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Original Article

Interactions of physical activity and lung function on cognitive health in older adults: Joint association and mediation analysis

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ABSTRACT

Background: Maintaining cognitive health in old adults has become a significant public health challenge, with lung function and physical activity (PA) as essential modifiable factors. However, the joint and mediation effects of these two factors with cognition remain unclear.
Objectives: This study assesses the joint association and mediation effects of lung function and PA with cognition.
Design, setting, and participants: We utilized cross-sectional data from the 2011–2012 U.S. National Health and Nutrition Examination Survey, including adults aged 60–79 assessed for lung function, PA, and cognition.
Main outcomes and measures: Lung function included forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), peak expiratory flow (PEF) and FEV_1/FVC. PA was assessed using the Global Physical Activity Questionnaire, covering occupational PA (OPA), transportation-related PA (TPA), and leisure-time PA (LTPA). Cognition was evaluated using the Digit Symbol Substitution Test, Animal Fluency Test, Delayed Recall Test and Immediate Recall Test. Weighted multiple linear regression models were used to analyze the separate and joint associations of lung function and PA with cognition, while also exploring potential mediation effects between these factors.
Results: A total of 927 participants, representing 35,525,782 U.S. residents, were included, with a weighted median age of 65 (IQR, 63 -71) years, and 53.6 % were female. The results showed a significant positive association between lung function and cognitive function, with FEV_1, FVC, and PEF all positively correlated, while the FEV_1/FVC showed no notable link. Further analysis revealed the best cognitive performance observed in participants with active LTPA and the highest quartile of lung function, indicating a joint association of LTPA and lung function with cognition. Mediation analysis indicated that lung function mediated 24.1 % (95 %CI: 6.3 % - 47.0 %, $P = 0.03$) of the relationship between LTPA and cognition, while cognition mediated 10.2 % (95 %CI: 0.5 % - 27.0 %, $P = 0.04$) of the relationship between LTPA and lung function.
Conclusion: Lung function and cognition may have a bidirectional relationship. The combination of active LTPA and better lung function was strongly associated with higher cognition, highlighting the need to strengthen exercise focused on lung function to maintain cognitive health in older adults.

1. Introduction

As the global population ages, the challenges posed by cognitive impairment and dementia are becoming increasingly severe in healthcare and public health. Cognitive impairment affects up to 30 % of older adults [1,2]. Currently, around 55 million people worldwide are living with dementia, and this figure is expected to rise to 139 million by 2050 [3]. Cognitive impairment and dementia not only reduce quality of life and independence, but also increase healthcare demands, placing a heavy economic burden on families, healthcare systems, and society [3,4]. Due to the lack of effective treatments, identifying and intervening on modifiable risk factors is crucial for preventing and alleviating cognitive impairment.

Recent evidence has shown a significant association between declining lung function and future cognitive deterioration [5–7]. A large prospective cohort study involving 431,834 dementia-free individuals

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revealed that impaired lung function in middle age is associated with an increased risk of subsequent dementia [5]. Declining lung function can lead to cognitive impairment through various mechanisms, including chronic hypoxia, chronic systemic inflammation, and dysbiosis of lung microbiota [8–11].

Chronic hypoxia induced by impaired lung function leads to several pathological changes, including an increase in the production of amyloid-beta (Aβ) and pathological tau proteins, abnormal accumulation of autophagosomes, elevated oxidative stress levels, and activation of microglia and astrocytes, which release neuroinflammatory factors [8,10,11]. Additionally, the inflammatory cells, mediators, and oxidative stress markers elevated due to impaired lung function can "spill over" through the alveolar-capillary barrier into the systemic circulation, causing neuroinflammation, neuronal damage, and ultimately leading to cognitive dysfunction [10]. Lastly, impaired lung function causes dysbiosis of the lung microbiota. This dysbiosis, through both neural and humoral pathways, affects central nervous system, contributing to cognitive function decline [9].

However, few studies have explored the impact of cognitive impairment on lung function. It is noteworthy that pneumonia is the most common direct cause of death in Alzheimer's disease (AD) and other dementia patients [4,12–14]. A pre-COVID-19 autopsy study revealed that over half of AD patients died directly from respiratory diseases [14], suggesting potential pulmonary complications in AD patients.

Unhealthy lifestyles, such as a sedentary lifestyle, are modifiable risk factors in the onset of cognitive impairment and dementia [4]. Studies showed that physical activity (PA) or exercise can effectively prevent and delay cognitive decline in older adults [15–17]. Higher PA levels in middle-aged and older adults were associated with a 35 % reduced risk of cognitive decline and a 20 % lower risk of dementia [17].

Given that both PA and lung function exert positive effects on cognition, and considering the potential bidirectional relationship between lung function and cognition, it is plausible that complex interactions exist among PA, lung function, and cognition. Specifically, PA and lung function may have a joint association with cognitive function. Additionally, PA is an important strategy for delaying and improving the decline in lung function. Exercise has been shown to significantly improve lung function and cognitive function in patients with asthma and chronic obstructive pulmonary disease (COPD) [18,19], suggesting that PA may indirectly affect cognitive function by improving lung function. Similarly, PA may also exert an indirect effect on lung function through its impact on cognition. Furthermore, impaired lung function could limit the ability and motivation to engage in PA [20], thereby exacerbating cognitive decline in a vicious cycle. However, research exploring these complex interactions and underlying mechanisms remains insufficient.

Therefore, this study aims to explore the associations and potential interactions among PA, lung function, and cognition using data from the National Health and Nutrition Examination Survey (NHANES). Through this research, we hope to provide new evidence for exercise interventions that maintain cognitive health in older adults.

2. Methods

2.1. Study design and participants

We utilized data from the NHANES, a cross-sectional survey conducted by the National Center for Health Statistics (NCHS). It assesses the health of noninstitutionalized U.S. civilians through a complex, nationally representative sampling design. The protocols of the NHANES study were approved by the Institutional Review Board of the National Center of Health Statistics, and all participants provided informed written consent at enrollment.

Since only the 2011–2012 NHANES cycle assessed both PA, lung function, and cognitive function, we selected data from this cycle. NHANES 2011–2012 assessed cognitive function only in individuals aged 60 and older and evaluated lung function in participants aged 79 and younger, so this study included participants aged 60–79. Exclusion criteria were: (1) missing cognitive function data; (2) lack of lung function data; (3) lung function tests that did not meet the standards of the American Thoracic Society (ATS)/European Respiratory Society (ERS) (grades D, E, and F were excluded) [21,22]; (4) unavailability of PA assessment data. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [23].

