BMJ Public Health

Relationship between diabetes-related clinical characteristics and preserved ratio impaired spirometry (PRISm): findings from NHANES 2007–2012

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To cite: Tang X, Huang K, Chu X, *et al*. Relationship between diabetes-related clinical characteristics and preserved ratio impaired spirometry (PRISm): findings from NHANES 2007–2012. *BMJ Public Health* 2024;**2**:e001313. doi:10.1136/bmjph-2024-001313

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bmjph-2024-001313).

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Received 13 April 2024
Accepted 16 October 2024

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ABSTRACT

Introduction To analyse the relationship between diabetes, its severity (including blood glucose levels, disease duration, antidiabetic drug use and number of comorbidities) and preserved ratio impaired spirometry (PRISm) using data from the National Health and Nutrition Examination Survey (NHANES).

Methods This cross-sectional study collected data from the NHANES database from 2007 to 2012. PRISm was defined as having a forced expiratory volume in 1 s (FEV1) to forced vital capacity (FVC) ratio ≥0.7 and an FEV1 predicted value <80%. We examined the relationship between diabetes duration, fasting plasma glucose (FPG), glycated haemoglobin (HbA1c), log-transformed homeostasis model assessment for insulin resistance, C reactive protein and the number of comorbidities with PRISm in the entire population. We analysed the relationship between antidiabetic drug use and PRISm, specifically in the diabetes population. Logistic regression models were used, and results were reported as OR.

Results A total of 5783 participants with normal spirometry or PRISm were included in the analysis. Diabetes was associated with 2.19 times higher odds of PRISm compared with non-diabetic participants. Longer disease duration increased PRISm odds by 2% per year. Each 1-unit increase in HbA1c and each 10 mg/dL increase in FPG were associated with 24% and 6% higher odds of PRISm, respectively. No relationship was found between insulin resistance and PRISm after adjusting for covariates. An increase of 1 mg/dL in CRP was associated with 18% higher odds of PRISm. A higher number of diabetes-related comorbidities was strongly associated with PRISm. No significant relationship was found between antidiabetic drug use and PRISm.

Conclusions Severe diabetes status, such as higher blood glucose levels, longer disease duration and a greater number of comorbidities, is associated with an increased risk of PRISm. Effective blood glucose control, self-management and regular monitoring of lung function are crucial for diabetes management.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous research has established that diabetes adversely affects various organs, including the kidneys and cardiovascular system, and contributes to obesity. However, the specific relationship between diabetes, its severity and preserved ratio impaired spirometry (PRISm) has been less well studied. The influence of diabetes-related factors, such as blood glucose levels and comorbidities, on lung function remains unclear, highlighting the need for further investigation.

WHAT THIS STUDY ADDS

⇒ This study reveals that patients with diabetes without comorbidities do not show an increased risk of PRISm, whereas those with higher blood glucose levels, longer disease duration and more comorbidities are significantly more likely to have PRISm. It also identifies that insulin resistance and inflammation have only a minor role in this relationship. Notably, the study underscores the importance of controlling blood glucose levels and managing diabetes severity to mitigate the risk of PRISm.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings suggest that prioritising stringent blood glucose control and regular monitoring of lung function in diabetic patients is crucial. This study could influence clinical practices by emphasising early intervention and management strategies to prevent PRISm in patients with diabetes. Additionally, it highlights the need for longitudinal research to further explore the causal relationship between diabetes management and PRISm outcomes, potentially shaping future clinical guidelines and policies.

INTRODUCTION

Preserved ratio impaired spirometry (PRISm) is characterised by a decrease in the predicted value of forced expiratory volume in 1 s (FEV1) while maintaining a normal ratio of FEV1 to forced vital capacity (FVC).[1] The global prevalence of PRISm is estimated to be between 5% and 20% globally, with higher rates observed in smokers.[2 3] PRISm is associated with increased respiratory symptoms

and flare-ups and is regarded as an early stage of chronic obstructive pulmonary disease (COPD),[2] whose prevalence increased after the age of 40.[4] Compared with normal spirometry, PRISm is associated with worse health outcomes, emphasising the need to identify risk factors to prevent its occurrence.[5–7]

Similar to COPD, diabetes is a chronic disease that imposes a significant disease burden, with its prevalence expected to reach 10.4% by 2040.[8] In the context of poor eating habits and the increasing prevalence of obesity, the onset age of diabetes is trending younger,[9] indicating longer disease durations and more challenging blood glucose control. Recent evidence highlights the negative effects of diabetes on lung function,[1 10] suggesting that the lung could be a target organ of diabetes. The potential mechanism may involve insulin resistance[11 12] and systemic inflammation.[13 14]

Previous studies have revealed a positive relationship between diabetes and PRISm,[15 16] but they did not consider diabetes-related measurements, such as duration and comorbidities. Diabetes commonly affects micro- and macro-vessels, and previous studies have shown an inverse relationship between kidney function,[17] cardiovascular-related factors[18] and lung function. However, no studies have measured the combined effects of these factors in diabetes mellitus on PRISm. One study using the UK Biobank database found that diabetes duration is a risk factor for COPD.[19] Longer disease duration usually indicates diabetes progression, but no study has focused on the relationship between diabetes severity and PRISm, which can be measured by disease duration, blood glucose levels and comorbidities.

The potential mechanisms underlying the relationship between diabetes and PRISm may include the following. First, the alveolar-capillary network of the lung, the largest microvascular bed in the human body, can be a target for diabetic microangiopathy, potentially causing PRISm[20] Second, a recent study found that liraglutide (a GLP-1 agonist) improves FVC and decreases serum surfactant protein D (SP-D) levels in the lung,[21] positively impacting pulmonary function and the alveolar-capillary barrier. This suggests that a GLP-1 deficit in diabetes may play a role in PRISm, linked with small airway dysfunction and reduced total lung capacity.[22] Third, the linkage between insulin resistance and PRISm may be related to the inability of insulin receptors located in type II alveolar epithelial cells to stimulate surfactant production.[23 24] Other documented mechanisms underlying PRISm in diabetes include leptin resistance and leptin-induced inflammation,[25–28] low-grade chronic inflammation[29–31] and autonomic neuropathy.[32] Finally, a genetic association between type 2 diabetes and PRISm has been established recently.[33]

The relationship between diabetes severity and PRISm remains unclear. Therefore, we aim to explore the relationship between diabetes severity (including blood glucose level, disease duration, use of antidiabetic drugs and number of comorbidities) and PRISm.

