

Association Between Pulmonary Function, Respiratory Muscle Strength and Cognitive Function in Chinese Community-Dwelling Older Adults

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Purpose: Decline in pulmonary function (PF) and respiratory muscle strength (RMS) is influenced by environmental and genetic factors and is inconsistently linked to cognitive outcomes. This study explores the associations between PF, RMS, and cognitive function among community-dwelling older adults in China, analyzing interactions with APOE ϵ 4 and the mediating effect of serum total bilirubin.

Patients and Methods: About 1,081 Hubei Memory and Aging Cohort (HMACS) participants underwent PF (PEF, FEV1 and FVC), RMS (MIP and MEP) assessment, cognitive tests, APOE genotyping, and bilirubin measurement. Multivariate logistic regression and general linear regression were used to analyze associations.

Results: Among 1,081 participants (mean age 70.52 ± 5.55 years), 26.1% had cognitive impairment. Lower PF and RMS scores were associated with cognitive impairment. Higher comprehensive PF (c-PF) and RMS indices protected against cognitive impairment (eg, c-PF: OR = 0.482–0.609, $P < 0.05$; MEP: OR = 0.464, $P = 0.005$). PF and RMS indices correlated positively with global cognition, memory, language, and executive function. Sex differences were noted, with males ($n = 449$, 41.5%) showing associations between MIP/MEP and global cognition, memory, and language, while females ($n = 632$, 58.5%) showed broader associations. APOE ϵ 4 status ($n = 330$) did not affect these associations. Serum total bilirubin levels ($n = 977$) correlated with pulmonary and cognitive function but did not mediate the associations.

Conclusion: PF (especially PEF) and RMS (especially MEP) indices are significantly associated with cognitive function and impairment in older adults, independent of APOE ϵ 4 status. These findings provide biomarkers for assessing cognitive health risk and a basis for interventions targeting PF and RMS to preserve cognitive function.

Keywords: pulmonary function, respiratory muscle strength, cognitive impairment, cross-sectional study, older adults

Introduction

Pulmonary function (PF) and respiratory muscle strength (RMS)—key respiratory indicators—decline with aging or disease, showing asynchronous reductions in forced vital capacity (FVC), forced expiratory volume in one second (FEV1) and peak expiratory flow (PEF), and are co-regulated by environmental and genetic factors.^{1,2}

Existing studies link PF to cognition, with shared risks including aging, hypertension, cardiovascular disease, frailty, and smoking.^{3–5} European cohorts confirm poor baseline PF raises dementia and cognitive impairment risks,^{6–8} but conclusions remain controversial, potentially due to genetic (eg, APOE ϵ 4) and environmental interactions.^{9,10} Chinese community studies are limited: while PF correlates with global cognition,^{3,11} most focus on single indicators (eg, PEF, FEV1), lacking systematic analysis of PF/RMS with cognitive impairment or domain-specific decline. Thus, multi-indicator PF/RMS decline associations with cognitive outcomes in older adults need clarification.

The PF-cognition link may involve systemic inflammation, cerebral hypoperfusion from chronic hypoxia, microvascular damage, and brain atrophy.^{5,6} Total bilirubin, an endogenous antioxidant, may mediate this via free radical scavenging (protecting pulmonary tissue)^{12,13} and inhibiting oxidative stress/inflammation (alleviating neuronal damage);^{14,15} Reduced total bilirubin is linked to cognitive decline and stroke risk,^{16,17} supporting potential mediation.

Current cognitive impairment biomarkers have limitations: invasive cerebrospinal fluid markers,^{18–20} variable-sensitivity blood markers, costly/complex neuroimaging, and non-standardized extracellular vesicles.²¹ In contrast, PF/RMS indices are non-invasive, convenient, and reflect systemic health, addressing gaps in large-scale screening, long-term monitoring, and primary care—offering new insights for early cognitive impairment warning.

This study explores associations between PF (PEF, FEV1 and FVC), RMS (MIP and MEP), and cognitive impairment/function in Chinese community-dwelling older adults, analyzing APOE ϵ 4 interactions and total bilirubin mediation.

Methods

Study Design and Participants

Data were from the Hubei Memory and Aging Cohort Study (HMACS; ChiCTR1800019164), established in 2018 to investigate cognitive impairment prevalence, risk/protective factors in community-dwelling older adults (design/assessment details reported previously).²² For cohort establishment, urban participants were recruited by randomly selecting 4 districts in the Wuhan metropolitan area of Hubei Province and then 31 neighborhoods within these districts, while rural participants were from 4 randomly selected townships in Dawu County (a remote mountain area) and 48 villages under these townships, and all eligible participants were identified from the electronic health records (EHRs) of local hospitals and health centers and met the following a priori inclusion criteria: 1) registered residents in the sampled neighborhoods/villages with valid EHRs; 2) aged ≥ 65 years; 3) no prior diagnosis of dementia; 4) no medical records of schizophrenia, major depressive disorder, or life-threatening diseases; 5) able to complete physical and cognitive examinations. Residents living in nursing homes or psychiatric hospitals were excluded. PF testing was added in May 2023.