2.2. Cognitive function assessment

Cognitive function was assessed using four tests: the Digit Symbol Substitution Test (DSST), Animal Fluency Test (AFT), Immediate Recall Test (IRT), and Delayed Recall Test (DRT) (Method S1). The DSST is widely regarded for its high sensitivity in detecting cognitive impairment even in individuals with generally good cognitive function. It may be more sensitive than the Mini-Mental State Examination (MMSE) in measuring dementia [24]. To preliminarily present the demographic characteristics of our study participants, and based on established thresholds for classifying cognitive impairment in previous literature [24–28], we used the 25th percentile of DSST to categorize participants into a normal cognition group and a low cognition group. Additionally, to create a composite score reflecting overall cognitive performance, each test score (DSST, AFT, IRT, and DRT) was standardized based on the sample's mean and standard deviation (SD). The average of these four standardized scores was then used as the global cognitive function score (z-score) [29,30].

2.3. Lung function assessment

Lung function was measured using the Ohio 822/827 dry rolling barrel spirometer, following the standards of the ATS/ERS [21,22]. The lung function variables measured in this study included forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), peak expiratory flow (PEF), and the FEV_1/FVC ratio. Similarly, FEV_1, FVC, and PEF were standardized based on their mean and SD, and their average was used as the global lung function score. According to ATS/ERS criteria for diagnosing lung function disorders, a decrease in the FEV_1/FVC ratio indicates obstructive ventilatory impairment, while restrictive ventilatory impairment is primarily characterized by a significant decrease in FVC, with a normal or increased FEV_1/FVC ratio [31].

2.4. Physical activity

PA was assessed using the Global Physical Activity Questionnaire, which includes occupation-related physical activity (OPA), transportation-related physical activity (TPA), and leisure-time physical activity (LTPA) (Method S2) [32,33]. Total PA is the sum of OPA, TPA, and LTPA. According to U.S. PA guidelines [34], total PA and domain-specific PA were categorized as follows: inactive group (0 MET·min/week), insufficiently active group (> 0 MET·min/week but < 600 MET·min/week), and sufficiently active group (≥ 600 MET·min/week).

2.5. Covariates

Demographic information extracted from the database included age, sex, race/ethnicity (non-Hispanic white, non-Hispanic black, other Hispanic, Mexican American, and other races), education level (less than 12th grade, high school grad/general education diploma or equivalent, some college or associate of arts degree, and college graduate or above), marital status (married/living together, widowed/divorced/separated, and never married), family income poverty ratio, smoking status (current smoker, former smoker, and never smoker), and alcohol consumption (non-drinker, 1–5 times per month, and more than 5 times per month). Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Additionally, data on hypertension, diabetes, and respiratory illness were also extracted.

2.6. Statistical analysis

Following NHANES analysis guidelines [35], all analyses utilized sampling weights, stratification, and clustering to account for the complex survey design. Continuous variables with a normal distribution were described using means (SD), while non-normally distributed variables were described using medians (interquartile range, IQR). Categorical variables were summarized using frequencies (proportions). Independent samples *t*-tests were used to compare two groups for continuous variables that were normally distributed with equal variance; rank-sum tests were applied for comparisons between two groups for non-normally distributed or unequal variance continuous variables. Categorical variables were analyzed using chi-square or Fisher's exact tests as appropriate. Based on the STROBE statement [23], weighted linear regression models assessed associations between lung function or PA and cognitive function, with results presented as Model 1 (unadjusted), Model 2 (adjusted for age, sex, BMI, and race), and Model 3 (further adjusted for smoking, drinking, marital status, education, hypertension, diabetes, respiratory illness, and family income poverty ratio). The restricted cubic spline (RCS) method evaluated nonlinear associations between lung function or PA and cognitive function [36,37]. In the joint analysis of PA and lung function on cognitive function, due to smaller sample sizes, the categories of total PA and LTPA were merged into inactive (0 MET·min/week) and active groups (> 0 MET·min/week) [38,39]. Mediation analysis was used to assess the indirect effects of PA on cognition through lung function, as well as the indirect effects of PA on lung function through cognitive function, in order to confirm the bidirectional influence between lung function and cognitive function [39]. We further conducted sensitivity analyses to assess the robustness of the results, including subgroup analyses and multiple imputations [40]. Multiple imputations utilized the chained equations method in R, repeated five times, to address missing data on BMI, education level, and smoking status [40,41]. A two-tailed P-value of < 0.05 was considered statistically significant, with data processing and graphical generation performed using R 4.4.0 (http://www.r-project.org/).

3. Results

3.1. Baseline characteristics of the participants

During the 2011–2012 cycle of NHANES, a total of 9756 participants were surveyed. We included 1428 participants aged 60–79 years in this study, all of whom were required to undergo assessments of PA, lung function, and cognitive function. Then, we excluded 280 participants who lacked cognitive function data, 179 participants who lacked lung function data, and a further 42 participants whose lung function tests did not meet ATS/ERS standards. Ultimately, 927 participants were included in this study (Fig. S1), representing 35,525,782 people in the U.S. The weighted median age was 65 (IQR, 63 - 71) years, with female accounting for 53.6 %, and non-Hispanic Whites constituting the majority of the study population (79.1 %).

In this study, 240 participants (13 %) were categorized as low cognition. Table 1 shows the low cognition group is older, has a higher proportion of non-Hispanic Blacks and Hispanics, lower educational attainment, a higher rate of current smoking, a lower family income poverty ratio, and higher prevalence rates of hypertension and diabetes compared to the normal cognition group.

The low cognition group had significantly lower FEV_1, FVC, and PEF values than the normal cognition group ($P < 0.01$), but no significant difference in the FEV_1/FVC ratio ($P = 0.31$). They also reported lower total PA levels ($P = 0.02$), with significant differences in LTPA ($P < 0.001$) and a higher proportion of inactive LTPA participants (70.7 % vs. 49.0 %, $P < 0.001$). No significant differences were found in OPA and TPA between the groups ($P > 0.05$ for all). Table S1 summarizes the unweighted demographic characteristics of the participants and shows similar results.

3.2. Association between lung function and cognitive function

Table 2 presents the results of linear regression models analyzing the association between lung function and cognitive function. In the fully adjusted model, lung function was positively associated with cognitive function, with each 1 SD increase in global lung function corresponding to a 0.14 SD increase in global cognitive function (95 % CI: 0.04 - 0.23, $P < 0.001$). FEV_1, FVC, and PEF were positively associated with cognitive function, while FEV_1/FVC was not ($P > 0.05$). Additionally, global lung function was significantly correlated with DSST and AFT scores, increasing by 3.5 points (95 % CI: 1.0 - 6.0, $P < 0.001$) and 1.3 points (95 % CI: 0.21 - 2.3, $P < 0.001$) per 1 SD increase in global lung function, respectively, but was not significantly associated with DRT and IRT total scores.