MATERIALS AND METHODS

Study population

We designed the current study using population-based data from the National Health and Nutrition Examination Survey (NHANES) for the years 2007–2012.[34] The NHANES data, detailed at http://www.cdc.gov/nchs/nhanes.htm, is a nationally representative, continuous cross-sectional study that includes the US population of all ages and races. The purpose of NHANES is to assess the nutritional and health status of adults and children in the USA. The survey collects information on demographic, socioeconomic, dietary and health-related factors through interviews, as well as medical, dental and physiological measurements and laboratory tests. We chose three cycles of NHANES (2007–2008, 2009–2010 and 2011–2012) to collect information on lung function tests.

In the current study, participants were excluded if they were under 40 years of age, had missing or low-quality spirometry data and lacked information about diabetes.

Ethics approval statement

The National Centre for Health Statistics Research Ethics Review Board approved the NHANES protocol, and written informed consent was obtained from all participants prior to data collection.

The NCHS Research Ethics Review Board (ERB) approved the ethics approval statement for NHANES 2007–2012 (NHANES 2011–2012: Protocol #2011–17; NHANES 2009–2010: Continuation of Protocol #2005–06; NHANES 2007–2008: Continuation of Protocol #2005–06).

Diabetes-related measurements

Diabetes was defined based on self-reported diagnosis, use of insulin or oral antidiabetic medications, fasting plasma glucose (FPG) ≥126 mg/dL or glycated haemoglobin (HbA1c) ≥6.5%. The diabetes duration was calculated by subtracting the age at diagnosis, collected through self-reports, from the age at the time of the survey.[35] If the age at diagnosis and the age at the survey were the same, the disease duration was considered to be 1 year. If a patient had no previous diabetes diagnosis but had abnormal laboratory results, the disease duration was also considered to be 1 year. Information on the use of insulin or oral antidiabetic medications was collected through interview questionnaires, and both were regarded as antidiabetic drug use. Insulin resistance was assessed using the homeostasis model assessment for insulin resistance index (HOMA-IR), calculated as fasting plasma insulin (mU/L)×FPG (mmol/L)/22.5.[36] Three comorbidities were identified: chronic kidney disease (CKD), cardiovascular disease (CVD) and obesity. CKD was characterised by self-reported estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 or albumin/creatinine ratio (ACR) ≥30 mg/g. CVD was defined by the presence of any of the following self-reported conditions: coronary heart disease, congestive heart failure, heart attack,

stroke and angina. Obesity was defined as a body mass index (BMI) greater than 30 kg/m^2.

Spirometry

The lung function test was performed using similar spirometers (Ohio 822/827; Ohio Medical Instrument Company, Cincinnati, Ohio, USA) in the standing position unless the participant had physical limitations. Participants were instructed to perform three acceptable exhalation manoeuvres according to the American Thoracic Society (ATS) criteria. The two highest values for FVC and FEV1, each taken from an acceptable forced expiratory manoeuvre, were required to demonstrate minimal variability. For this study, we chose prebronchodilator spirometry data with quality ratings of A (exceeds ATS data collection standards) and B (meets ATS data collection standards). The predicted pulmonary function of FEV1 was calculated based on an individual's age, sex, height and race according to previously published equations.[37] Another equation from 1999, derived from the same population database, was also used to confirm our findings.[38] PRISm was defined as having an FEV1/FVC ratio ≥0.7 and an FEV1 predicted <80%. Obstructive spirometry was defined as having an FEV1/FVC <0.7,[5] and normal spirometry was defined as having an FEV1/FVC ratio ≥0.7 and an FEV1 predicted ≥80%. In the current analysis, we included only participants with normal spirometry and PRISm.

Other variables definition

Age, sex, race, annual household income, education level, alcohol status (never, former and current) and current smoking status (never, former and current) were self-reported during household interviews. Weight and height were measured during physical examinations, and BMI was calculated as weight (kg) divided by the square of height (m^2). Hyperlipidaemia was identified by self-reported use of cholesterol-lowering drugs or plasma lipid levels in the laboratory (fasting serum total cholesterol ≥6.2 mmol/L or triglyceride ≥1.70 mmol/L.).[39]

Statistical analysis

Given that NHANES employs a complex, multistage probability sampling design to select representative participants, we incorporated sample weights, clustering and stratification in all analyses to obtain national estimates.[40] Continuous variables are expressed as means with SE and categorical variables as proportions after weighting. Laboratory measurements and lung function values were also performed using medians with IQR. A weighted t-test (for continuous variables) or a weighted χ^2 test (for categorical variables) was used to determine between-group differences in the current analysis. Multiple logistic regression models were applied to assess the multivariable associations between diabetes measurements and the risk of PRISm using OR and 95% CI. Analyses of the relationship between diabetes, diabetes duration, FPG, HbA1c, log-transformed HOMA-IR, C reactive protein (CRP), number of comorbidities and PRISm were conducted in the whole population. The analysis of the relationship between the use of antidiabetic drugs and PRISm was conducted within the diabetes population. For the analysis of diabetes duration, participants without diabetes were regarded to have a 0-year disease duration, and those with newly diagnosed diabetes of less than 1 year were regarded to have a 1-year disease duration. Analysis of the relationship between HbA1c, FPG and PRISm was further done in the normal and high-value groups, with a cut-off value of 6% in HbA1c and 110 mg/dL in FPG. All analyses were done in unadjusted models. Model 1 (adjusted for age and sex), model 2 (adjusted for age, sex, race, smoking status, BMI, education level and annual household income) and model 3 (adjusted for age, sex, race, smoking status, BMI, education level, annual household income, CKD, CVD and hyperlipidaemia). A trend test was conducted to assess the relationship between the number of diabetic comorbidities and PRISm. Missing data were excluded from the current analysis. Additionally, we performed an analysis solely on patients with diabetes.