Of 1,820 initial participants, 739 were excluded based on strict, a priori defined eligibility criteria to ensure data quality and analytical validity ([Figure S1](#) for detailed exclusion workflow). The primary exclusion criteria were: (1) age < 65 years ($n = 97$; consistent with gerontological definitions of “older adults,” our study focused on participants ≥ 65 years); (2) non-cooperation with PF assessment ($n = 198$); (3) severe hearing/visual impairment ($n = 122$, which would compromise the validity of cognitive and PF measurements); and (4) other reasons ($n = 32$). Among the remaining 1,371 participants who completed the baseline interview, 290 were further excluded due to incomplete neuropsychological data ($n = 116$), repeated/unreliable PF data ($n = 141$), or poor coordination during PF testing ($n = 33$). Ultimately, 1,081 participants were included in the final analysis.

To evaluate potential selection bias, we compared baseline characteristics—including age, sex, educational attainment, physical activity levels, and chronic conditions—between included ($n = 1,081$) and excluded ($n = 739$) participants. No statistically significant differences were observed across all variables (all $p > 0.05$), with detailed comparisons provided in [Table S1](#).

This study was conducted in compliance with the Declaration of Helsinki. All procedures involving human participants were approved by the Medical Ethics Committee of Wuhan University of Science and Technology (Approval No.201845), and written informed consent was obtained from each participant prior to enrollment.

Measurements

Assessment of PF

PF was measured by trained physicians using a calibrated portable spirometer (X2210205000420 X2, SecG Medical Equipment Co., Ltd.) with three flow and volume settings. All assessments strictly adhered to the 2005 ATS/ERS international standards for spirometry. Participants sat with pinched noses, using a disposable mouthpiece: after 2 calm breaths, they inhaled deeply and exhaled continuously at maximum speed/force for ≥ 6 seconds. The test was repeated at least twice (a third if differences exceeded 5%).

PF predicted values were calculated via Global Lung Initiative 2012 equations,²³ accounting for sex, age, height, weight, and ethnicity; values $< 80\%$ of predicted were abnormal. The comprehensive PF (c-PF) index was the mean of z-scores for PEF, FEV1, and FVC and higher values indicate better function.

Assessment of RMS

MIP and MEP were measured via a calibrated portable RMS meter (MicroRPM, CareFusion, USA; flow sensor, accuracy $\pm 3\%$). Assessments followed the 2019 ATS/ERS guidelines for respiratory muscle testing: Participants sat with a disposable mouthpiece and nose clip. MIP was the maximum value from maximal inhalation (≥ 2 seconds) after calm exhalation to functional residual capacity; MEP was the maximum from maximal exhalation (≥ 2 seconds) after deep inhalation to total lung capacity. Each was measured at least 3 times (1-minute intervals), with the maximum valid value used. Valid measurements required a pressure plateau ≥ 1 second and $\leq 10\%$ difference between the two highest values. Inter-rater reliability was evaluated via duplicate assessments of 50 randomly selected participants by two trained physicians, yielding an intraclass correlation coefficient (ICC) of 0.92, confirming high reliability.

Results were reported as absolute values (cmH₂O) and % predicted (GLI-2012 Southeast Asia equations).²⁴ MIP < 60 cmH₂O (or $< 80\%$ predicted) indicated inspiratory dysfunction; MEP < 100 cmH₂O (or $< 70\%$ predicted) indicated expiratory dysfunction. The comprehensive RMS (c-RMS) index was the mean of MIP and MEP z-scores; higher values reflect better function.

Assessment of Neuropsychological and Diagnosis of Cognitive Impairment

Neurologists and trained medical postgraduates conducted standardized face-to-face assessments, including four subdomains and global cognitive function: memory (Auditory Verbal Learning Test), language (30-item Boston Naming Test, Animal Fluency Test), executive function (Trail Making Test A/B), and attention (Digit Span Test), global cognitive function was calculated as the mean of the four subdomains z-scores.

Cognitive impairment (MCI and dementia) was diagnosed per Chinese expert consensus.²⁵ MCI followed Petersen criteria;²⁶ dementia adhered to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria, confirmed via three steps: initial diagnosis by cognitive experts, review by data-collecting physicians, and final adjudication by senior neurologists.²⁷

Test for APOE ϵ Genotyping

APOE ϵ genotyping was performed using the MassARRAY iPLEX Gold system (Agena Bioscience, Inc). After clinical sample collection, DNA was extracted per standard protocols. Following PCR amplification, shrimp alkaline phosphatase (SAP) treatment removed excess deoxynucleoside triphosphates. Extension primers and iPLEX mixture were added to complete extension. After desalination, products were loaded onto chip plates for mass spectrometric analysis.

Biochemical and Hematological Biomarkers

Measured biomarkers included: inflammatory-related (leukocyte count; neutrophil, monocyte, lymphocyte, basophil, eosinophil percentages and absolute counts; high-sensitivity C-reactive protein; platelet count, volume distribution width, platelet-crit); erythrocyte-related (hematocrit, red blood cell count, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration); liver function-related (alanine aminotransferase, aspartate aminotransferase, AST/ALT ratio, total bilirubin, globulin, albumin, total protein, albumin/globulin ratio); renal function-related (urea, uric acid, creatinine, pH, urine specific gravity); and metabolites (homocysteine, vitamin B12, folic acid, total cholesterol, fasting blood glucose, low/high-density lipoprotein cholesterol, triglycerides).