RCS visualizations showed a positive nonlinear relationship between global lung function, FEV_1, and FVC with cognitive function (P-non-linear = 0.01, 0.01, and 0.004, respectively), while PEF had a positive linear association (P-non-linear = 0.20), and FEV_1/FVC was not significantly associated (Fig. 1A-E). Fig. 1F-I indicate that global lung function had a positive nonlinear relationship with DSST (P-non-linear < 0.001) and a positive linear relationship with AFT (P-non-linear = 0.38), with no significant associations for DRT and IRT total scores. Table S2 and Figure S2 present detailed results of the linear regression models and RCS visualizations for various indicators of lung function and cognitive function, respectively.

3.3. Association between PA and cognitive function

Next, we further analyzed the linear relationship between total PA, specific domain PA, and cognitive function. In the fully adjusted model, total PA was positively associated with global cognition, AFT, and DSST, but not with DRT or IRT total scores. Compared with the Inactive group, the sufficiently active group showed an increase of 0.22 SD in global cognitive function (95 % CI: 0.01 - 0.43, $P = 0.01$), 2.13 points in AFT (95 % CI: 0.48 - 0.85, $P = 0.003$), and 4.24 points in DSST (95 % CI: 0.36 - 8.07, $P = 0.02$). Similarly, LTPA was positively associated with global cognition, AFT, and DSST scores, while no significant associations were observed with DRT or IRT scores (Table S3, Fig. S3). Compared with the Inactive group, the Sufficiently active LTPA group showed an increase of 0.23 SD in global cognitive function (95 % CI: 0.02 - 0.44, $P = 0.02$), 2.35 points in AFT (95 % CI: 0.52 - 4.02, $P = 0.003$), and 4.72 points in DSST (95 % CI: 0.97 - 8.38, $P = 0.003$). However, there were no significant associations between OPA, TPA, and cognitive function (Table S4 and S5, Fig. S4).

3.4. Joint association of PA and lung function with cognitive function

Following the analysis of the independent associations between PA, lung function, and cognition, we examined their combined effects. The joint analysis revealed that the active LTPA combined with good lung function was linked to better cognitive performance. Specifically, in the fully adjusted model, compared to the inactive LTPA and the lowest quartile of global lung function group (Q1), the active LTPA and the highest quartile of lung function group (Q4) showed the best cognitive function ($\beta = 0.83$, 95 % CI: 0.56 - 1.10, $P = 0.009$) (Table 3). Similarly, compared to the combination of inactive LTPA and Q1 lung function, the combination of active LTPA and Q4 lung function also exhibited the best cognitive performance: FEV_1 ($\beta = 0.75$, 95 % CI: 0.51 - 0.99, $P < 0.001$); FVC ($\beta = 0.81$, 95 % CI: 0.57 - 1.06, $P = 0.007$); and PEF ($\beta = 0.75$, 95 % CI: 0.50 - 0.99, $P = 0.009$). Additionally, total PA and lung function also exhibited joint association with cognition (Table S6).

Interaction analysis revealed that lung function was significantly positively associated with global cognitive function at low or insufficient LTPA levels, and not at sufficient LTPA level. However, the interaction between LTPA and lung function was not statistically significant (*P* for interaction > 0.05) (Fig. S5).

Table 1
Demographic and clinical characteristics of the study population.

Characteristics	Overall, $N = 927$ (100 %)	Distribution of cognitive performance		
		Normal cognition, $N = 687$ (87 %)	Low cognition, $N = 240$ (13 %)	P Value
Age, median (IQR), y	65 (63 - 71)	65 (63 - 70)	70 (63 - 75)	**0.007**
Sex, n (%)				0.31
Female	468 (53.6)	369 (54.2)	99 (49.7)	
Male	459 (46.4)	318 (45.8)	141 (50.3)	
Body mass index, mean (SD), kg/m^2	29.3 (6.2)	29.3 (6.1)	29.4 (6.9)	0.97
Race, n (%)				**<0.001**
Mexican American	70 (2.7)	46 (2.0)	24 (7.6)	
Other Hispanic	116 (4.1)	55 (2.2)	61 (17.3)	
Non-Hispanic White	355 (79.1)	319 (84.0)	36 (45.3)	
Non-Hispanic Black	285 (8.8)	187 (6.7)	98 (23.8)	
Other/multiracial	101 (5.3)	80 (5.1)	21 (6.1)	
Education level, n (%)				**< 0.001**
Less than 12th grade	242 (15.5)	94 (9.6)	148 (56.4)	
High school grad/GED or equivalent	208 (21.0)	162 (20.7)	46 (23.3)	
Some college or AA degree	259 (29.7)	226 (32.2)	33 (11.9)	
College graduate or above	217 (33.9)	204 (37.5)	13 (8.4)	
Smoke group, n (%)				**0.02**
Current smoker	136 (13.4)	87 (12.1)	49 (22.4)	
Former smoker	336 (37.2)	255 (37.5)	81 (34.9)	
Never smoker	454 (49.4)	344 (50.4)	110 (42.7)	
Alcohol intake, n (%)				**0.004**
Non-drinker	281 (23.8)	194 (21.7)	87 (39.0)	
1–5 drinks/month	453 (47.3)	324 (47.4)	129 (46.4)	
5+ drinks/month	187 (28.9)	166 (30.9)	21 (14.6)	
Marital status, n (%)				0.05
Married/Living together	538 (68.3)	411 (70.2)	127 (54.9)	
Widowed/divorced/separated	301 (25.4)	214 (24.0)	87 (35.0)	
Never married	79 (6.3)	57 (5.8)	22 (10.1)	
Family income poverty ratio, median (IQR)	3.4 (1.8 - 5.0)	3.8 (2.1 - 5.0)	1.6 (1.0 - 2.7)	**< 0.001**
Hypertension, n (%)	543 (54.8)	386 (52.5)	157 (70.7)	**0.004**
Diabetes, n (%)	216 (19.0)	135 (16.3)	81 (38.0)	**0.004**
Respiratory illness, n (%)	184 (20.9)	141 (20.9)	43 (21.1)	0.95
Forced expiratory volume in 1 second, mean (SD), ml	2494 (746)	2539 (745)	2177 (669)	**< 0.001**
Forced vital capacity, mean (SD), ml	3454 (1020)	3504 (1017)	3105 (965)	**0.002**
Peak expiratory flow, mean (SD), ml/s	7166 (2151)	7334 (2105)	5996 (2106)	**< 0.001**
FEV_1/FVC, mean (SD)	0.7 (0.1)	0.7 (0.1)	0.7 (0.1)	0.31
Total physical activity, median (IQR), MET·min/week	960 (0 - 2640)	1020 (0 - 2880)	360 (0 - 1625)	**0.02**
Total physical activity group, n (%)				**0.001**
Inactive	281 (27.7)	184 (25.3)	97 (44.1)	
Insufficiently active	279 (29.3)	215 (29.4)	64 (28.8)	
Sufficiently active	367 (43.0)	288 (45.3)	79 (27.1)	
Occupation-related physical activity, median (IQR), MET·min/week	0 (0 - 855)	0 (0 - 866)	0 (0 - 493)	0.19
Occupation-related physical activity group, n (%)				0.12
Inactive	601 (60.0)	421 (58.6)	180 (70.2)	
Insufficiently active	80 (10.3)	70 (11.0)	10 (5.2)	
Sufficiently active	246 (29.7)	196 (30.4)	50 (24.6)	
Transportation-related physical activity, median (IQR), MET·min/week	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0.41
Transportation-related physical activity group, n (%)				0.51
Inactive	691 (77.4)	509 (76.8)	182 (81.6)	
Insufficiently active	87 (8.0)	69 (8.3)	18 (5.8)	
Sufficiently active	149 (14.6)	109 (14.9)	40 (12.7)	
Leisure-time physical activity, median (IQR), MET·min/week	0 (0 - 960)	120 (0 - 1030)	0 (0 - 120)	**< 0.001**
Leisure-time physical activity group, n (%)				**< 0.001**
Inactive	522 (51.7)	361 (49.0)	161 (70.7)	
Insufficiently active	138 (13.2)	101 (13.0)	37 (14.4)	
Sufficiently active	267 (35.1)	225 (38.0)	42 (14.9)	