The current analyses were performed using the 'survey' package of R software (V.4.2.1), and a two-tailed p-value of <0.05 was considered to indicate statistical significance. All analyses were weighted to represent the US population and to account for the intricate survey design.

RESULTS

Characteristics of the participants

A total of 30 442 participants were selected from NHANES 2007–2012. We excluded participants younger than 40 years (n=18 679), those lacking lung function test information or performing poorly in the test (n=4649) and those lacking diabetes information (n=6). The remaining 7108 participants were grouped based on lung function test results into normal spirometry (n=5102), PRISm (n=681) and obstructive spirometry (n=1325). For the current analysis, we chose participants with normal spirometry and PRISm. Among these participants, 1041 (14.52%) people with normal spirometry were diagnosed with diabetes mellitus, and 274 (38.51%) with PRISm were diagnosed with diabetes (figure 1).

The basic characteristics of the enrolled participants are summarised in table 1. Compared with those with normal spirometry, participants with PRISm were older, had lower annual household income, lower education levels, a higher proportion of smokers and a higher BMI. In laboratory measurements, people with PRISm had higher levels of fasting glucose, HbA1c, HOMA-IR and CRP than those with normal spirometry. Regarding comorbidities, the proportions of CKD, CVD, hyperlipidaemia and diabetes mellitus were higher in participants with PRISm than in those with normal spirometry.

We further repeated the analysis using the predicted value equation from 1999, defining 649 participants with PRISm. Online supplemental table 1 provides the basic

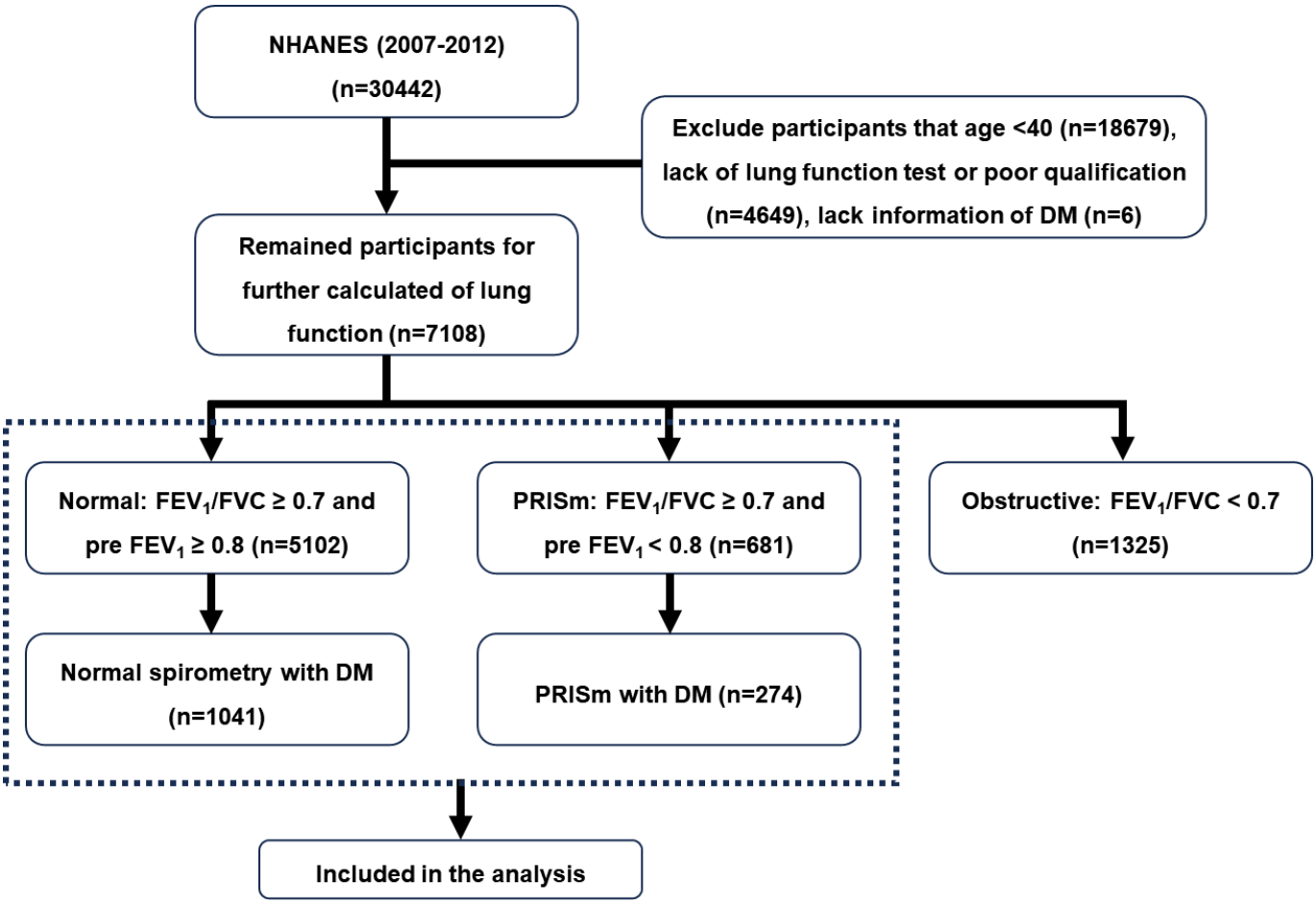

Figure 1 Flow chart of inclusion and exclusion of study participants. DM, diabetes mellitus; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; NHANES, National Health and Nutrition Examination Survey; PRISm, preserved ratio impaired spirometry.

information for participants with normal spirometry and PRISm using the 1999 equation.

The relationship between diabetes and PRISm

We analysed the relationship between diabetes and PRISm, and all results were statistically significant. In the unadjusted model (OR 3.69, 95% CI 2.89 to 4.70), model 1 (OR 3.46, 95% CI 2.72 to 4.39), model 2 (OR 2.50, 95% CI 1.92 to 3.26) and model 3 (OR 2.19, 95% CI 1.64 to 2.92), diabetes was consistently associated with PRISm (online supplemental table 2).

