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The association between preserved ratio impaired spirometry (PRISm) and cognitive function among American older adults: the mediating role of systolic blood pressure

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Abstract

Background Recent studies have drawn attention to the association between preserved ratio impaired spirometry (PRISm) and cognitive function decline. High systolic blood pressure (SBP) is a known risk factor for both PRISm and dementia. This study aimed to investigate whether elevated SBP may mediate the relationship between PRISm and cognitive function in older adults.

Methods This study analyzed 732 participants aged ≥ 60 years who had completed spirometry and cognitive function tests in the National Health and Nutrition Examination Survey (NHANES) 2011–2012. Multivariable linear regression was employed to assess the relationship between PRISm and cognitive function, as measured through the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Word Learning sub-test, the Animal Fluency test (AFT), the Digit Symbol Substitution test (DSST), and global cognition tests. All cognitive tests were modeled as z-scores, and global cognition was calculated as the sum of the z-scores of the CERAD, AFT, and DSST. Mediation analyses were conducted to test the mediating effect of SBP on the association between PRISm and cognitive function.

Results Participants with PRISm had lower AFT (β = -0.300; 95% confidence interval [CI] = -0.479 to -0.122; $p = 0.001$), DSST (β = -0.157; 95% CI = -0.309 to -0.004; $p = 0.044$), and global cognition scores (β = -0.211; 95% CI = -0.369 to -0.053; $p = 0.009$) than those with normal spirometry, after adjusting for all potential confounders. SBP was considerably associated with AFT (β = -0.084; 95% CI = -0.162 to -0.005; $p = 0.038$) and DSST (β = -0.132; 95% CI = -0.207 to -0.057; $p < 0.001$), mediating 7.9% and 18.0% of the association of PRISm with cognitive function, respectively. Furthermore, SBP mediated 17.1% of the association of PRISm with global cognition.

Conclusions The findings suggested the potential role of SBP as a mediator of associations between PRISm and cognitive decline in older adults.

Keywords Cognitive function, Mediation analysis, Preserved ratio impaired spirometry, Systolic blood pressure

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Introduction

Dementia, a group of symptoms affecting memory, thinking, and social abilities interferes with daily activities, thus leading to death and disability among older adults [1]. With the worldwide increase in population aging, cognitive impairment is likely to become a public health disaster [2]. According to the World Health Organization's Global Dementia Observatory report, the number of patients with dementia is expected to increase to 139 million by the year 2050 [3]. Vascular risk factors, including hypertension, play a crucial role in the pathophysiology of dementia, with up to 50% of patients with Alzheimer's disease (AD) exhibiting mixed pathology, including cerebrovascular lesions, after postmortem examination [4].

Hypertension is a modifiable primary risk factor for all-cause dementia, especially vascular cognitive impairment [5]. Long-term elevation of blood pressure has profound effects on the cerebral vasculature and brain parenchyma, substantially increasing the risk of dementia in individuals with hypertension [6]. Hypertension promotes the development and accumulation of atherosclerotic plaques in the extracranial arteries, reduces nitric oxide signaling, accelerates inflammation and immune cell accumulation, and increases the risk of cognitive decline [7]. A previous study on blood pressure and dementia indicated that higher systolic blood pressure (SBP) could predict a 5-year risk of all-cause dementia [8]. Consistent with this research, several other studies have suggested that elevated SBP in older was adults is associated with faster cognitive decline and an increased risk of dementia and that its impact becomes more substantial with advancing age [9]. Additionally, evidence from randomized clinical trials has shown that controlling SBP to a target of 120 mmHg could reduce the risk of mild cognitive impairment [10]. Therefore, reducing SBP to lower the risk of cognitive impairment may be a crucial measure for preventing dementia.

Previous studies have indicated that chronic lung disease and impaired lung function are potential risk factors for dementia or cognitive impairment [11]. Preserved ratio impaired spirometry (PRISm) has been demonstrated to be associated with an increased incidence of metabolic syndrome, obesity, congestive heart failure, type 2 diabetes, and coronary artery disease [12]. PRISm is characterized by a reduced forced expiratory volume in 1 s ($FEV_1 \leq 80\%$ of predicted value) and a preserved FEV_1 to forced vital capacity (FVC) ratio (FEV_1/FVC) greater than 0.7, previously known as restrictive pulmonary function impairment, or unclassified/nonspecific chronic obstructive pattern [13]. The prevalence of PRISm in older adults ranges from 3–20% [14]. Recent studies suggested that the overall cognition of patients with PRISm was poorer than that of those with normal spirometry [15], and the risk of developing all types of dementia increased [11]. Compared to other impaired lung function patterns, such as COPD (FEV1/FVC < 0.70), PRISm is considered to indicate a potentially reversible preclinical state, that can be reversed to a state with normal spirometry [16]. Therefore, early identification and clinical intervention for PRISm may be an effective means to reduce the incidence of dementia.