Abbreviations: FEV_1/FVC, Forced Expiratory Volume in 1 second / Forced Vital Capacity. GED, general education diploma; AA, associate of arts; Continuous variables are presented as mean (SD) or median (IQR), as appropriate; categorical variables are presented as frequency (percentage).

3.5. Mediation of lung function and cognition in PA effects

Next, we conducted a mediation analysis to explore the complex interactions between PA, lung function, and cognitive function. Fig. 2A illustrates that LTPA has a significant direct effect on cognitive function, and is positively correlated with lung function, which in turn is positively correlated with cognitive function. Lung function acted as a mediator in the relationship between LTPA and global cognition, with a mediation effect of 24.1 % (95 % CI: 6.3 % - 47.0 %, $P = 0.03$). Further analysis showed that FEV_1, FVC and PEF all served as mediators in the association between LTPA and global cognition ($P = 0.03$, 0.04 and 0.03, respectively).

Fig. 2B demonstrates that cognition mediated 10.2 % (95 % CI: 0.5 % - 27.0 %, $P = 0.04$) of the association between LTPA and global lung

Table 2
Linear regression analysis of the association between lung function and cognitive function.

Cognitive function	Lung function	Model 1		Model 2		Model 3	
		Beta (95 % CI)	*P* value	Beta (95 % CI)	*P* value	Beta (95 % CI)	*P* value
Global cognitive function	**Global lung function**	0.12 (0.06, 0.18)	**< 0.001**	0.26 (0.16, 0.36)	**< 0.001**	0.14 (0.04, 0.23)	**< 0.001**
Global cognitive function	**FEV_1 (ml, quartile)**		**< 0.001**		**< 0.001**		**0.009**
	Q1 (1541 ± 272)	Reference		Reference		Reference	
	Q2 (2065 ± 121)	0.50 (0.24, 0.76)		0.35 (0.12, 0.58)		0.25 (0.04, 0.46)	
	Q3 (2517 ± 159)	0.42 (0.24, 0.61)		0.42 (0.25, 0.58)		0.30 (0.06, 0.54)	
	Q4 (3297 ± 413)	0.49 (0.28, 0.69)		0.61 (0.36, 0.87)		0.32 (0.07, 0.57)	
	FVC (ml, quartile)		**< 0.001**		**< 0.001**		**< 0.001**
	Q1 (2132 ± 312)	Reference		Reference		Reference	
	Q2 (2787 ± 155)	0.50 (0.21, 0.78)		0.44 (0.20, 0.68)		0.34 (0.06, 0.63)	
	Q3 (3394 ± 192)	0.49 (0.28, 0.69)		0.55 (0.31, 0.79)		0.35 (0.08, 0.61)	
	Q4 (4509 ± 607)	0.38 (0.13, 0.63)		0.69 (0.39, 0.99)		0.40 (0.14, 0.66)	
	PEF (ml/s, quartile)		**< 0.001**		**< 0.001**		**0.001**
	Q1 (4349 ± 953)	Reference		Reference		Reference	
	Q2 (6058 ± 378)	0.39 (0.21, 0.58)		0.23 (0.06, 0.40)		0.15 (−0.05, 0.34)	
	Q3 (7448 ± 462)	0.40 (0.25, 0.55)		0.39 (0.27, 0.50)		0.28 (0.10, 0.46)	
	Q4 (9665 ± 1066)	0.37 (0.19, 0.55)		0.60 (0.38, 0.82)		0.28 (0.03, 0.54)	
	FEV_1/FVC (quartile)		**0.005**		0.40		0.81
	Q1 (0.63 ± 0.07)	Reference		Reference		Reference	
	Q2 (0.72 ± 0.01)	0.07 (−0.16, 0.29)		−0.04 (−0.25, 0.18)		0.01 (−0.22, 0.24)	
	Q3 (0.77 ± 0.01)	0.22 (0.08, 0.37)		0.07 (−0.05, 0.20)		0.05 (−0.09, 0.19)	
	Q4 (0.83 ± 0.03)	0.12 (−0.05, 0.29)		0.01 (−0.15, 0.17)		0.05 (−0.16, 0.25)	
DSST Sore	**Global lung function**	3.14 (1.82, 4.52)	**< 0.001**	6.83 (4.81, 8.92)	**< 0.001**	3.52 (1.02, 6.05)	**< 0.001**
AFT Sore	**Global lung function**	1.58 (0.82, 2.39)	**< 0.001**	2.13 (1.02, 3.25)	**< 0.001**	1.31 (0.22, 2.32)	**0.005**
DRT Sore	**Global lung function**	−0.02 (−0.24, 0.21)	0.91	0.22 (−0.15, 0.59)	0.20	0.10 (−0.28, 0.48)	0.50
IRT Total Sore	**Global lung function**	0.12 (−0.14, 0.38)	0.32	0.73 (0.26, 1.2)	**< 0.001**	0.31 (−0.05, 0.67)	**0.04**

Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow; DSST, digit symbol substitution test; AFT, animal fluency test; DRT, delayed recall test; IRT, immediate recall test. Q1, first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile. Model 1 served as the unadjusted analysis; Model 2: adjusted for age, sex, BMI and race; Model 3: adjusted for age, sex, BMI, race, marital status, smoking status, alcohol use, hypertension, diabetes, respiratory illness, education level, and family income poverty ratio.

function. Further analysis revealed that AFT and DSST mediated the association between LTPA and global lung function ($P < 0.05$), while DRT did not show a significant mediation effect ($P = 0.58$). Similarly, cognition also mediated the association between total PA and lung function, while lung function mediated the relationship between total PA and cognition (Fig. S6). These findings suggest that the positive effect of PA on cognitive health may be partly mediated by an improvement in lung function, and the improvement in lung function may, in turn, be partly mediated by PA-related enhancement in cognitive function.