Confounders

Confounders included demographic factors (sex, age, education, dwelling status, spouse, monthly income); lifestyle factors (smoking, drinking, physical activities, intellectual activities, BMI); and comorbidities (history of hypertension, diabetes, hyperlipidemia, coronary heart disease, cerebrovascular disease).

Statistical Analysis

Multiple Imputation by Chained Equations (MICE) addressed covariates with <10% missingness via 100 imputations (5 iterations); further details are provided in [Table S2](#). Imputation diagnostics confirmed model convergence (stable trace plots for all variables) and no significant differences between imputed and observed data distributions. Normally distributed continuous data are presented as $\bar{x} \pm s$; categorical data as n (%). Group differences were compared via chi-square and t-tests. Multivariate logistic regression and trend tests analyzed c-PF-cognitive impairment associations across four models: model 1 (c-PF only); model 2 (plus sociodemographics); model 3 (plus lifestyle); model 4 (plus comorbidities). Restricted cubic splines (knots at 10th, 50th, 90th percentiles of c-PF) visualized relationships. General linear regression analyzed associations of PF indices (PEF, FEV1 and FVC) and RMS indices (MIP and MEP) with global cognition and cognitive subdomains (standardized scores), with sex-stratified analyses for RMS indices.

Participants were grouped by PF (normal/abnormal) and APOE ϵ 4 status (negative/positive); ANOVA compared global cognition between groups, with LSD post-hoc tests. Laboratory blood biomarkers (inflammation-, red blood cell-, liver/renal function-, and metabolite-related) were correlated with c-PF and cognitive function via Pearson's r to identify potential mediators for mediation analysis.

Sensitivity analyses included subgroup analyses (by sex, age, smoking) with interaction tests, and association exploration after excluding participants with PF test quality < Grade D, extremely severe mixed ventilatory dysfunction, or dementia.

Analyses used IBM SPSS 26.0 and R 4.1.3. A two-tailed $P < 0.05$ was statistically significant.

Results

Study Flow and Clinical Characteristics

A total of 1,081 eligible HMAACS participants were included (mean age 70.52 ± 5.55 , mean education 12.04 ± 3.29 years), with 449 (41.5%) males. Among them, 799 (73.9%) had normal cognition and 282 (26.1%) had cognitive impairment. The latter showed lower global cognition and PF scores, with a higher proportion in Q1 for c-PF, MIP, and MEP ([Table 1](#)). APOE genotyping was completed in 330 participants, of whom 78 (23.6%) were ϵ 4 carriers and 252 (76.4%) were non-carriers.

Table 1 Characteristics of Study Participants by Cognitive Status

Characteristics	All Participants 1,081 (100%)	Normal 799 (73.9%)	Cognitive Impairment 282 (26.1%)	χ^2/t	P
Sex (Male), n (%)	449 (41.5%)	345 (43.2%)	104 (36.9%)	3.406	0.065
Age, $\bar{x} \pm s$	70.52 ± 5.55	70.24 ± 5.42	71.30 ± 5.85	-2.650	0.008
Education, $\bar{x} \pm s$	12.04 ± 3.29	12.40 ± 3.09	11.02 ± 3.62	5.708	< 0.001
Dwelling status (Living alone), n (%)	110 (10.2%)	79 (9.9%)	31 (11.0%)	0.279	0.598
Spouse (Yes), n (%)	899 (83.2%)	672 (84.1%)	227 (80.5%)	1.939	0.164
Monthly income, n (%)					
< CNY 2,000	35 (3.2%)	23 (2.9%)	12 (4.3%)	19.070	< 0.001
CNY 2,000 ~ 4,000	500 (46.3%)	341 (42.7%)	159 (56.4%)		
> CNY 4,000	546 (50.5%)	435 (54.4%)	111 (39.4%)		

(Continued)

Table 1 (Continued).