In summary, both elevated blood pressure and impaired pulmonary function (including PRISm) are associated with dementia. Additionally, studies have shown a significant negative correlation between FEV_1 and SBP [17]. However, it is still unclear whether SBP mediates the potential association between PRISm and cognitive function. Therefore, the primary objective of this study was to examine the association between PRISm and cognitive impairment using data from the National Health and Nutrition Examination Survey (NHANES) dataset. The secondary objective was to determine the role of blood pressure in mediating this association.

Methods

Study design and population

This cross-sectional study used a public data set of spirometry and cognitive function tests collected from the NHANES 2011–2012. NHANES, conducted by the National Center for Health Statistics (NCHS), is a continuous initiative designed to evaluate the health and nutritional well-being of both adults and children across the United States. The survey integrates both interviews and physical assessments obtained from a stratified, multistage probability sample of noninstitutionalized civilians residing in the United States [18]. The data collected in the NHANES underwent review and approval by the Research Ethics Review Board of the NCHS. Additionally, all participants provided written consent prior to their participation in the study. This study analyzed only data from publicly accessible databases, thus obviating the need for additional ethical review. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria to report our study.

Our study used only data from the NHANES 2011–2012 survey because only this survey included participants who completed both spirometry and cognitive function assessments. The following participants were excluded: (1) those with incomplete cognitive function data ($n=8069$); (2) those with missing spirometry data ($n=408$); (3) those with missing blood pressure data ($n=282$); and (4) those with a $FEV_1/FVC < 0.7$ ($n=265$). Due to the limited number of participants in the NHANES 2011–2012 survey who completed both cognitive assessment questionnaires and spirometry, the response rate was only 7.5%. Finally, 732 participants were included in this study (Fig. 1).

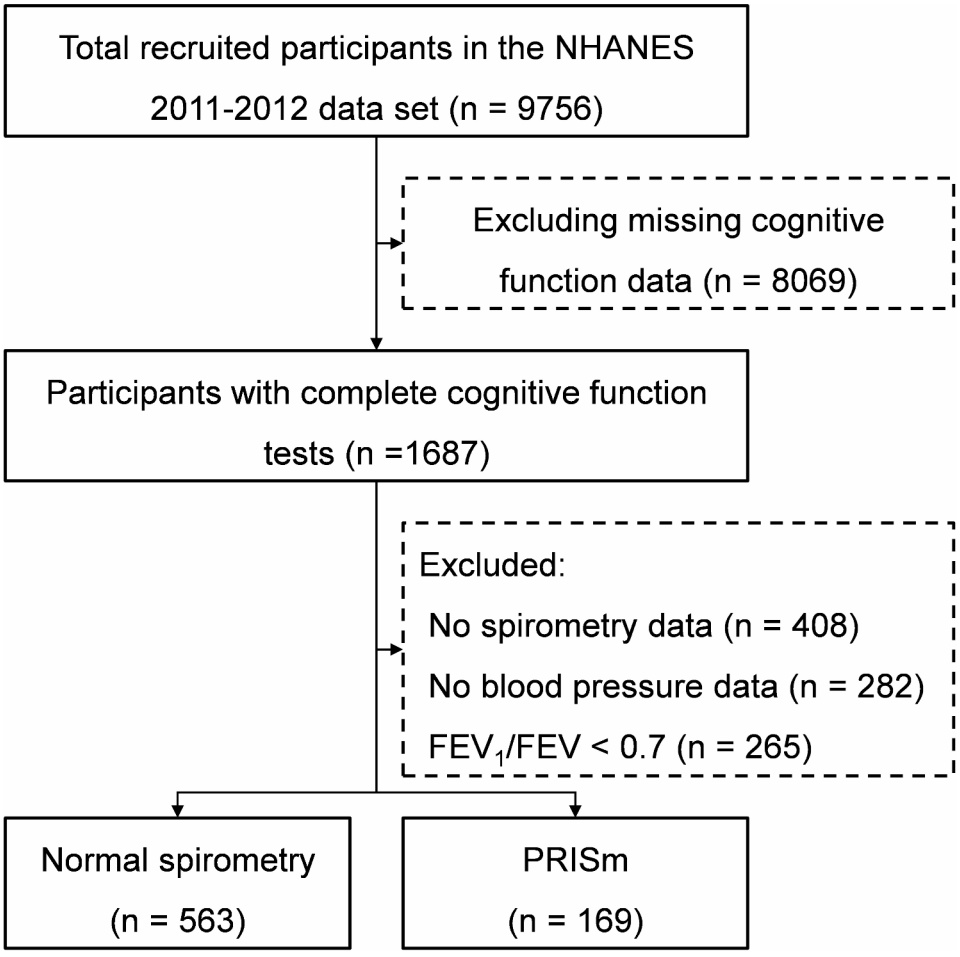

Fig. 1 Flow diagram of participants included for the analysis in the NHANES 2011–2012 data set. NHANES, National Health and Nutrition Examination Survey