3.6. Sensitivity analysis

Finally, we performed sensitivity analyses to assess the robustness of our results. Subgroup analyses showed that the positive association between global lung function and global cognitive function remained significant across various subgroups, including age, sex, BMI, smoking status, hypertension, diabetes, and respiratory illness (Table S7). Additionally, LTPA and global lung function showed joint associations across all above subgroups (Tables S8–14). There was no significant difference in the variables before and after imputation (Table S15). After imputation, the analysis continued to show a significant positive association between lung function and cognition (Table S16), with consistency across different subgroups (Table S17).

4. Discussion

In this study, we found that lung function was significantly positive association with cognitive function, with FEV_1, FVC, and PEF positively correlated, while FEV_1/FVC showed no significant correlation. The study also revealed significant positive correlations between total PA, LTPA, and cognitive function, while no correlations were found between OPA, TPA, and cognitive function. Further analysis suggested that PA and lung function have a joint association with cognitive function. Lung function partially mediated the relationship between PA and cognitive function, and cognitive function also mediated the association between PA and lung function. These findings highlight the importance of considering both lung function and PA in cognitive health; enhancing lung function based on PA may help slow cognitive decline and promote healthy aging in older adults.

Substantial evidence has indicated that lung dysfunction is one of the important modifiable risk factors for cognitive impairment and dementia [7,42]. Our findings align with previous studies that reported a significant positive correlation between lung function and cognitive function in older adults [7,42]. We further observed that FVC was positively correlated with cognition, while FEV_1/FVC showed no correlation. This pattern is characteristic of restrictive ventilatory impairment [31], suggesting that restrictive lung dysfunction is more closely associated with cognitive dysfunction. There is limited research on which type of pulmonary dysfunction is more strongly associated with cognitive function. Most studies have reported a closer correlation between restrictive ventilatory dysfunction and cognition compared to obstructive dysfunction [43–47]. But a study involving adults in Taiwan found that a low MMSE score was associated with obstructive lung diseases but not with restrictive lung diseases [48]. The discrepancies in these results may stem from variations in the study population's demographic characteristics and the assessment tools employed [48]. The mechanisms underlying these associations remain unclear. It is known that cerebrovascular diseases, which contribute to cognitive decline and dementia, are more common in individuals with restrictive ventilation patterns [49,50]. Restrictive ventilatory disorders can arise from changes in lung parenchyma or diseases affecting the pleura, chest wall, or neuromuscular system, leading to reduced lung volumes, ventilation-perfusion mismatch, and hypoxemia, which in turn cause impair cognitive function [44]. Moreover, restrictive ventilatory patterns (rather than obstructive patterns) are associated with the prevalence of obesity, diabetes and metabolic syndrome [51–53], which may contribute to cognitive impairment and dementia [4].

Table 3
Joint association of LTPA and lung function with cognitive function.

lung function	LTPA group	Model 1		Model 2		Model 3	
		Beta (95 % CI)	*P* value	Beta (95 % CI)	*P* value	Beta (95 % CI)	*P* value
Global lung function							
Q1	Inactive	Reference		Reference		Reference	
Q2	Inactive	0.26 (0.06, 0.45)	**0.03**	0.29 (0.11, 0.47)	**0.02**	0.29 (0.12, 0.47)	**0.04**
Q3	Inactive	0.28 (0.05, 0.51)	**0.04**	0.52 (0.29, 0.76)	**0.003**	0.51 (0.27, 0.74)	**0.02**
Q4	Inactive	0.07 (−0.17, 0.31)	0.58	0.54 (0.24, 0.85)	**0.01**	0.50 (0.20, 0.79)	**0.04**
Q1	Active	0.23 (0.03, 0.43)	0.05	0.18 (−0.02, 0.38)	0.12	0.18 (0.00, 0.36)	0.15
Q2	Active	0.52 (0.29, 0.75)	**0.002**	0.52 (0.31, 0.74)	**0.002**	0.45 (0.24, 0.66)	**0.02**
Q3	Active	0.55 (0.40, 0.71)	**< 0.001**	0.65 (0.47, 0.84)	**< 0.001**	0.61 (0.42, 0.81)	**0.009**
Q4	Active	0.43 (0.18, 0.67)	**0.007**	0.92 (0.63, 1.20)	**< 0.001**	0.83 (0.56, 1.10)	**0.009**
Forced expiratory volume in 1 second (FEV_1)							
Q1	Inactive	Reference		Reference		Reference	
Q2	Inactive	0.52 (0.23, 0.82)	**0.006**	0.37 (0.14, 0.61)	**0.02**	0.35 (0.13, 0.56)	**0.04**
Q3	Inactive	0.30 (−0.02, 0.61)	0.10	0.34 (0.13, 0.54)	**0.02**	0.34 (0.09, 0.59)	0.08
Q4	Inactive	0.44 (0.14, 0.74)	**0.02**	0.52 (0.25, 0.79)	**0.007**	0.48 (0.22, 0.75)	**0.04**
Q1	Active	0.34 (0.08, 0.60)	**0.03**	0.28 (0.09, 0.47)	**0.02**	0.23 (0.05, 0.41)	0.09
Q2	Active	0.69 (0.41, 0.98)	**0.001**	0.52 (0.28, 0.76)	**0.004**	0.46 (0.25, 0.67)	**0.02**
Q3	Active	0.68 (0.51, 0.86)	**< 0.001**	0.62 (0.42, 0.82)	**< 0.001**	0.58 (0.36, 0.79)	**0.01**
Q4	Active	0.70 (0.46, 0.93)	**< 0.001**	0.83 (0.59, 1.06)	**< 0.001**	0.75 (0.51, 0.99)	**< 0.001**
Forced vital capacity (FVC)							
Q1	Inactive	Reference		Reference		Reference	
Q2	Inactive	0.57 (0.25, 0.88)	**0.006**	0.50 (0.27, 0.74)	**0.004**	0.45 (0.22, 0.67)	**0.03**
Q3	Inactive	0.40 (0.07, 0.73)	**0.04**	0.50 (0.29, 0.71)	**0.002**	0.44 (0.25, 0.64)	**0.02**
Q4	Inactive	0.28 (−0.02, 0.59)	0.10	0.54 (0.26, 0.81)	**0.006**	0.45 (0.21, 0.68)	**0.03**
Q1	Active	0.36 (0.11, 0.62)	**0.02**	0.27 (0.09, 0.46)	**0.02**	0.25 (0.08, 0.41)	0.07
Q2	Active	0.66 (0.39, 0.94)	**0.001**	0.57 (0.33, 0.81)	**0.003**	0.51 (0.28, 0.73)	**0.02**
Q3	Active	0.77 (0.56, 0.98)	**< 0.001**	0.75 (0.50, 0.99)	**0.001**	0.66 (0.46, 0.86)	**0.007**
Q4	Active	0.66 (0.43, 0.89)	**< 0.001**	0.94 (0.67, 1.22)	**< 0.001**	0.81 (0.57, 1.06)	**0.007**
Peak expiratory flow (PEF)							
Q1	Inactive	Reference		Reference		Reference	
Q2	Inactive	0.36 (0.10, 0.62)	**0.02**	0.28 (0.10, 0.46)	**0.02**	0.28 (0.10, 0.45)	0.05
Q3	Inactive	0.37 (0.15, 0.60)	**0.008**	0.39 (0.18, 0.60)	**0.008**	0.40 (0.19, 0.62)	**0.04**
Q4	Inactive	0.33 (0.08, 0.58)	**0.03**	0.54 (0.28, 0.80)	**0.005**	0.52 (0.25, 0.78)	**0.03**
Q1	Active	0.37 (0.06, 0.68)	**0.04**	0.40 (0.14, 0.65)	**0.02**	0.36 (0.09, 0.63)	0.08
Q2	Active	0.64 (0.43, 0.85)	**< 0.001**	0.43 (0.23, 0.62)	**0.004**	0.39 (0.21, 0.56)	**0.02**
Q3	Active	0.64 (0.44, 0.84)	**< 0.001**	0.61 (0.47, 0.75)	**< 0.001**	0.56 (0.44, 0.69)	**0.003**
Q4	Active	0.58 (0.35, 0.81)	**< 0.001**	0.82 (0.55, 1.08)	**0.001**	0.75 (0.50, 0.99)	**0.009**