Characteristics	All Participants 1,081 (100%)	Normal 799 (73.9%)	Cognitive Impairment 282 (26.1%)	χ^2/t	P
BMI, kg/m ² , n (%)					
< 18.5	41 (3.8%)	32 (4.0%)	9 (3.2%)	5.356	0.147
18.5 ≤ BMI < 24	494 (45.7%)	379 (47.4%)	115 (40.8%)		
24 ≤ BMI < 28	440 (40.7%)	316 (39.5%)	124 (44.0%)		
≥ 28	106 (9.8%)	72 (9.0%)	34 (12.1%)		
Smoking (Yes), n (%)	259 (24.0%)	201 (25.2%)	58 (20.6%)	2.409	0.121
Drinking (Yes), n (%)	260 (24.1%)	199 (24.9%)	61 (21.6%)	1.224	0.269
Physical activities (Yes), n (%)	955 (88.3%)	706 (88.4%)	249 (88.3%)	0.001	0.978
Intellectual activities (Yes), n (%)	689 (63.7%)	523 (65.5%)	166 (58.9%)	3.918	0.048
Hypertension (Yes), n (%)	633 (58.6%)	462 (57.8%)	171 (60.6%)	0.681	0.409
Diabetes (Yes), n (%)	278 (25.7%)	205 (25.7%)	73 (25.9%)	0.006	0.940
Hyperlipidemia (Yes), n (%)	379 (35.1%)	280 (35.0%)	99 (35.1%)	0.000	0.985
Coronary heart disease (Yes), n (%)	173 (16.0%)	129 (16.1%)	44 (15.6%)	0.046	0.831
Cerebrovascular disease (Yes), n (%)	106 (9.8%)	80 (10.0%)	26 (9.2%)	0.148	0.700
ADL, $\bar{x} \pm s$	20.35 ± 1.78	20.31 ± 1.82	20.48 ± 1.66	-1.445	0.149
MoCA-B, $\bar{x} \pm s$	26.06 ± 3.36	27.09 ± 2.48	23.17 ± 3.81	16.079	< 0.001
Lung function measures, $\bar{x} \pm s$					
PEF (L/s)	3.40 ± 1.37	3.49 ± 1.36	3.16 ± 1.36	3.445	0.001
FEV1 (L)	2.06 ± 0.57	2.10 ± 0.56	1.94 ± 0.59	4.092	< 0.001
FVC (L)	2.75 ± 0.86	2.80 ± 0.85	2.59 ± 0.85	3.581	< 0.001
MIP (cmH ₂ O)	40.19 ± 15.41	41.17 ± 15.33	37.43 ± 15.32	3.520	< 0.001
MEP (cmH ₂ O)	56.64 ± 24.57	58.51 ± 24.59	51.37 ± 23.77	4.224	0.001
c-PF category, n (%)					
Q1	271 (25.0%)	173 (21.6%)	98 (34.8%)	22.972	< 0.001
Q2	270 (25.0%)	197 (24.7%)	73 (25.9%)		
Q3	270 (25.0%)	215 (26.9%)	55 (19.4%)		
Q4	270 (25.0%)	214 (26.8%)	56 (19.9%)		
MIP category, n (%)					
Q1	269 (24.9%)	181 (22.7%)	88 (31.2%)	12.683	0.005
Q2	254 (23.5%)	183 (22.9%)	71 (25.2%)		
Q3	281 (26.0%)	213 (26.7%)	68 (24.1%)		
Q4	277 (25.6%)	222 (27.8%)	55 (19.5%)		
MEP category, n (%)					
Q1	266 (24.6%)	173 (21.7%)	93 (33.0%)	19.035	< 0.001
Q2	265 (24.5%)	196 (24.5%)	69 (24.5%)		
Q3	271 (25.1%)	203 (25.4%)	68 (24.1%)		
Q4	279 (25.8%)	227 (28.4%)	52 (18.4%)		
Cognitive tests, $\bar{x} \pm s$					
Global (Z-score)	0.00 ± 1.00	0.30 ± 0.89	-0.85 ± 0.79	19.148	< 0.001
Memory (Z-score)	-0.02 ± 0.96	0.22 ± 0.91	-0.70 ± 0.75	16.629	< 0.001
Language (Z-score)	0.00 ± 1.00	0.19 ± 0.97	-0.53 ± 0.89	10.560	< 0.001
Execution (Z-score)	0.00 ± 1.00	0.21 ± 0.90	-0.61 ± 1.02	11.405	< 0.001
Attention (Z-score)	0.00 ± 0.83	0.16 ± 0.80	-0.46 ± 0.75	11.076	< 0.001

Note: Bold values indicate statistical significance at $p < 0.05$.

Abbreviations: BMI, body mass index; CNY, China Yuan; PEF, peak expiratory flow; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; MIP, maximal inspiratory pressure; MEP, maximum expiratory pressure; ADL, Activities of Daily Living; MoCA-B, Montreal Cognitive Assessment-B; c-PF, comprehensive pulmonary function; Z-, standardized score.

Correlation Between PF and RMS Indices

PF indices (PEF, FEV1 and FVC) and RMS indices (MIP and MEP) correlated positively ($r = 0.442$ – 0.932 , all $P < 0.01$), with strongest correlations between PEF-MEP ($r = 0.932$) and FEV1-FVC ($r = 0.805$) (Table S3).

In regression Model 1 (cognitive function) including PEF, FEV1, FVC, MIP and MEP, strong multicollinearity (eg, VIF = 8.057 for PEF, 7.986 for MEP) masked associations for PEF and FEV1 (Table S4). After constructing c-PF (combining PEF, FEV1 and FVC) for Model 2, c-PF, MIP and MEP (all VIF < 2.8) showed significant associations with cognitive function.

Correlation Between c-PF and Cognitive Impairment

In the fully adjusted multiple logistic regression model (Figure 1), higher c-PF scores were significantly associated with a reduced risk of cognitive impairment. Across c-PF quartiles, this risk reduction was statistically significant for Q2 (OR = 0.609, *P* = 0.025), Q3 (OR = 0.482, *P* = 0.003) and Q4 (OR = 0.525, *P* = 0.017) relative to Q1, with a clear downward trend (*P* for trend = 0.016). For RMS indices, MIP showed significant risk reductions in Q3 (OR = 0.612, *P* = 0.027) and Q4 (OR = 0.485, *P* = 0.004) (vs Q1), while MEP only reached significance in Q4 (OR = 0.464, *P* = 0.002) (vs Q1); both indices exhibited significant downward trends in cognitive impairment risk with increasing quartiles (*P* for trend = 0.001 and 0.003, respectively).

Treated as continuous, each 1-unit increase in c-PF was linked to 25.0% lower risk (OR = 0.750, *P* = 0.016), with a non-linear association (*P* non-linear = 0.017; Figure 2A).