The significant relationship between diabetes and PRISm was also confirmed using the 1999 equation (OR 2.16, 95% CI 1.66 to 2.81) (online supplemental table 3).

The relationship between diabetes duration and PRISm

We further analysed the relationship between diabetes duration and PRISm. Compared with non-diabetic individuals, those with longer disease duration had a stronger association with PRISm. Participants with diabetes duration of 1–4 years, 5–9 years, 10–14 years and more than 15 years were associated with 1.83, 2.99, 3.23 and 1.64 times the risk of PRISm, respectively, compared with non-diabetic participants (1–4 years: OR 1.83, 95% CI 1.08 to 3.11; 5–9 years: OR 2.99, 95% CI 1.72 to 5.22; 10–14 years: OR 3.23, 95% CI 1.88 to 5.55; and ≥15 years: OR 1.64, 95% CI 1.02 to 2.65) (figure 2 and online supplemental table 4).

We regarded disease duration as a continuous variable; the results showed that for each additional year of diabetes duration, the association with PRISm increased by 1.04 times (OR 1.04, 95% CI 1.02 to 1.06) after adjusting for all related factors (figure 2 and online supplemental table 4). The significant results were consistent when using the 1999 equation to measure PRISm (OR 1.03 and 95% CI 1.01 to 1.04) (online supplemental table 5). Further analysis within the diabetic population revealed no significant difference between disease duration and PRISm after adjusting for other diseases (online supplemental table 6).

The relationship between diabetes-related laboratory measurements and PRISm

We analysed the relationship between some diabetes-related laboratory measurements—HbA1c, fasting glucose level, HOMA-IR (an index of insulin resistance) and CRP (an index of inflammation)—and PRISm to explore possible explanations for the association between diabetes and PRISm.

Table 1 Characteristics of included participants

	Total	Normal spirometry	PRISm	P value
n	5783	5102	681	
Age, years, mean (SE)	53.79 (0.19)	53.56 (0.20)	56.04 (0.57)	<0.001
Sex, n (%)				
Female	3161 (54.66)	2786 (55.39)	375 (56.78)	0.61
Male	2622 (45.34)	2316 (44.61)	306 (43.22)	
Body mass index, kg/m^2, mean (SE)	29.61 (0.14)	29.32 (0.14)	32.56 (0.51)	<0.0001
Race, n (%)				
Mexican American	950 (16.43)	876 (7.04)	74 (4.73)	<0.0001
Non-Hispanic Black	1272 (22)	1096 (9.93)	176 (14.37)	
Non-Hispanic White	2430 (42.02)	2200 (73.08)	230 (58.69)	
Other Hispanic	680 (11.76)	596 (4.78)	84 (5.94)	
Other race	451 (7.8)	334 (5.17)	117 (16.27)	
Annual household income, n (%)				
<$65 000	3644 (65.66)	3162 (51.13)	482 (62.33)	<0.001
≥$65 000	1906 (34.34)	1734 (48.87)	172 (37.67)	
Education level, n (%)				
College and above	2994 (51.81)	2681 (62.66)	313 (51.92)	<0.001
Middle and high school	2113 (36.56)	1830 (31.91)	283 (41.45)	
Primary school and less	672 (11.63)	587 (5.43)	85 (6.63)	
Smoke, n (%)				
Never	3250 (56.23)	2910 (58.47)	340 (50.21)	0.01
Former	1557 (26.94)	1365 (26.83)	192 (29.00)	
Current	973 (16.83)	824 (14.70)	149 (20.79)	
Alcohol, n (%)	4689 (86.67%)	4167 (90.32%)	522 (85.81%)	<0.0001
Fast glucose, mg/dL, mean (SE)	109.12 (1.07)	107.68 (1.00)	122.20 (3.38)	<0.0001
Fast glucose, mg/dL, median (IQR)	101.00 (94.00–111.00)	101.00 (94.00–109.00)	108.00 (96.00–125.00)	<0.0001
HbA1c, %, mean (SE)	5.74 (0.02)	5.70 (0.02)	6.23 (0.07)	<0.0001
HbA1c, %, median (IQR)	5.50 (5.30–5.80)	5.50(5.30–5.80)	5.80(5.50–6.50)	<0.0001
HOMA-IR, uU/mL, mean (SE)	3.97 (0.16)	3.79 (0.15)	5.60 (0.45)	<0.001
HOMA-IR, uU/mL, median (IQR)	2.64 (1.62–4.68)	2.55 (1.57–4.46)	3.53 (2.13– 6.54)	<0.001
CRP, mg/dL, mean (SE)	0.38 (0.01)	0.36 (0.01)	0.56 (0.07)	0.01
CRP, mg/dL, median (IQR)	0.18 (0.07–0.40)	0.17 (0.07–0.39)	0.31 (0.14– 0.70)	<0.0001
Lung function test				
FVC, mL, mean (SE)	3851.69 (20.40)	3953.44 (18.96)	2835.67 (45.51)	<0.0001
FVC, mL, median (IQR)	3737.00 (3079.00–4566.00)	3839.00 (3198.00–4640.00)	2653.00 (2255.00–3354.00)	<0.0001
FVC% pred, mean (SE)	0.99 (0.00)	1.02 (0.00)	0.76 (0.00)	<0.0001
FVC% pred, median (IQR)	0.99 (0.90–1.08)	1.01 (0.93–1.09)	0.77 (0.720.82)	<0.0001
FEV_1, mL, mean (SE)	3015.07 (15.67)	3100.71 (14.10)	2159.87 (30.57)	<0.0001
FEV_1, mL, median (IQR)	2935.00 (2417.00–3559.00)	3020.00 (2516.00–3619.00)	2040.00 (1736.00–2551.00)	<0.0001
FEV_1% pred, mean (SE)	0.98 (0.00)	1.00 (0.00)	0.73 (0.00)	<0.0001
FEV_1% pred, median (IQR)	0.98 (0.89–1.06)	0.99 (0.92–1.08)	0.75 (0.70–0.78)	<0.0001
FEV_1/FVC, mean (SE)	0.78 (0.00)	0.79 (0.00)	0.77 (0.00)	<0.0001
FEV_1/FVC, median (IQR)	0.78 (0.75–0.82)	0.79 (0.75–0.82)	0.76 (0.73–0.80)	<0.0001