Abbreviations: LTPA, leisure-time physical activity. Q1, first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile. Model 1 served as the unadjusted analysis; Model 2: adjusted for age, sex and race; Model 3: adjusted for age, sex, race, marital status, smoking status, and alcohol use and diabetes.

A lack of PA is another significant modifiable risk factor in the onset of dementia [4,15–17]. We evaluated the association between specific domains of PA and cognitive function in older adults. Among different domains of PA, only LTPA were significantly associated with cognitive function, suggesting that reinforcing LTPA interventions may help mitigate cognitive decline in older adults. Our findings are consistent with those of other studies [32,54]. Research by He et al. found that only LTPA was significantly associated with a lower risk of depressive symptoms, while OPA and TPA were not correlated [32]. The mechanisms underlying these findings have not been fully elucidated. The main component of LTPA, exercise, refers to PA that is planned, organized, and reproducible to improve or maintain physical health [55]. Due to these characteristics, LTPA is more likely to provide sufficient intensity and a broader range of activities, such as aerobic and resistance exercises, which can collectively improve cardiorespiratory fitness, muscle fitness, and brain health [55,56]. Additionally, LTPA is often associated with social interaction, psychological relaxation, and enjoyment—factors that may help reduce stress, anxiety, and depression, thereby enhancing cognitive function [55]. Moreover, LTPA has been shown to improve sleep quality, and as sleep disturbances are linked to cognitive impairment, better sleep from LTPA may further benefit cognitive health [55]. In contrast, OPA and TPA typically involve repetitive tasks with limited social interaction, often linked to stress, insomnia, and negative emotions, which may weaken the cognitive benefits of PA [57–59].

Furthermore, in our study, LTPA was significantly positively correlated with DSST and AFT, but not with DRT or IRT. The DSST and AFT focus more on assessing executive function, while DRT and IRT are more focused on verbal memory [60,61]. These findings suggest that LTPA is more strongly associated with executive function, which is consistent with previous studies [56,62]. Since executive function is crucial for functional independence, such improvements are important for healthy aging [56].

Based on these findings about PA domains, the joint analysis was then carried out to examined both individual and combined effects on cognitive function. This analysis could offering more comprehensive intervention guidance for cognitive impairments [38]. Our study suggests a combined effect of PA and lung function in enhancing cognitive function. Currently, lung function improvement is primarily achieved through pulmonary rehabilitation, where exercise plays a central role [63,64]. Therefore, it is essential to actively encourage older adults with lung dysfunction or low exercise levels to participate in exercise to mitigate cognitive decline. It is recommend that older adults should engage in at least 150 mins of moderate-intensity or 75 mins of high-intensity PA per week, which should include a combination of aerobic, resistance, and balance exercises, to maintain cognitive health [34,56,65].

Next, we discussed the potential mechanisms of the interaction between PA, lung function and cognition. Exercise or PA may improves cognitive function through multiple mechanisms, including direct effects such as enhancing the metabolism of Aβ and tau proteins, increasing the secretion of brain-derived neurotrophic factor (BDNF), and inhibiting neuroinflammation [66–68]. In addition to these direct effects, exercise also contributes to cognitive health indirectly by enhancing cardiovascular and respiratory function, increasing cerebral blood flow, and improving sleep quality [66–68]. Our research found that lung func-