Subgroup analyses (stratified by sex, age, and smoking status) showed better c-PF was linked to lower cognitive impairment risk in females (OR = 0.671, *P* = 0.027), individuals 70–80 years (OR = 0.560, *P* = 0.004), and smokers (OR = 0.599, *P* = 0.039). A significant c-PF × age interaction emerged (*P* for interaction = 0.020, Figure S2), with the protective effect of c-PF on cognitive impairment being more pronounced in those 70–80 years, this interaction is visualized in a plot (Figure S3).

Correlation Between PF Indices, RMS Indices and Cognitive Function

Correlation Between PF Indices and Cognitive Function

Multivariate fully adjusted models demonstrated consistent positive associations between PF indices (PEF, FEV1, FVC) and cognitive function (Table S5 and Figure 3). All three PF indices correlated positively with global cognition, language function, and executive function. Among these, PEF showed the broadest associations—it additionally correlated with

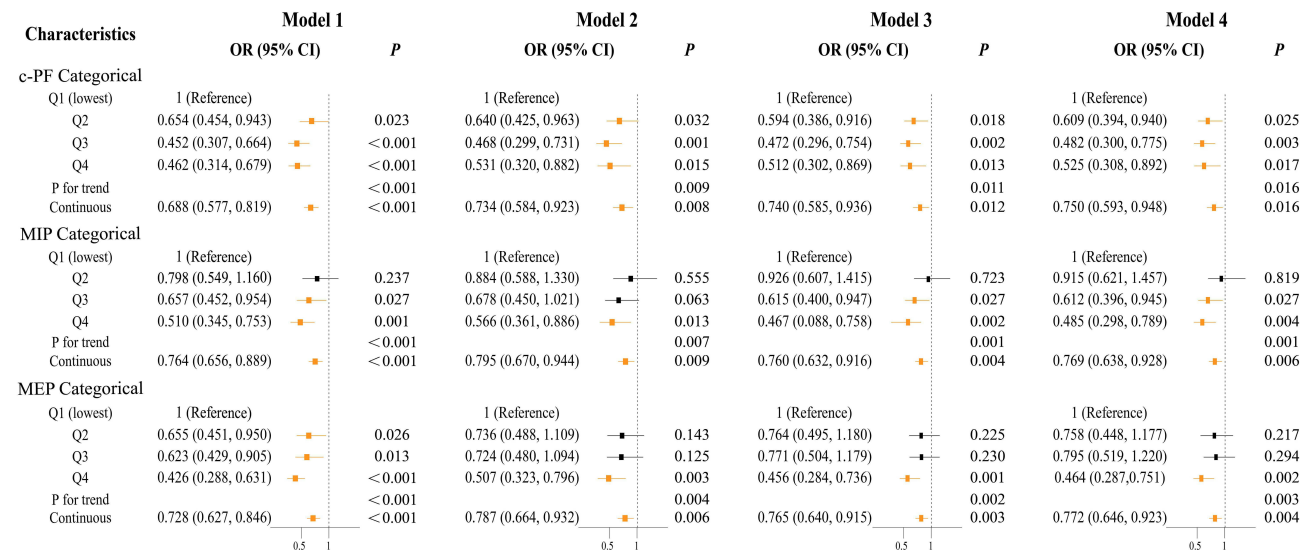


Figure 1 Association of c-PF, RMS indices (MIP and MEP) and cognitive impairment by logistic regression.

Notes: Model 1: Crude Model. Model 2: Adjusted for baseline age, sex, education, monthly income, spouse and dwelling status. Model 3: Further adjust for lifestyle variables such as smoking, drinking, BMI, physical activities and intellectual activities. Model 4: Further adjust for comorbidities such as hypertension, diabetes, hyperlipidemia, coronary heart disease and cerebrovascular diseases. All continuous variables (c-PF, MIP and MEP) were included in the analysis after being standardized by z-score.

Abbreviations: CI, confidence interval; OR, odd ratio; c-PF, comprehensive pulmonary function; c-RMS, comprehensive respiratory muscle strength; Q, quartile; MIP, maximal inspiratory pressure; MEP, maximum expiratory pressure.