Assessment of spirometry

Spirometry was conducted with participants standing upright during NHANES 2011–2012, employing spirometers (Ohio 822/827; Ohio Medical Instrument Company, OH, USA). The process adhered to the standardized protocol endorsed by the American Thoracic Society (ATS) [19]. The participants were subjected to multiple tests to ensure acceptable and reproducible spirometry. Participants who failed after 8 tests were excluded, and the 3 highest values were recorded for each participant. The raw data from FEV_1, FVC, and FEV_1/FVC of each participant were used for subsequent analysis. The calculation of FEV_1% predicted and FVC% predicted used reference equations provided by the Global Lung Function Initiative (GLI) [20]. Subsequently, we divided the actual values by the predicted values to compute the percentage predicted for both FVC and FEV_1. PRISm was defined as FEV_1 < 80% predicted and FEV_1/FVC ratio ≥ 0.70, whereas normal spirometry was defined as FEV_1 ≥ 80% predicted and FEV_1/FVC ratio ≥ 0.70 [21].

Cognitive function assessment

In the NHANES 2011–2012 survey, participants aged 60 years and older underwent 3 cognitive assessments, which encompassed the Consortium to Establish a Registry for Alzheimer's Disease (CERAD), the animal fluency test (AFT), and the Digit Symbol Substitution Test (DSST). Higher scores on all cognitive function tests indicate improved cognitive performance.

The CERAD word learning assessment was used to assess immediate and delayed verbal memory through 3 successive learning sessions and a subsequent delayed recall task [22, 23]. During the learning trials, participants vocalized 10 unconnected words before attempting to recall as many words as they could. Delayed recall followed the completion of the AFT and DSST. The scores of the 3 trials and delayed recall were aggregated to obtain the total CERAD score for each participant [24].

The AFT was used to examine categorical verbal fluency, which is a facet of executive function [25]. The participants were instructed to enumerate as many animals as possible within a duration of 1 min. One point

was assigned for each named animal, and the sum of the number of named animals constituted the total AFT score of the participant.

The DSST, an integrated version of the Wechsler Adult Intelligence Scale, was used to evaluate processing speed, sustained attention, and working memory [26, 27]. The participants were asked to match symbols to numbers within 133 boxes in 2 min, and the score reflecting the total number of accurate matches ranged from 0 to 133.

Considering individual differences between various cognitive tests, we calculated a global cognitive score for each participant [28]. In this study, global cognition was generated by aggregating the standardized Z scores from each assessment (CERAD, AFT, and DSST) [29]. The calculation was performed as described in a previous study [24].

Mediator and covariate assessment

The blood pressure levels were measured by trained clinicians using a mercury sphygmomanometer and an appropriately sized cuff. After a period of quiet rest while seated for 5 min, three successive blood pressure measurements were taken once the maximum inflation level for the participant was established. The average of all obtainable measurements was used to determine the levels of SBP and diastolic blood pressure (DBP). Quality control and physician training in the NHANES study have been described in detail previously [4]. This study used continuous SBP as the mediator, with the change in SBP being 1 mmHg for the blood pressure estimates.

Various variables were selected as potential confounders that might influence blood pressure and cognitive function. These covariates included the following: (1) demographic data (age, sex, race, and education level); (2) examination data (weight and standing height) and body mass index (BMI), which was calculated by dividing weight in kilograms by the square of measured height in meters; (3) laboratory data (total cholesterol, high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, triglyceride, glycohemoglobin, white blood cell count, neutrophil count, and lymphocyte count); and (4) questionnaire data (smoking status, pack-years of smoking, alcohol intake, hypertension, diabetes mellitus, stroke, heart failure, and coronary artery disease).

Statistical analysis

Data analyses were conducted using SPSS (version 26.0, SPSS Inc., IL, USA) and R software (version 4.3.2). A Kolmogorov–Smirnov test was used to explore whether the continuous variables accorded with normal distribution. Continuous variables with a normal distribution were expressed as mean values with their standard deviations (SD), whereas categorical variables were expressed as numbers with their corresponding percentages. Differences between participants with normal spirometry or PRISm were evaluated using the independent samples *t* tests (for continuous variables) or chi-square tests (for categorical variables). Linear regression models were utilized to compute the β-coefficient (95% confidence interval [CI]) illustrating the impact of PRISm on cognitive function (the Z-scores of CERAD, AFT, DSST, and global cognition) under various conditions (Model 0: adjusted for age, sex, and race; Model 1: adjusted for variables in Model 0 plus education level, smoking status, pack-years of smoking, and BMI; and Model 2: adjusted for variables in Model 1 plus HDL cholesterol, glycohemoglobin, white blood cell count, neutrophil count, hypertension, diabetes mellitus, stroke, heart failure, and coronary artery disease).