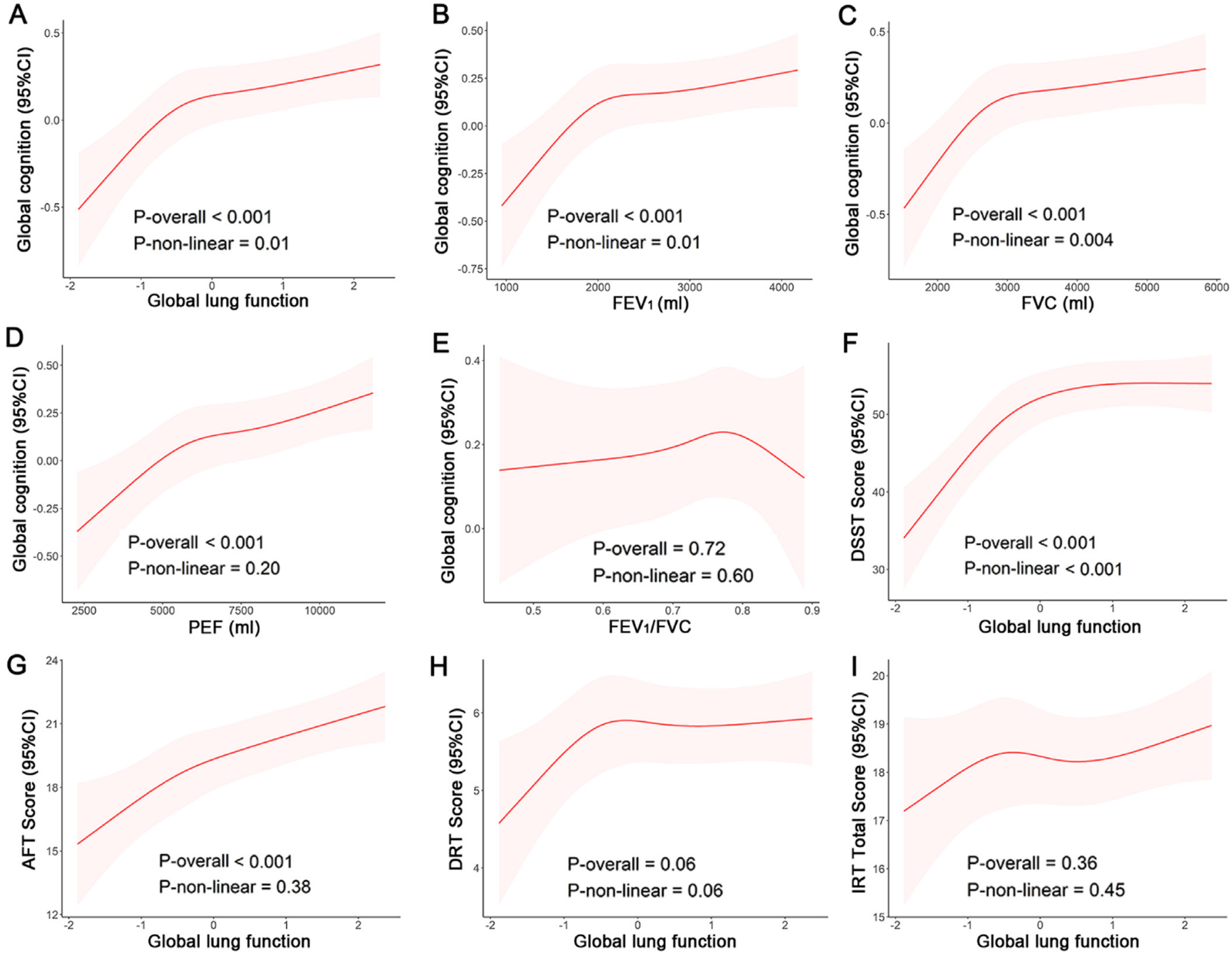

Fig. 1. Multivariable-adjusted restricted cubic spline curves of the association between lung function and cognitive function. (A-E) Associations between global lung function (A), FEV_1 (B), FVC (C), PEF (D), and FEV_1/FVC (E) with global cognitive function; (F-I) associations between global lung function with DSST (F), AFT (G), DRT (H), and IRT total score (I). Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow; DSST, digit symbol substitution test; AFT, animal fluency test; DRT, delayed recall test; IRT, immediate recall test. Data was adjusted for age, sex, BMI, race, marital status, smoking status, alcohol use, hypertension, diabetes, respiratory illness, education level, and family income poverty ratio. Shaded areas indicate 95 % Confidence Intervals.

tion mediates the relationship between exercise and cognition, with a mediation effect of 24.1 %. This suggests that nearly a quarter of the cognitive benefits from exercise could be attributed to its positive effect on lung health. Improvements in lung function may serve as an important pathway through which exercise exerts its positive effects on cognitive health. Clinically, this suggests that interventions to improve lung function, such as pulmonary rehabilitation or aerobic exercise [63,64], could help mitigate cognitive decline.

Lung dysfunction may lead to cognitive impairment through several underlying mechanisms. Chronic hypoxia in the central nervous system is one such mechanism. It upregulates the activity of beta-secretase 1 (BACE1), promoting the production of Aβ, while simultaneously reducing the levels of Aβ-degrading enzyme neprilysin (NEP). Additionally, chronic hypoxia enhances the seeding, propagation, and accumulation of pathological tau proteins, contributing to tau-related neurodegeneration. Chronic hypoxia also leads to mitochondrial dysfunction, oxidative stress, and synaptic dysfunction in the central nervous system [8,10,11]. Another mechanism involves chronic systemic inflammation, as lung dysfunction or pulmonary diseases are frequently accompanied by increased production of inflammatory cytokines and oxidative stress markers. These molecules can "spill over" from the alveolar-capillary barrier into systemic circulation, resulting in a chronic low-grade inflammatory state that further contributes to neuroinflammation in the central nervous system [10]. Finally, lung dysfunction or pulmonary diseases can lead to dysbiosis of the lung microbiome, where microorganisms and their metabolic products may enter the central nervous system via neural or humoral pathways, contributing to neuroinflammation [9].

In this context, the indirect effects of exercise on cognition through lung function may involve the following mechanisms. Exercise improves lung function, which alleviates chronic hypoxia and, in turn, enhances the metabolism of Aβ and Tau, as well as reduces mitochondrial dysfunction, oxidative stress, and synaptic dysfunction [8,11,18,19]. Additionally, it reduces chronic systemic inflammation associated with lung dysfunction, which helps alleviate inflammation in the central nervous system [66–69]. Lastly, exercise may restore lung microbiome balance, thereby mitigating inflammation and oxidative stress in the central nervous system that are caused by lung microbiome dysbiosis [70].

Our study also revealed that cognitive function mediates the relationship between exercise and lung function, with a mediation effect of 10.2 %. This suggests that approximately 10 % of the positive impact of exercise on lung function could be attributed to its beneficial effects on cognition. Improvements in cognitive function may act as a poten-

