L, et al. Low-grade systemic inflammation: a partial mediator of the relationship between diabetes and lung function. *Ann Epidemiol*. 2018;28(1):26–32.
- American Diabetes A. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2014;37(Suppl 1):S81–S90.
- Davies NM, Holmes MV, Davey Smith G. Reading mendelian randomisation studies: a guide, glossary, and checklist for clinicians. *BMJ*. 2018;362:k601.
- Pingault J-B, O'Reilly PF, Schoeler T, Ploubidis GB, Rijdsdijk F, Dudbridge F. Using genetic data to strengthen causal inference in observational research. *Nat Rev Genet*. 2018;19(9):566–580.
- Skrivankova VW, Richmond RC, Woolf BAR, Yarmolinsky J, Davies NM, Swanson SA, et al. Strengthening the reporting of observational studies in epidemiology using mendelian randomization: the STROBE-MR Statement. *JAMA*. 2021;326(16):1614–1621.
- Murphy N, Song M, Papadimitriou N, Carreras-Torres R, Langenberg C, Martin RM, et al. Associations between glycaemic traits and colorectal cancer: A mendelian randomization analysis. *J Natl Cancer Inst*. 2022;114(5):740–752.
- Sved JA, Hill WG. One hundred years of linkage disequilibrium. *Genetics*. 2018;209(3):629–636.
- Pierce BL, Ahsan H, Vanderweele TJ. Power and instrument strength requirements for mendelian randomization studies using multiple genetic variants. *Int J Epidemiol*. 2011;40(3):740–752.
- Verbanck M, Chen C-Y, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from mendelian randomization between complex traits and diseases. *Nat Genet*. 2018;50(5):693–698.
- Kamat MA, Blackshaw JA, Young R, Surendran P, Burgess S, Danesh J, et al. PhenoScanner V2: an expanded tool for searching human genotype-phenotype associations. *Bioinformatics*. 2019;35(22):4851–4853.
- Staley JR, et al. PhenoScanner: a database of human genotype-phenotype associations. *Bioinformatics*. 2016;32(20):3207–3209.
- Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. *Genet Epidemiol*. 2013;37(7):658–665.
- Hemani G, Zheng J, Elsworth B, Wade KH, Haberland V, Baird D, et al. The MR-BASE platform supports systematic causal inference across the human phenome. *Elife*. 2018;7, e34408.
- Carter AR, Sanderson E, Hammerton G, Richmond RC, Smith GD, Heron J, et al. Mendelian randomisation for mediation analysis: current methods and challenges for implementation. *Eur J Epidemiol*. 2021;36(5):465–478.
- Zhao SS, Holmes MV, Zheng J, Sanderson E, Carter AR, et al. The impact of education inequality on rheumatoid arthritis risk is mediated by smoking and body mass index: mendelian randomization study. *Rheumatology*. 2022;61(5):2167–2175.
- Varbo A, Benn M, Smith GD, Timpson NJ, Tybjaerg-Hansen A, Nordestgaard BG, et al. Remnant cholesterol, low-density lipoprotein cholesterol, and blood pressure as mediators from obesity to ischemic heart disease. *Circ Res*. 2015;116(4):665–673.
- Scott RA, Lagou V, Welch RP, Wheeler E, Montasser ME, Luan J, et al. Large-scale association analyses identify new loci influencing glycaemic traits and provide insight into the underlying biological pathways. *Nat Genet*. 2012;44(9):991–1005.
- Katz A, Nambi SS, Mather K, Baron AD, Follmann DA, Sullivan G, et al. Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. *J Clin Endocrinol Metab*. 2000;85(7):2402–2410.
- Burrows B, Cline MG, Knudson RJ, Taussig LM, Lebowitz MD. A descriptive analysis of the growth and decline of the FVC and FEV1. *Chest*. 1983;83(5):717–724.
- Davis TM, Knuiman M, Kendall P, Vu H, Davis WA. Reduced pulmonary function and its associations in type 2 diabetes: the Fremantle Diabetes Study. *Diabetes Res Clin Pract*. 2000;50(2):153–159.
- Davis WA, Knuiman M, Kendall P, Grange V, Davis TME. Fremantle Diabetes Study. Glycemic exposure is associated with reduced pulmonary function in type 2 diabetes: the Fremantle Diabetes Study. *Diabetes Care*. 2004;27(3):752–757.
- Shafiq G, Khamseh ME, Rezaei N, Aghili R, Malek M. Alteration of pulmonary function in diabetic nephropathy. *J Diabetes Metab Disord*. 2013;12(1):15.

32. Cebal J, Mut F, Sforza D, Löhner R, Scrivano E, Lylyk P. Clinical application of image-based CFD for cerebral aneurysms. *Int J Numer Method Biomed Eng.* 2011;27(7):977–992.
33. Onor IO, Stirling DL, Williams SR, Bediako D, Borghol A, Harris MB, et al. Clinical effects of cigarette smoking: epidemiologic impact and review of pharmacotherapy options. *Int J Environ Res Public Health.* 2017;14(10):1147.
34. Allinson JP, Hardy R, Donaldson GC, Shaheen SO, Kuh D, Wedzicha JA. The presence of chronic mucus hypersecretion across adult life in relation to chronic obstructive pulmonary disease development. *Am J Respir Crit Care Med.* 2016;193(6):662–672.
35. Allinson JP, Hardy R, Donaldson GC, Shaheen SO, Kuh D, Wedzicha JA. Combined impact of smoking and early-life exposures on adult lung function trajectories. *Am J Respir Crit Care Med.* 2017;196(8):1021–1030.
36. Lee PN, Fry JS. Systematic review of the evidence relating FEV1 decline to giving up smoking. *BMC Med.* 2010;8:84.
37. Willemsse BWM, Postma DS, Timens W, ten Hacken NHT. The impact of smoking cessation on respiratory symptoms, lung function, airway hyperresponsiveness and inflammation. *Eur Respir J.* 2004;23(3):464–476.
38. Sparrow D, Weiss ST, Vokonas PS, Cupples LA, Ekerdt DJ, Colton T. Forced vital capacity and the risk of hypertension. The Normative Aging Study. *Am J Epidemiol.* 1988;127(4):734–741.
39. Selby JV, Friedman GD, Quesenberry Jr CP. Precursors of essential hypertension: pulmonary function, heart rate, uric acid, serum cholesterol, and other serum chemistries. *Am J Epidemiol.* 1990;131(6):1017–1027.
40. Wu Y, Vollmer WM, Buist AS, Tsai R, Cen R, Wu X, et al. Relationship between lung function and blood pressure in Chinese men and women of Beijing and Guangzhou. PRC-USA Cardiovascular and Cardiopulmonary Epidemiology Research Group. *Int J Epidemiol.* 1998;27(1):49–56.
41. Schnabel E, Karrasch S, Schulz H, Gläser S, Meisinger C, Heier M, et al. Cooperative Health Research in the Region of Augsburg (KORA) Study Group. High blood pressure, antihypertensive medication and lung function in a general adult population. *Respir Res.* 2011;12(1):50.
42. Koo H-K, Kim DK, Chung HS, Lee C-H. Association between metabolic syndrome and rate of lung function decline: a longitudinal analysis. *Int J Tuberc Lung Dis.* 2013;17(11):1507–1514.
43. DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol.* 1979;237(3):E214–E223.