Continued

Table 1 Continued

	Total	Normal spirometry	PRISm	P value
FEV_1/FVC %pred, mean (SE)	0.99 (0.00)	0.99 (0.00)	0.96 (0.00)	<0.0001
FEV_1/FVC % pred, median (IQR)	0.99 (0.94–1.02)	0.99 (0.95–1.03)	0.96 (0.92–1.00)	<0.0001
Chronic kidney disease, n (%)	894 (16.16)	713 (11.08)	181 (21.74)	<0.0001
Cardiovascular disease, n (%)	551 (9.53)	415 (6.34)	136 (19.04)	<0.0001
DM, n (%)	1315 (22.74)	1041 (14.52)	274 (38.51)	<0.0001
DM with no comorbidity, n (%)	278 (4.86)	246 (3.31)	32 (3.64)	
DM with one comorbidity, n (%)	591 (10.33)	483 (7.20)	108 (18.02)	
DM with two comorbidities, n (%)	301 (5.26)	219 (2.74)	82 (10.51)	
DM with three comorbidities, n (%)	83 (1.45)	50 (0.75)	33 (4.26)	
Hyperlipidaemia, n (%)	4559 (78.85)	4004 (79.09)	555 (84.35)	0.02

CRP, C reactive protein; DM, diabetes mellitus; $FEF_{25–75}$, forced expiratory flow from 25% to 75% of FVC; FEV1, forced expiratory volume in 1 s; FEV_3, forced expiratory volume in 3 s; FVC, forced vital capacity; HbA1c, glycated haemoglobin; HOMA-IR, homeostasis model of assessment for insulin resistance index; PEF, peak expiratory flow; PRISm, preserved ratio impaired spirometry.

In the entire population, each 1-unit increase in HbA1c was associated with a 1.24 times increased likelihood of PRISm (OR 1.24, 95% CI 1.12 to 1.37) after adjusting for covariates (figure 3 and online supplemental table 7). When restricting the analysis in the normal HbA1c group, no significant relationship was found between HbA1c and PRISm in model 2 (OR 1.53, 95% CI 0.75 to 3.10) and model 3 (OR 1.44, 95% CI 0.70 to 2.94). In the high HbA1c group, the significant association between HbA1c and PRISm still existed in model 2 (OR 1.19, 95% CI 1.05 to 1.35), but diminished in model 3 (OR 1.13, 95% CI 0.99 to 1.29) (online supplemental figure 1, table 7).

Similarly, each 10 mg/dL increase in fasting glucose level was associated with a higher likelihood of PRISm (OR 1.06, 95% CI 1.03 to 1.09) (figure 3 and online supplemental table 7). After adjusting for potential covariables, the relationship between FPG and PRISm was still significant in the high-value group (OR 1.05, 95% CI 1.01 to 1.09), but diminished in the normal-value group (OR 0.89, 95% CI 0.65 to 1.22) (online supplemental figure 2, table 7). These findings suggest that a hyperglycaemic environment may be a risk factor for PRISm.

In the unadjusted model, each 1-unit increase in log-transformed HOMA-IR was associated with a 1.65 times increased likelihood of PRISm (OR 1.65, 95% CI 1.36 to

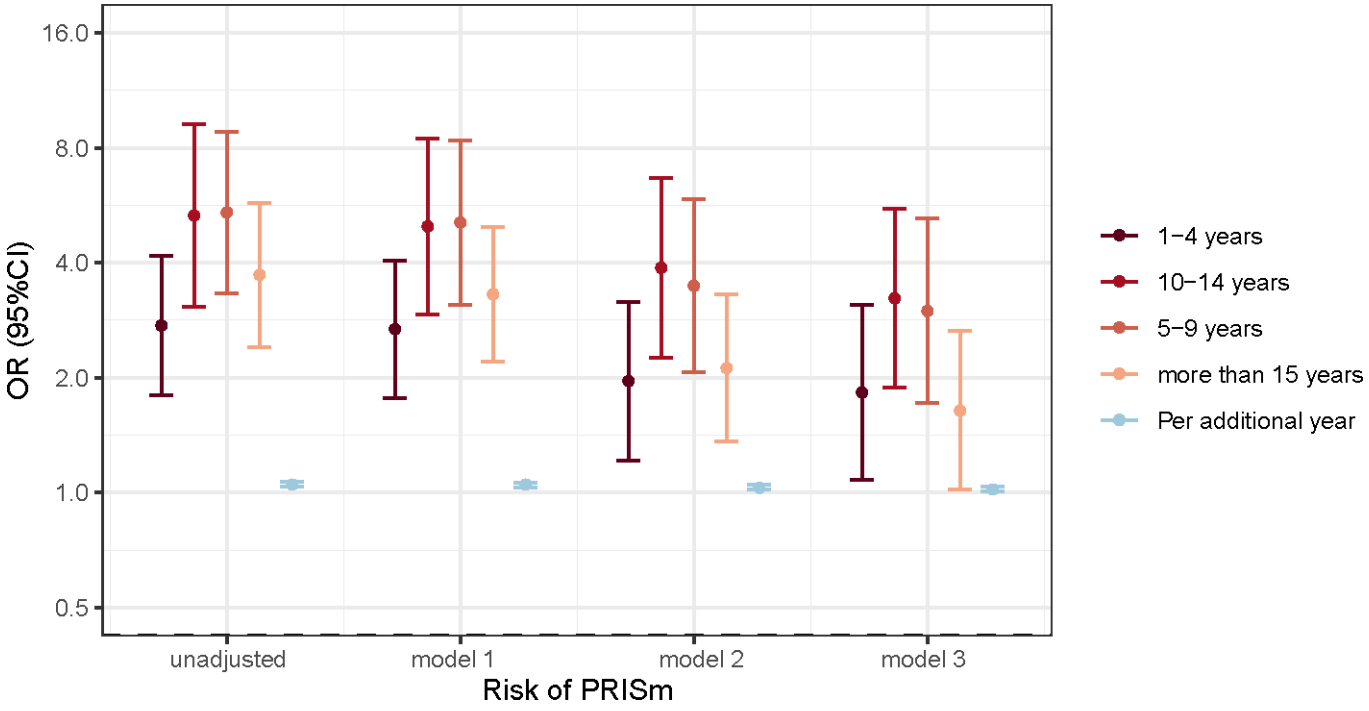

Figure 2 The relationship between diabetes duration and PRISm. PRISm, preserved ratio impaired spirometry