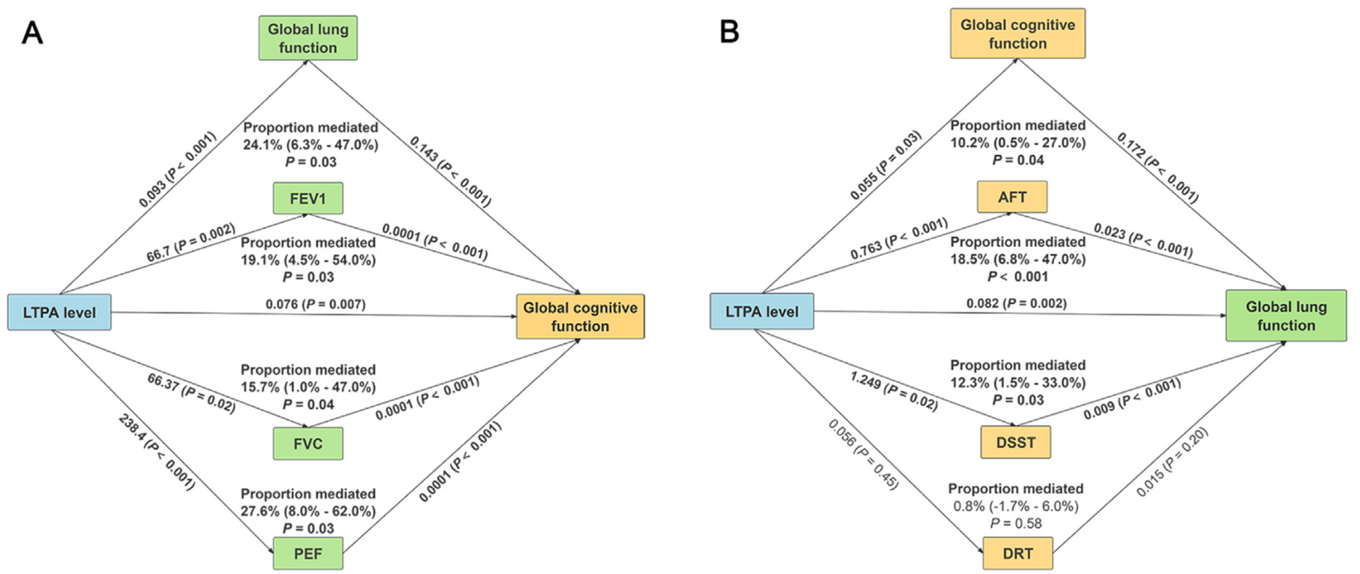

Fig. 2. Mediation of lung function and cognitive function in LTPA effects. (A) Mediation of lung function in the relationship between LTPA and global cognitive function; (B) mediation of cognition in the relationship between LTPA and global lung function. Abbreviations: LTPA, leisure-time physical activity; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow; AFT, animal fluency test; DSST, digit symbol substitution test; DRT, delayed recall test. Data was adjusted for age, sex, BMI, race, marital status, smoking status, alcohol use, hypertension, diabetes, respiratory illness and education level.

tial pathway through which exercise affects lung health. Previous studies have shown that exercise can enhance cognitive function [4,15–17]; however, there is limited research on whether cognitive function can affect lung function. Current evidence indicates that individuals with cognitive impairment or dementia may experience pulmonary complications that lead to declines in lung function [4,12–14]. Lung dysfunction in AD and dementia may arise through several underlying mechanisms. First, elevated peripheral systemic inflammation is commonly observed in AD and dementia. Studies show that inflammatory cytokines such as IL-10, IL-1β, IL-4, and IL-2 are dysregulated in AD and mild cognitive impairment (MCI), and this inflammation may contribute to lung function decline [71,72]. Second, the deposition of AD-related pathological proteins, such as Aβ and tau, in brainstem respiratory centers may impair lung function. Pretnar-Oblak et al. reported tau deposition in the medulla oblongata of an AD patient with respiratory difficulties [73], and Dutschmann et al. observed tau accumulation in the brainstem nuclei of Tau-P301 L AD mice [74]. These protein deposits may disrupt respiratory control, leading to impaired lung function. Finally, circulating Aβ may exert toxic effects on the lungs, triggering inflammation and further reducing lung function. Aβ, a toxic aggregate, is known to provoke excessive inflammatory responses, contributing to dysfunction in organs such as the heart and liver [75]. Autopsy studies have also revealed Aβ deposition in lung tissue in AD patients [76], potentially contributing to increased inflammation and further pulmonary impairment. The bidirectional relationship between lung function and cognition suggests that interventions targeting either of these domains could benefit both. For example, PA programs that incorporate breathing exercises may improve both lung function and cognitive health.

This study has several strengths. Initially, this study fills the gap in understanding the joint association of PA and lung function with cognition among old adults. Secondly, it employs mediation analysis to suggest a potential bidirectional relationship between lung function and cognitive function, while also providing preliminary evidence of the complex interactions that may exist between PA, lung function, and cognitive function. Third, it expands on previous research by investigating the associations between specific types of lung dysfunction, different domains of PA, and cognitive function.

However, while these findings are promising, further validation is needed to confirm these associations. Future studies should consider adopting longitudinal designs to better capture the causal relationships between PA, lung function, and cognition over time. Additionally, large-scale cohort studies involving more diverse populations could help generalize these findings. Clinical trials combining exercise training with breathing exercises or lung rehabilitation could provide more direct evidence for the observed associations. Furthermore, conducting single interventions targeting lung function (e.g., partial lung resection) in animal models to observe their effects on cognitive function, or vice versa, as well as incorporating biomarkers of lung function and cognition, could offer deeper insights into the biological pathways linking these factors.

Additionally, this study has also several limitations. First, as with any cross-sectional observational study, this study is unable to establish causal relationships between PA, lung function, and cognitive function. The observed associations may be influenced by reverse causality. For example, declines in lung function could lead to reduced PA, which in turn may contribute to cognitive decline, rather than the opposite. Future studies should employ longitudinal or experimental designs to more effectively determine the causal links between these factors. Second, it used data from the 2011–2012 NHANES cycle, where all relevant measures were available; thus, it is important to acknowledge the potential for selection bias. Future studies should utilize data from other cycles or clinical databases to expand the sample size to further validate the preliminary findings of this study. Third, as NHANES predominantly includes Non-Hispanic White participants, caution is needed when generalizing the results, and further research on other racial groups is required for validation. Fourth, due to sample size limitations, the classification of PA in the joint analysis of PA and lung function on cognition was relatively broad. Future studies with larger sample sizes are needed to refine PA categorization. Fifth, measurement errors due to self-reported questionnaires for PA and cognitive assessments may introduce biases, potentially affecting the results. Future research should aim to use more objective measurements to minimize these biases and improve accuracy.

5. Conclusion

Our study demonstrates that PA and lung function are jointly associated with cognitive function. Lung function mediates the relationship between PA and cognitive function, while cognitive function also acts as a mediator between PA and lung function. These findings highlight the potential bidirectional effects between lung function and cognition, emphasizing the need to strengthen PA focused on lung function to extend the cognitive health period in older adults.

Declaration of generative AI and AI-assisted technologies in the writing process

We declare that no generative AI or AI-assisted technologies were used in the writing process of this manuscript.

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Data sharing statement

No.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Peng Hu: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Dan Song:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Tian Heng:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Formal analysis, Data curation. **Ling-Ling Yang:** Writing – review & editing, Validation, Supervision, Formal analysis, Data curation. **Chuan-Chuan Bai:** Writing – review & editing, Validation, Formal analysis, Data curation. **Rui He:** Writing – review & editing, Validation, Data curation. **Tao Liu:** Writing – review & editing, Validation, Data curation. **Ya-Xi Luo:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Xiu-Qing Yao:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Funding acquisition, Data curation, Conceptualization.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2025.100090.

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