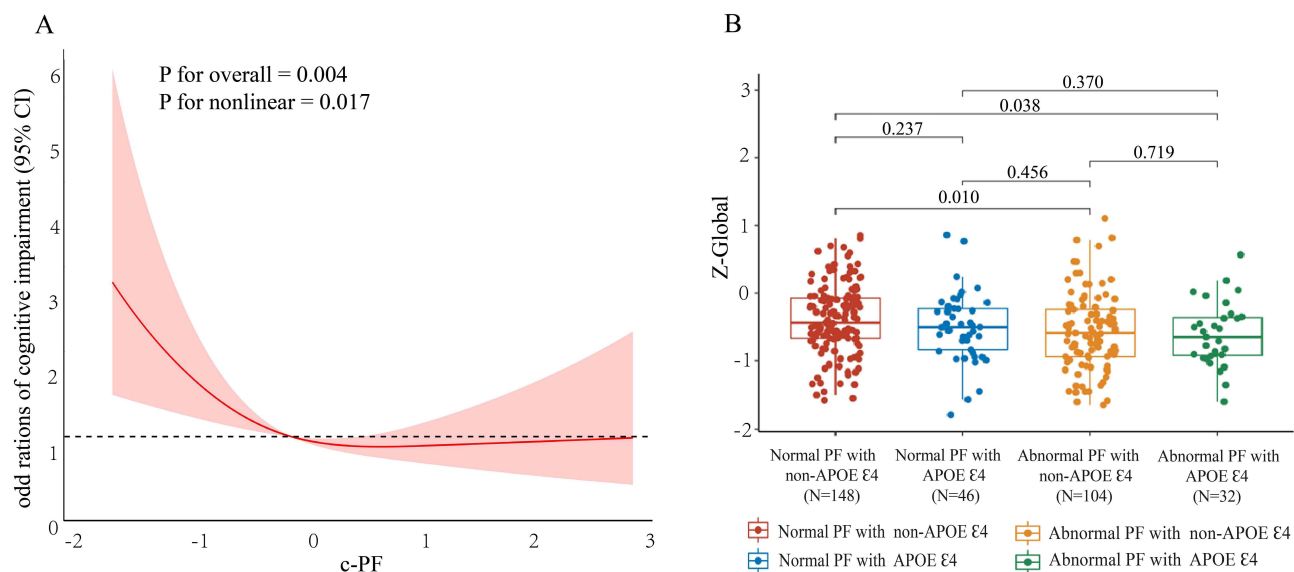


Figure 2 Comprehensive PF and cognition.

Notes: (A) The nonlinear relationship between c-PF and the risk of cognitive dysfunction. (B) PF combined with APOE status is associated with overall cognitive function. All models are covariant baseline age, sex, education, income, spouse, dwelling status, smoking, drinking, BMI, physical activities, intellectual activities, hypertension, diabetes, hyperlipidemia, coronary heart disease and cerebrovascular diseases.

Abbreviations: PF, pulmonary function; c-PF, comprehensive pulmonary function; Z-, standardized score.

memory and attention—while FEV1 also linked to memory, and FVC's associations were limited to global cognition, language function, and executive function.

PF (normal/abnormal) combined with APOE ε4 status (positive/negative) ($n = 330$) was analyzed for associations with cognition. Results showed significant differences in global cognitive scores across the four groups (one-way ANOVA: $F = 0.294$, $P = 0.032$). LSD post-hoc tests revealed that regardless of APOE ε4 status, abnormal PF was associated with lower cognitive scores than normal PF (Figure 2B and Table S6).

Correlation Between RMS and Cognitive Function

For RMS indices, MIP and MEP exhibited differential positive associations with cognitive domains, with results visualized in Figure 3 and detailed in Table S7. MIP correlated only with global cognition and executive function, whereas MEP showed more extensive positive links, spanning global cognition, memory, language, attention, and executive function.

When stratified by sex (Tables S8, S9): In males, both MIP and MEP correlated positively with global cognition, memory, and language, with MEP further linked to executive function; in females, MIP associated only with executive function, whereas MEP maintained the same broad positive associations—with global cognition, memory, language, attention, and executive function—observed in the overall population.

Sensitivity analyses (excluding participants with PF test quality < Grade D ($n = 36$), extremely severe mixed ventilatory dysfunction ($n = 81$), and dementia ($n = 12$)) confirmed all PF (PEF, FEV1 and FVC) and RMS (MIP and MEP) indices remained positively correlated with total cognitive function, with stronger associations for PEF and MEP (Tables S10–S12).

Mediation Effect Analysis of Laboratory Indicators

Correlation analyses of blood biomarkers (inflammation-, red blood cell-, liver/renal function-, and metabolism-related) with c-PF and cognitive function showed multiple indicators (eg, monocytes, lymphocyte count, red blood cell count, total bilirubin, mean hemoglobin content/concentration) correlated significantly with c-PF, while only total bilirubin, urea, and urine pH correlated with cognitive function (Table S13).

Total bilirubin—correlating significantly with both—was included in mediation analysis. Stepwise regression showed significance, but unstable confidence intervals for indirect effects yielded no valid results (Table S14 and Table 2).