Mediation analyses were performed to assess the mediating effect of SBP on the relationship between PRISm (normal spirometry as a reference) and cognitive function. All continuous variables underwent z-transformation to reduce bias when performing mediation analysis [30]. Three pathways (a, b, and c) were employed to evaluate mediation with the process modeling framework delineated by Hayes (PROCESS macro v4.2) [31]. Path a evaluated the link between PRISm (exposure) and SBP (mediator). Path b gauged the relationship between SBP (mediator) and cognitive assessment (outcome). Path c, representing the total effect, quantified the direct association between PRISm (exposure) and cognitive assessment (outcome). The mediated proportion was calculated using the following formula: $\beta_{\text{indirect effect}}/\beta_{\text{total effect}} \times 100\%$ [32]. All *p*-values were computed as two-tailed, with statistical significance defined as $p<0.05$.

Results

Characteristics of study populations

Participants with PRISm were predominantly female, younger, had a higher prevalence of current smokers, lower educational background, and an increased prevalence of diabetes compared with those with normal spirometry (Table 1). Furthermore, participants with PRISm demonstrated elevated SBP values (137.1 mmHg vs. 131.5 mmHg, $p=0.001$), but there was no significant difference in DBP values (70.9 mmHg vs. 71.1 mmHg, $p=0.856$) compared with those with normal spirometry. The spirometric values, including FEV_1% predicted (69.7% vs. 98.7%, $p<0.001$), FVC% predicted (68.9% vs. 95.2%, $p<0.001$), and FEV_1/FVC (76.7% vs. 78.1%, $p=0.001$), were markedly lower in participants with PRISm than in those with normal spirometry. Similarly, cognitive function evaluated using the AFT test ($p<0.001$), the DSST test ($p=0.004$), and the global cognitive score ($p=0.003$) showed a significant decrease in participants with PRISm.

Table 1 Baseline characteristics of the study population

	Normal spirometry (*n* = 563)	PRISm (*n* = 169)	*P* value
Continuous variables, mean (SD)			
Age (year)	66.9 (5.4)	65.6 (4.8)	0.003
Body mass index (kg/m^2)	29.5 (6.4)	31.1 (7.0)	0.006
Systolic blood pressure (mmHg)	131.5 (18.0)	137.1 (19.5)	0.001
Diastolic blood pressure (mmHg)	71.1 (12.1)	70.9 (16.1)	0.856
Total cholesterol (mmol/L)	5.8 (3.9)	5.7 (4.3)	0.921
HDL cholesterol (mmol/L)	1.4 (0.4)	1.3 (0.4)	0.001
LDL cholesterol (mmol/L)	3.0 (0.9)	2.8 (1.0)	0.149
Triglyceride (mmol/L)	7.8 (2.2)	7.5 (2.8)	0.467
Glycohemoglobin (%)	6.0 (1.2)	6.4 (1.2)	< 0.001
White blood cell count (10^3/μL)	6.5 (2.8)	7.1 (3.0)	0.019
Neutrophil count (10^3/μL)	3.8 (1.5)	4.1 (1.8)	0.022
Lymphocyte count (10^3/μL)	2.0 (1.9)	2.3 (2.1)	0.142
FVC (%, predicted)	95.2 (13.0)	68.9 (9.2)	< 0.001
FEV_1 (%, predicted)	98.7 (12.5)	69.7 (8.4)	< 0.001
FEV_1/FVC (%)	78.1 (5.1)	76.7 (4.9)	0.001
CERAD	24.8 (6.2)	24.6 (6.0)	0.719
Animal fluency test	17.2 (5.6)	15.2 (5.5)	< 0.001
Digit symbol substitution test	49.0 (18.6)	44.9 (15.7)	0.004
Global cognition score	0.3 (2.5)	-0.3 (2.2)	0.003
Categorical variables, n (%)			
Female	299 (53.1)	99 (58.6)	0.210
Race or ethnicity			< 0.001
Non-Hispanic White	206 (36.6)	25 (14.8)	
Non-Hispanic Black	150 (26.6)	91 (53.8)	
Others	207 (36.8)	53 (31.4)	
Education level			0.066
≤High school	263 (46.7)	96 (56.8)	
College	157 (27.9)	40 (23.7)	
> College	143 (25.4)	33 (19.5)	
Smoking[a]	243 (43.2)	85 (50.3)	0.102
Pack-years of smoking	17.5 (1.9)	24.6 (4.1)	0.118
Alcohol intake ≥ 12 drinks/year	376 (66.8)	105 (62.1)	0.264
Hypertension	304 (54.0)	118 (69.8)	< 0.001
Diabetes mellitus	107 (19.0)	58 (34.3)	< 0.001
Stroke	28 (5.0)	13 (7.7)	0.178
Heart failure	18 (3.2)	21 (12.4)	< 0.001
Coronary artery disease	42 (7.5)	37 (21.9)	< 0.001