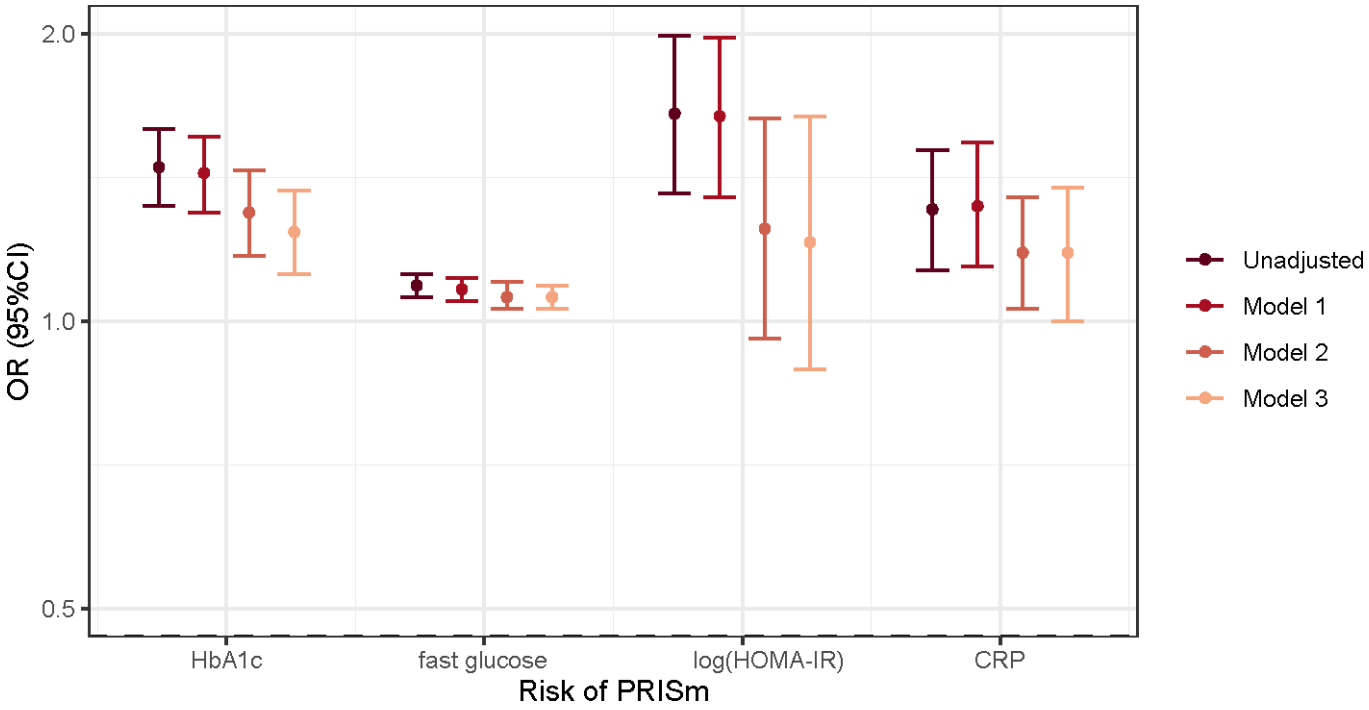

Figure 3 The relationship between laboratory measurements and PRISm. PRISm, preserved ratio impaired spirometry.

1.99). However, this association diminished in model 2 (OR 1.25, 95% CI 0.96 to 1.63) and model 3 (OR 1.21, 95% CI 0.89 to 1.64). CRP, a marker of inflammation, showed that each 1 mg/dL increase was associated with a 1.18 times increased likelihood of PRISm (OR 1.18, 95% CI 1.00 to 1.38), indicating that inflammation may be a contributing factor to the association between diabetes and PRISm (figure 3). When using the 1999 equation to measure PRISm, the relationship between CRP and PRISm became non-significant in model 3 after adjusting for comorbidities (OR 1.18, 95% CI 0.99 to 1.40). This suggests that comorbidities play a crucial role in the relationship between diabetes and PRISm (online supplemental table 8). Further analysis in patients with diabetes showed no significant association between laboratory measurements and PRISm after adjusting for comorbidities (online supplemental table 9).

The relationship between the number of comorbidities and PRISm

Diabetes commonly affects the kidneys and micro- and macro-vessels and is often associated with obesity. Therefore, we analysed the relationship between the number of comorbidities (CKD, CVD and obesity) and PRISm, excluding model 3 in this analysis.

In the whole population, using non-diabetes individuals as the reference group, diabetes with one comorbidity was associated with an increased risk of PRISm (OR 2.54, 95% CI 1.76 to 3.66). The risk increased with the number of comorbidities: two comorbidities (OR 3.42, 95% CI 2.20 to 5.33) and three comorbidities (OR 3.69, 95% CI 1.75 to 7.78). Diabetes without comorbidities showed no significant association with PRISm (OR 1.21, 95% CI 0.67 to 2.15). Trend analysis showed that the risk of PRISm increased with the number of diabetes-related comorbidities (p-trend<0.0001) (figure 4 and online supplemental table 10). Similar results were obtained when using the 1999 equation to measure PRISm (online supplemental table 11). Significant results were also observed when analysing only patients with diabetes (online supplemental table 12).