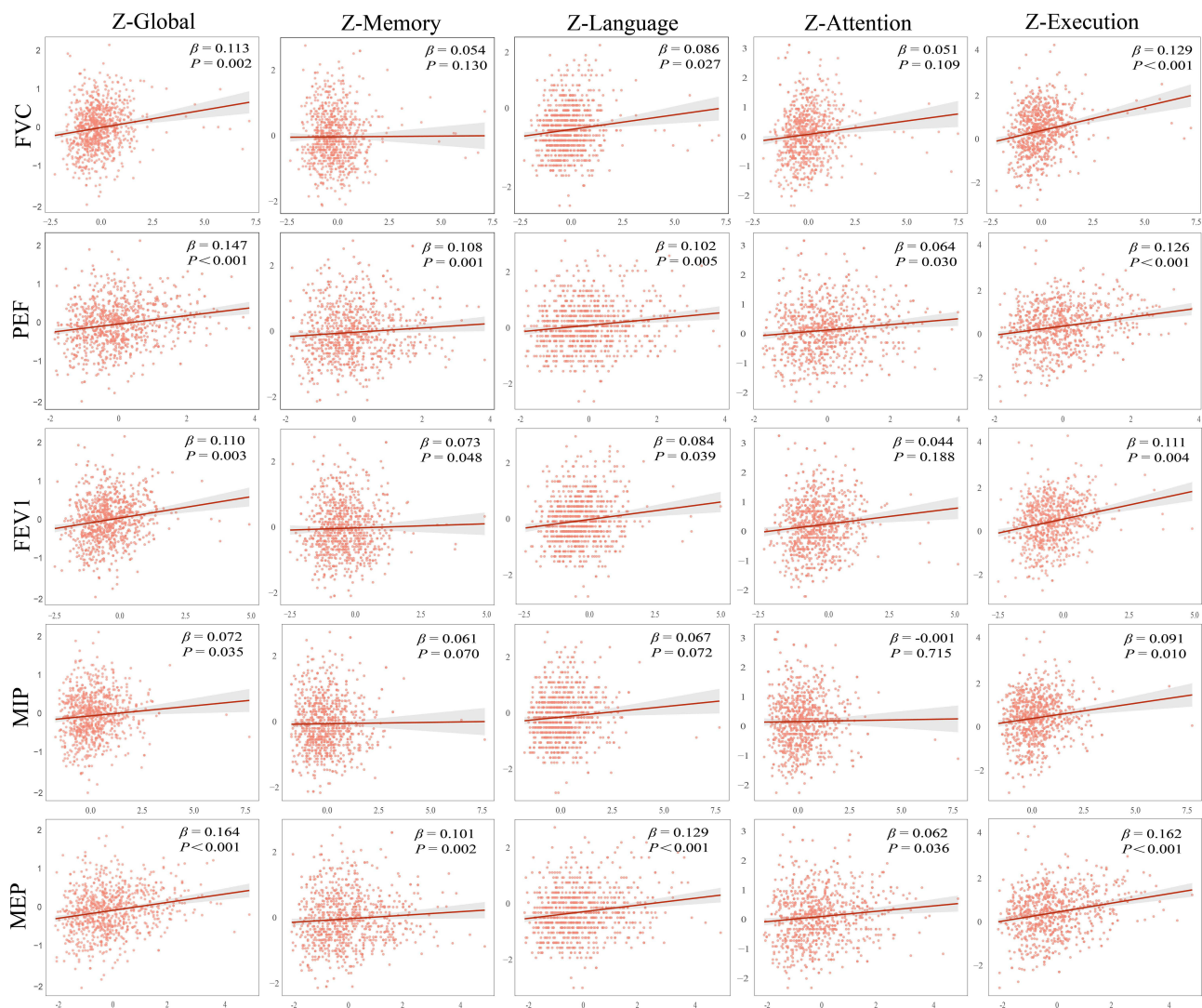


Figure 3 Linear association between PF indices, RMS indices and various cognitive domains.

Notes: All continuous variables (PEF, FEV1, FVC, MIP and MEP) were included in the analysis after being standardized by Z-score. The coordinate axes have been uniformly scaled for visualization. The true standardized β is marked in the upper right corner. All β are standardized regression coefficients, and the corresponding models have controlled for baseline age, sex, education, monthly income, spouse, dwelling status, smoking, drinking, BMI, physical activities, intellectual activities, hypertension, diabetes, hyperlipidemia, coronary heart disease and cerebrovascular diseases. The straight lines in the figure are the fitting lines at the original scale and are only for visualization. Statistical tests use the standardized model.

Abbreviations: FEV1, forced expiratory volume in one second; FVC, forced vital capacity; PEF, peak expiratory flow; MIP, maximal inspiratory pressure; MEP, maximum expiratory pressure; Z-, standardized score.

Discussion

In Chinese community-dwelling older adults, PF (PEF, FEV1 and FVC) and RMS (MIP and MEP) synergistically relate to cognitive function. They negatively correlate with cognitive impairment risk (dose-effect relationship) and positively associate with global cognition—especially executive and language functions—with PEF and MEP showing stronger links. APOE $\epsilon 4$ does not moderate the PF-cognition relationship. Though total bilirubin correlates with both c-PF and cognition, its mediating effect was not validly confirmed.

European cohort studies link declining baseline PF to higher dementia and cognitive impairment risk, likely via chronic hypoxia and inflammation.^{11,27,28} Our study aligns: higher c-PF quartiles associate with lower cognitive impairment risk (significant trend), validating cross-ethnic shared regulatory mechanisms between PF and cognition in Chinese older adults, supporting PF as a universal cognitive health marker.

Table 2 Summary of Total Bilirubin Mediating Effects

	Effect	Boost SE	Boost LLCI	Boost ULCI
Indirect effect	0.0229	0.0152	−0.0065	0.0159
Direct effect	0.3194	0.0794	0.1636	0.4751
Total effect	0.3423	0.0789	0.1875	0.4967

Note: Adjusted for baseline age, sex, education, monthly income, spouse, dwelling status, smoking, drinking, BMI, physical activities, intellectual activities, hypertension, diabetes, hyperlipidemia, coronary heart disease.

We identified a non-linear c-PF-cognition relationship (P non-linear = 0.017), with a “threshold range”: risk reduction was strongest from Q1 to Q3 (51.8% lower in Q3 vs Q1), slowing thereafter. Clinically, c-PF levels in the upper-middle range (eg, Q3) are associated with relatively lower cognitive impairment risk—this observation may provide practical reference for interventions targeting older adults with irreversible PF decline, though no causal relationship between maintaining PF and cognitive protection can be established.