[a]Smoking: ever smoking and current smoking were considered to have a smoking status and never smoking was thought to have a non-smoking status

Data are presented as mean (SD) or frequency (%). All *P* values were calculated with a two-sided significance level of 0.05. CERAD, Consortium to Establish a Registry for Alzheimer's Disease; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; HDL, high density lipoprotein; LDL, low density lipoprotein; PRISm, preserved ratio impaired spirometry; SD, standard deviation

Lung function and cognition

Table 2 depicts the associations between lung function and cognitive assessment after adjustments. In Model 0, participants with PRISm exhibited negative associations with three cognitive function tests and global cognition compared with those with normal spirometry. Of these associations, the impact magnitude in the CERAD test was relatively minor (β = -0.166; 95% CI = -0.331 to -0.001; p=0.049). In the multivariate adjusted Model 1 (adjusted for Model 0 plus education level, smoking status, pack-years of smoking, and BMI), participants with PRISm had substantially poorer verbal fluency (AFT: β = -0.410; 95% CI = -0.712 to -0.108; p=0.008), poor processing speed (DSST: β = -0.213; 95% CI = -0.355 to -0.072; p=0.003), and global cognition (β = -0.403; 95% CI = -0.710 to -0.095; p=0.011). Similar trends were noted in the multivariable models adjusted for all covariates (Model 2). Participants with PRISm were negatively associated with AFT (β = -0.300; 95% CI = -0.479 to -0.122; p=0.001), DSST (β = -0.157; 95% CI = -0.309

Table 2 The associations between PRISm and cognitive functions

	β coefficient (95% CI)		
	Model 0	**Model 1**	**Model 2**
CERAD			
Normal spirometry	0 [reference]	0 [reference]	0 [reference]
PRISm	**-0.166 (-0.331, -0.001) ***	-0.145 (-0.430, 0.140)	-0.069 (-0.243, 0.105)
Animal fluency test			
Normal spirometry	0 [reference]	0 [reference]	0 [reference]
PRISm	**-0.439 (-0.612, -0.267) *****	**-0.410 (-0.712, -0.108) ****	**-0.300 (-0.479, -0.122) ****
Digit symbol substitution test			
Normal spirometry	0 [reference]	0 [reference]	0 [reference]
PRISm	**-0.341 (-0.505, -0.176) *****	**-0.213 (-0.355, -0.072) ****	**-0.157 (-0.309, -0.004) ***
Global cognition score			
Normal spirometry	0 [reference]	0 [reference]	0 [reference]
PRISm	**-0.391 (-0.557, -0.225) *****	**-0.403 (-0.710, -0.095) ***	**-0.211 (-0.369, -0.053) ****

Model 0: adjusted for age, sex, and race; Model 1: adjusted for Model 0 plus education level, smoking status, pack-years of smoking, and body mass index; Model 2: adjusted for Model 1 plus HDL cholesterol, glycohemoglobin, white blood cell count, neutrophil count, hypertension, diabetes mellitus, stroke, heart failure, and coronary artery disease

* $p<0.05$, ** $p<0.01$, *** $p<0.001$. CERAD, Consortium to Establish a Registry for Alzheimer's Disease; PRISm, preserved ratio impaired spirometry; SE, standard error

Table 3 Mediation effects of systolic blood pressure on the association between PRISm and cognitive function[a]

β coefficient (95% CI)	CERAD	AFT	DSST	Global cognition
Mediator: Systolic blood pressure				
Path a	0.335 (0.145, 0.526) ***	0.335 (0.143, 0.528) ***	0.319 (0.127, 0.511) **	0.342 (0.150, 0.535) ***
Path b	-0.099 (-0.177, -0.022) *	-0.084 (-0.162, -0.005) *	-0.132 (-0.207, -0.057) ***	-0.112 (-0.179, -0.044) **
Path c (total effect)	-0.094 (-0.280, 0.092)	-0.357 (-0.547, -0.167) ***	-0.234 (-0.418, -0.050) *	-0.277 (-0.460, -0.093) **
Path c' (direct effect)	-0.061 (-0.248, 0.126)	-0.329 (-0.520, -0.137) ***	-0.192 (-0.376, -0.008) *	-0.230 (-0.413, -0.046) *
Indirect effect	-0.033 (-0.069, -0.005) *	-0.028 (-0.063, -0.002) *	-0.042 (-0.079, -0.011)	-0.047 (-0.087, -0.014) *
Proportion mediated	NA	7.9%	18.0%	17.1%