The relationship between the use of antidiabetic drugs and PRISm

We divided patients with diabetes into two groups based on their use of antidiabetic drugs. Our results showed that taking antidiabetic drugs was not associated with PRISm (OR 1.37, 95% CI 0.82 to 2.31) (online supplemental figure 3,table 13). However, when using the 1999 equation to measure PRISm, a significant association was observed. Patients with diabetes on antidiabetic drugs showed an increased risk of PRISm in the unadjusted model (OR 1.66, 95% CI 1.08 to 2.57), model 1 (OR 1.65, 95% CI 1.06 to 2.57) and model 2 (OR 1.72, 95% CI 1.07 to 2.75). In model 3, after adjusting for additional factors, the association between taking antidiabetic drugs and PRISm was no longer significant (OR 1.58, 95% CI 0.94 to 2.64) (online supplemental table 14).

DISCUSSION

In this study, we focused on the relationship between diabetes-related measurements and PRISm using a large population-based database. Some notable findings include patients with diabetes without comorbidities were not associated with PRISm; higher blood glucose levels, longer disease duration and the presence of more comorbidities (indicating a more severe diabetes status) were

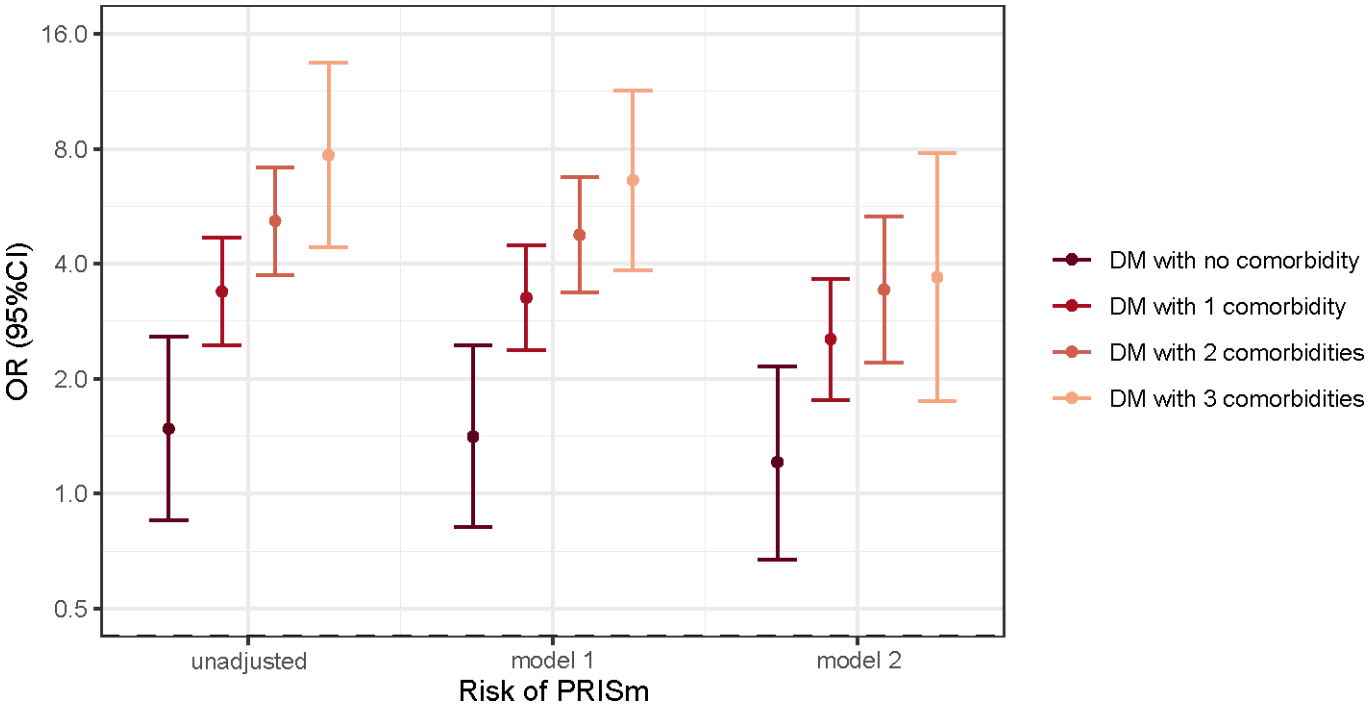

Figure 4 The relationship between the number of DM comorbidities and PRISm. DM, diabetes mellitus; PRISm, preserved ratio impaired spirometry.

associated with an increased risk of PRISm; and insulin resistance and inflammation appeared to play a weak role in the relationship between diabetes and PRISm.

Previous studies have often examined the broader relationship between diabetes and lung function rather than specifically focusing on PRISm. An inverse relationship between diabetes and lung function is increasingly documented. For instance, a study involving 1878 middle-aged adults found that FVC was reduced by 6.9% (range: −9.1% to −4.7%) in patients with diabetes compared with non-diabetic participants.[41] Similar results have been reported in other studies.[42 43] In addition to cross-sectional data, longitudinal studies have also been conducted. For example, the ARIC study, with a 3-year follow-up, showed a faster decline in FVC (%predicted) among patients with diabetes compared with non-diabetics (64 mL/year vs 58 mL/year).[42] A community-based cohort study followed 495 patients with diabetes for 7 years, observing a more than 10% decrease in predicted spirometry values, with annual declines of 68 mL/year for FVC, 71 mL/year for FEV1, 84 mL/year for vital capacity and 171 /min for peak expiratory flow.[44]

In our analysis, we found that longer diabetes duration was associated with an increased risk of PRISm. Supporting this, a study investigating the relationship between diabetes duration and the risk of COPD found that patients with diabetes duration of 1 to less than 3 years, 3 to less than 7 years and 7 years or longer had higher risks of COPD compared with those with diabetes duration of less than 1 year (HR 1.23, 95% CI 1.05 to 1.44; HR 1.20, 95% CI 1.04 to 1.39 and HR 1.18, 95% CI 1.01 to 1.37, respectively).[19] However, some studies present contrary findings regarding lung function decline. For instance, Lange *et al* observed a sharp decline in lung function only at the onset of diabetes, with no insignificant impairment in pulmonary function over a 5-year period for patients with diabetes.[45] Similarly, a case-control analysis reported consistently lower FEV1 and FVC in patients with diabetes at all time points but found no differences in the rates of FEV1 or FVC decline between patients with diabetes and controls.[46]

In a study of a Chinese population with a 10-year follow-up, an analysis of 11 107 adults showed each that 1 mmol/L increase in FPG level was associated with a 13 mL decrease (95% CI −2 mL to 25 mL) in FEV1 and a 0.46% decrease (95% CI −0.09% to 0.83%) in FEV1%.[47] This finding is consistent with our results: a 10 mmol/L increase in FPG was associated with a 1.06 times higher risk of PRISm, an abnormal lung function status. Other studies have also supported our findings showing that both FPG[48] and HbA1c[49] are independently and negatively correlated with spirometry values. We also examined the relationship between insulin resistance, inflammation (CRP) levels and PRISm, finding weak, significant results only in the unadjusted model and model 1. The significant relationship between log (HOMA-IR) and PRISm suggests that insulin resistance may mediate the relationship between diabetes and PRISm. Cross-sectional data of non-diabetic participants showed that fasting insulin and insulin resistance were negatively correlated with FVC and FEV1.[11] Another study extended this negative correlation to 1184 participants with diabetes.[12] Evidence from both healthy individuals[30] and patients with diabetes[29] showed strong

inverse associations between CRP levels and low lung function values.

The detrimental effects of diabetes on the kidneys, obesity and cardiovascular system are well established.[50] eGFR is a measure index of CKD, and a Mendelian randomisation analysis showed a causal association between a 10% increase in eGFR and increased FEV1/FVC z-scores (β 0.055, 95% CI 0.024 to 0.086).[17] Obesity is another significant risk factor. Compared with normal-weight individuals, those with persistent obesity had changes in %pred FEV1 (β −5.07%; 95% CI −1.51% to −8.62%) and %pred FEV1/FVC ratio (β −2.85%; 95% CI −0.18% to −5.51%).[51] Regarding CVD, an analysis of 5777 participants showed that among the 71 CVD-related plasma proteins, 13 were associated with predicted FEV1, 17 with predicted FVC and 1 with the FEV1/FVC ratio.[52] Previous studies have shown that CKD,[53] CVD[18] and obesity[54] are each associated with decreased lung function, but none have analysed the combined effects in diabetes. In our current study, we counted the number of comorbidities in patients with diabetes and found that a higher number of diabetes-related comorbidities was associated with an increased risk of PRISm.

In the current analysis, when using the 1999 equation to measure PRISm, we found that patients with diabetes undergoing treatment with antidiabetic drugs were associated with PRISm compared with those not taking any drugs. One possible explanation is that patients with mild diabetes can control their blood glucose levels through sensible diet and physical activity, while those with severe diabetes, often accompanied by more comorbidities, require antidiabetic drugs, including oral antidiabetic medication and insulin.

PRISm is a highly prevalent and unstable condition that can transition to other lung function states (eg, COPD) or even revert to normal spirometry.[2 6] Evidence has shown that participants who transition back to normal spirometry are not at increased risk for mortality.[7] Thus, it is essential to prevent PRISm at an early stage to avoid deterioration. Our study indicates that high blood glucose levels are detrimental to PRISm, emphasising the need for active blood glucose control as early as possible, especially in the current environment where diabetes onset is occurring at a younger age.[9] Interestingly, our study found that both longer disease duration and more comorbidities are associated with PRISm. These two factors indicate disease severity. Therefore, intensive blood glucose control, self-monitoring and self-management are especially important and necessary for the diabetes population, along with regular monitoring of lung function.

This study has several strengths. It is the first to explore the relationship between diabetes-related measurements and PRISm using a national cohort. However, our study also has some limitations, and results should be interpreted with caution. First, the cross-sectional nature of the study did not allow us to investigate casual relationships. Furthermore, studies have found that PRISm is a risk factor for developing diabetes.[16] Thus, a bidirectional association may be possible. Third, diabetes was partially self-reported. The strict definition of diabetes requires two measurements, FPG or HbA1c. In NHANES, the population only had one result of FPG and HbA1c, which may lead to overdiagnosis of diabetes. Fourth, the measurement of disease duration was based on patients' self-reports. Patients with no previously diagnosed diabetes but abnormal laboratory results were also considered as having diabetes, and their disease duration was regarded as 1 year, leading to possible misassessment. Future studies should investigate the relationship between diabetes-related measurements and PRISm in general and diabetic populations in cohorts with long follow-ups. Further validation of whether dynamic changes in plasma glucose levels are negatively associated with the risk of PRISm is also needed.

CONCLUSION

Diabetes without comorbidities is not associated with PRISm, while diabetes with high blood glucose, longer disease duration and more comorbidities is associated with PRISm. Insulin resistance and inflammation play a weak role in the relationship between diabetes and PRISm. Our study highlights the importance of blood glucose control and disease management, as well as the regular monitoring of lung function. Furthermore, longitudinal studies are needed to explore the causal relationship between blood glucose fluctuations and PRISm.

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Contributors XT, KH and XC conceived and designed the study. TY and CW supervised the work. XT did all the statistical analyses. TY and CW had full access and verification to all the data. KH and XC drafted the manuscript. YP, TH and YC revised the manuscript. All authors approved the final version before submission. TY was the guarantor who accept full responsibility for the finished work and/or the conduct of the study, had access to the data and controlled the decision to publish.

Funding This study is supported by CAMS Innovation Fund for Medical Sciences (CIFMS) (2022-I2M-C&T-B-107, 2021-I2M-1-049) and National High Level Hospital Clinical Research Funding (2022-NHLHCRF-LX-01-0107).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants. NCHS Research Ethics Review Board (ERB) approved the ethics approval statement for NHANES 2007-2012 (NHANES 2011-2012: Protocol #2011-17; NHANES 2009-2010: Continuation of Protocol #2005-06; NHANES 2007-2008: Continuation of Protocol #2005-06). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. National Center for Health Statistics. Division of Health and Nutrition Examination Surveys. NHANES Interactive Data Visualizations. 2023. https://www.cdc.gov/nchs/nhanes/index.htm.

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