[a]X: treating lung function as ordinal variables (0 = normal spirometry, 1 = PRISm); M: systolic blood pressure level; Y: CERAD, AFT, DSST, and global cognition scores

Path a evaluated the link between PRISm (exposure) and SBP (mediator). Path b gauged the relationship between SBP (mediator) and cognitive assessment (outcome). Path c, representing the total effect, quantified the association between PRISm (exposure) and cognitive assessment (outcome). The mediated proportion was calculated using the following formula: $\beta_{\text{indirect effect}}/\beta_{\text{total effect}} \times 100\%$

* $p<0.05$, ** $p<0.01$, *** $p<0.001$. All continuous variables were analyzed after the z transformation. All models were adjusted for age, sex, race, education level, smoking status, pack-years of smoking, body mass index, HDL cholesterol, glycohemoglobin, white blood cell count, neutrophil count, hypertension, diabetes mellitus, stroke, heart failure, and coronary artery disease. AFT, animal fluency test; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; DSST, digit symbol substitution test; NA, not applicable; PRISm, preserved ratio impaired spirometry; SE, standard error

to -0.004; $p=0.044$) and the global cognition score (β = -0.211; 95% CI = -0.369 to -0.053; $p=0.009$).

Mediation analysis

PRISm was significantly associated with AFT (β = -0.357; 95% CI = -0.547 to -0.167; $p<0.001$), DSST (β = -0.234; 95% CI = -0.418 to -0.050; $p=0.013$), and global cognition score (β = -0.277; 95% CI = -0.460 to -0.093; $p=0.003$) when adjusted for potential confounders (Table 3). After adjustment for covariates and lung function, SBP had an inverse association with verbal fluency (AFT: β = -0.084; 95% CI = -0.162 to -0.005; $p=0.038$), processing speed (DSST: β = -0.132; 95% CI = -0.207 to -0.057; $p<0.001$), and global cognition (β = -0.112; 95% CI = -0.179 to -0.004; $p=0.001$). The mediation analysis revealed that SBP mediated 7.9% of the association between PRISm and verbal fluency, 18.0% of the association with processing speed, and 17.1% of the association with global cognition (Table 3; Fig. 2).

Discussion

Our primary findings revealed that participants with PRISm were associated with measures of global cognitive performance and executive function (AFT and DSST), but not with memory function (CERAD). Moreover, SBP might partially mediate these associations (17.1% for global cognition score, 7.9% for AFT, and 18.0% for DSST).

Although the relationship between chronic obstructive pulmonary disease (COPD) and the risk of dementia remains controversial, an increasing number of prospective cohort studies have indicated a direct association between COPD and neurofunctional impairment as well as cognitive decline [33, 34]. PRISm is a subset of preclinical COPD characterized by a proportional reduction in FEV_1% and FVC%. A UK Biobank study involving 350,000 participants revealed that PRISm status was correlated with an increased risk of developing respiratory difficulty and cardiovascular disease and experiencing

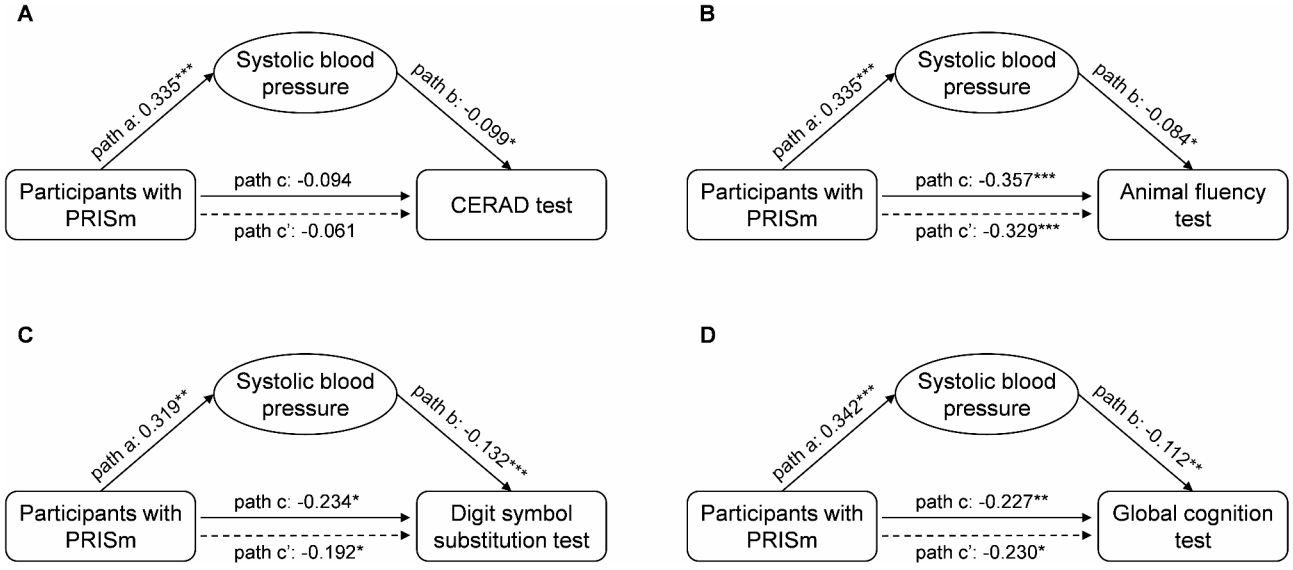

Fig. 2 Mediation analysis for PRISm, SBP and cognitive function. Path a: the relationship between PRISm (exposure) and SBP (mediator). Path b: the relationship between SBP (mediator) and cognitive function score (outcome). Path c: the relationship between PRISm (exposure) and cognitive function score (outcome). Path c': SBP mediation models of the relationship between PRISm (exposure) and cognitive function score (outcome). Mediation analyses were performed for CERAD (panel **A**), AFT (panel **B**), DSST (panel **C**), and global cognition (panel **D**) separately. *p* value<0.05, * *p*<0.05, ** *p*<0.01, *** *p*<0.001. AFT, animal fluency test; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; DSST, digit symbol substitution test; PRISm, preserved ratio impaired spirometry; SBP, systolic blood pressure

all-cause mortality [21]. These findings were confirmed by community-based cohort studies conducted in the United States [35], Rotterdam [14], and Canada [36], which indicated that compared to patients with normal spirometry, patients with PRISm had increased mortality rates and were at greater risk of experiencing adverse cardiovascular and respiratory outcomes. Recent research has focused on the relationship between PRISm and cognitive impairment, including its extreme manifestation, dementia. The results of two substudies based on the Rotterdam population suggested that compared to those with normal spirometry, participants with impaired baseline lung function had a 2.7-fold greater risk of developing cognitive decline [11, 15]. Our results were consistent with previous research results, establishing a substantial negative association between PRISm status and the scores on the AFT, DSST, and global cognitive function tests, even after adjusting for all potential influencing covariates.

The precise mechanisms responsible for the association between PRISm and cognitive decline remain unclear. Potential explanations for this association include shared pathogenic factors, systemic inflammation, and comorbidity risks. First, environmental pollution and inhalation exposure are correlated with the risk of PRISm [37], which is also a crucial risk factor for the development of dementia [38]. Heavy metal pollutants such as lead and mercury, when accumulated in serum, can not only damage alveolar type II epithelial cells and elastic fibers but also disrupt the blood-brain barrier and inhibit the aggregation of brain microtubule proteins, ultimately impairing the central nervous system [39]. Second, the comorbidities of PRISm, including obesity, diabetes, and metabolic syndrome, are also common risk factors for dementia. Previous studies have emphasized a remarkable association between the PRISm spirometry pattern and the risk of developing type 2 diabetes [40, 41]. Diabetes may increase the risk of neurodegeneration through tau-mediated mechanisms [42]. Additionally, elevated levels of inflammatory markers in PRISm may further induce glucose metabolism disturbances and insulin resistance, increasing the risk of dementia development [43]. Despite adjusting for these confounding factors in our models, a remarkable association between PRISm and cognitive impairment was still observed. Third, PRISm is strongly correlated with the occurrence of various cerebrovascular complications, including strokes and lacunar infarctions [15]. Cerebrovascular diseases may disrupt the homeostasis of amyloid proteins, leading to the deposition of insoluble amyloid proteins, the aggregation of tau proteins within neurons, and the formation of neurofibrillary tangles, ultimately resulting in neuronal dysfunction [44].

Identifying mediating factors, particularly those with adjustable characteristics, can aid in policy implementation and enhance intervention measures in both clinical and public health practices. The mediation analysis results indicated that the association between PRISm and cognitive decline (AFT by 7.9%, DSST by 18.0%, global cognition score by 17.1%) can be partially explained by

SBP. Vascular risk factors, including high blood pressure, are crucial in the pathogenesis of dementia, with more than half of patients with AD exhibiting mixed pathologic features, including cerebrovascular lesions upon autopsy [45]. Lipid deposition in vessel walls and microvascular fibrinoid necrosis are important underlying mechanisms of microvascular damage in patients with hypertension, and microvascular rarefaction may exacerbate preexisting cerebral white matter lesions with already low vascular density [46]. In addition to structural damage to cerebral vessels, hypertension is closely associated with the risk of developing cerebral vascular dysfunction. Studies have suggested that hypertension may decrease cerebral blood flow autoregulation through alterations in the structure of the cerebral vascular system, thus increasing the risk of developing cerebral ischemia [47]. Moreover, our results are supported by recent randomized clinical trials, which indicated that maintaining SBP below 120 mmHg effectively reduces the risk of developing mild cognitive impairment [10].

Disruption of the blood-brain barrier has long been considered a central mechanism of cerebral small vessel disease and an early biomarker of cognitive impairment [48], with previous research linking hypertension status with disruption of the blood-brain barrier [49]. Additionally, hypertension-induced deposition of amyloid-beta peptide, mediated by angiotensin II, can increase the risk of cerebral hemorrhage and accelerate cognitive decline [50]. Although the exact cellular and molecular mechanisms involved remain unclear, inflammation and oxidative stress may be key common factors in PRISm and hypertension-induced cerebral vascular changes and cognitive impairment. Considering our findings highlighting the mediating role of SBP in the relationship between PRISm status and the risk of developing cognitive decline, early identification of individuals at risk of developing cognitive impairment has emerged as a critical preventive strategy. Although the exact mechanisms and influencing factors remain unclear, PRISm is a reversible impaired lung function pattern, with studies indicating that it can be reverted to normal spirometry [51]. Therefore, the potential beneficial effects of early identification and intervention for PRISm on the risk of developing dementia could indicate PRISm as a modifiable risk factor that does not require measuring brain pathology and can be used for dementia prevention in memory clinics [52]. Controlling PRISm and SBP might have a synergistic effect on preventing cognitive decline or dementia. Managing associated risk factors can prevent or delay up to 40% of dementia cases [53], underscoring the importance of routine screening for PRISm and careful monitoring of blood pressure among older adults.

The main strength of this study was the use of unique resources from the NHANES database to examine the association between baseline PRISm and cognitive function tests in older adults. This study was novel because of the evaluation of the potential mediating role of blood pressure. Other strengths included the use of a large sample, the use of rigorous measurements of lung function, the use of multiple cognitive tests, and the use of adjustment models for various potential confounders. Nevertheless, this study also had several limitations. First, the NHANES survey included only US citizens, necessitating further research to establish the association between PRISm status and the risk of developing cognitive decline in Asians or other populations. Second, similar to most previous studies [16, 35], our study defined PRISm using pre-bronchodilator lung function values, and the definition of PRISm without considering post-bronchodilator lung volume measurements might have overlooked individuals with considerable bronchodilator responsiveness. Third, this is a cross-sectional study, and its ability to make causal inferences is limited. Before the results of the current study can be translated into practice, the directionality of the association between PRISm status and cognition status needs to be validated through long-term longitudinal research. Additionally, as a cross-sectional study, recall and selection bias may limit the generalizability of our conclusions. Finally, due to the low response rate, participants with missing spirometry and blood pressure data were excluded, which may have led to some degree of attrition bias.

Conclusions

In summary, our study suggested that PRISm status was associated with cognitive decline in older adults in the United States and that SBP potentially played a mediating role in the impact of PRISm on cognitive impairment. Early identification and management of PRISm, even the reversal of normal lung function, may reduce the pathological impact of hypertension on the progression of cognitive decline to dementia.

Abbreviations

AD	Alzheimer's disease
AFT	animal fluency test
BMI	body mass index
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
DBP	diastolic blood pressure
DSST	digit symbol substitution test
FEV_1	forced expiratory volume in 1 s
FVC	forced vital capacity
HDL	high-density lipoprotein
LDL	low-density lipoprotein
NCHS	National Center for Health Statistics
NHANES	National Health and Nutrition Examination Survey
PRISm	preserved ratio impaired spirometry
SBP	systolic blood pressure
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology

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Author contributions
QY had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. QY and TOY contributed to the study conception, study design, study management, data analysis, data interpretation, and manuscript writing. YCT, JJZ and TOY collected the data and performed data analysis, with verification of the analysis and results. TOY and YCT wrote the initial draft of the manuscript. QY made revisions to the manuscript. All authors provided critical feedback and made substantial revisions to the manuscript, and ultimately approved the final version for submission. The final responsibility for the decision to submit the manuscript for publication rested with all authors.

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Data availability
The data used in this study are publicly available as part of the National Health and Nutrition Examination Survey, which is distributed and sponsored by the Centers for Disease Control and Prevention (https://www.cdc.gov/nchs/nhanes/index.htm).

Declarations

Ethics approval and consent to participate
The data collected in the NHANES data set underwent review and approval by the Research Ethics Review Board of the NCHS. Additionally, all participants provided written consent prior to their involvement in the study. This study analyzed only data from publicly accessible databases, hence obviating the need for additional ethical review.

Competing interests
The authors declare no competing interests.

Consent to publish
Not applicable.

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