PEF shows the strongest cognition association, consistent with literature, due to high sensitivity to small airway function and early brain structural changes. Unlike FEV1/FVC (marking chronic obstruction), PEF detects small airway dysfunction earlier; hypoxia/inflammation from such lesions drive cognitive impairment. Low PEF links to higher COPD, dementia risk, and brain changes (eg, ventricular enlargement),^{7,29} while FEV1/FVC lags 2–5 years.^{29,30} Quantitatively, PEF decline correlates more strongly with dementia risk (RR = 1.84) than FEV1 (1.25) or FVC (1.40).³¹ Domain-specifically, PEF strongly associates with executive function (β = 0.126) and memory (β = 0.108), reflecting small airway lesion-induced prefrontal/hippocampal damage.^{30,32} It should be noted that other factors, such as respiratory rhythm abnormalities caused by small airway dysfunction (which may disrupt cerebral blood flow stability), could also contribute to cognitive changes, though current evidence for hypoxia/inflammation mechanisms is more robust.³³

PF and RMS indices act synergistically, not independently, on cognitive function, stemming from their close physiological links. As the “power source” of ventilation, RMS indices—especially MEP—correlate strongly with PF indices (eg, PEF, r = 0.932), forming a “respiratory muscle drive-ventilation efficiency” network.

Collinearity analysis supported this: including individual indices alone (Model 1) caused high correlation (eg, VIF > 7 for PEF and MEP), masking some associations. Constructing c-PF reduced collinearity (all VIF < 2.8; Model 2), and MEP’s β dropped from 0.224 (Model 1) to 0.128 (Model 2), indicating joint regulation via physiological synergies rather than independent pathways. This synergy arises because RMS provides ventilation’s motivational basis, while PF reflects efficiency; together, they support cerebral oxygenation and reduce inflammation—aligning with studies linking MEP to PEF,³⁴ MIP to FVC/FEV1,³⁵ and RMS-small airway synergy.³⁶ Alternative explanations, such as shared genetic factors regulating both respiratory and cognitive function, cannot be fully excluded, though physiological synergy remains the most parsimonious interpretation based on current data.³⁷

MEP, a core expiratory muscle strength index, shows the strongest cognitive association. Reduced MEP drives restrictive lung disease via expiratory muscle weakness, impairing alveolar gas evacuation and limiting lung expansion—pathology for restrictive dysfunction.³⁸ Restrictive impairment (dominated by muscle weakness) links more strongly to cognitive decline than obstructive disease: cohort studies found higher dementia/MCI risk in restrictive (OR = 1.58) vs obstructive (OR = 1.33) patients,³⁹ with restrictive injury tied to brain structural changes (eg, reduced frontoparietal gray matter).⁴⁰ Additionally, RMS metrics better reflect PF in cognitive impairment,⁴¹ supporting MEP’s unique role in the “respiratory-brain axis,” strengthening its cognitive association.

Sex-stratified analyses showed that in males, MIP and MEP associated with memory, language, and executive function, while in females, MEP correlated with more cognitive subdomains and MIP’s influence was limited—differences stemming from sex-specific physiology. Specifically, testosterone enhances respiratory muscle metabolic efficiency and innervation via androgen receptors,⁴² making male MIP/MEP associations with language and executive function more dependent on muscle strength (eg, MIP stabilizes airflow for language fluency,⁴³ MEP supports prefrontal function).⁴⁴ In contrast, estrogen mediates female respiratory muscle-neurovascular coupling,⁴⁵ improving vascular function and cerebrovascular reactivity⁴⁶ to support multiple cognitive domains—explaining MEP’s broad associations—while MIP’s limited female influence may

reflect lower inspiratory muscle strength,⁴⁴ overshadowed by estrogen's systemic regulation. Additionally, muscle structure/function reinforces this: males have higher absolute MIP/MEP,⁴⁴ with stronger respiratory muscles directly regulating processes linked to language and executive function (eg, vocal fold stability),⁴³ whereas in females with weaker muscles, MEP's cognitive associations may rely more on breathing pattern stability.

Our results showed APOE ϵ 4 does not modify the PF-cognition association: regardless of APOE ϵ 4 status, abnormal PF linked to lower cognitive scores, stemming from distinct cognitive influence pathways. APOE ϵ 4 drives Alzheimer's pathogenesis via β -amyloid deposition (eg, higher brain β -amyloid oligomer burden and synaptic binding in carriers),⁴⁷ while abnormal PF impacts cognition mainly through vascular mechanisms (eg, hypoxemia, inflammation-induced cerebral hypoperfusion and microvascular damage).³ APOE ϵ 4 weakly modulates vascular factors,⁴⁸ keeping their pathways independent. Clinically, improvements in PF are associated with slower cognitive decline in APOE ϵ 4-positive individuals (genetic high-risk groups), while maintaining good PF is associated with better cognitive outcomes in APOE ϵ 4-negative individuals—no causal effect of PF on cognitive decline can be inferred.

While our study found total bilirubin correlated with both c-PF and cognitive function, its mediating effect showed unstable confidence intervals, with no valid results. Two key factors may explain this: First, sample size limitation ($n = 1081$) likely reduced the precision of mediating effect estimates—previous studies have shown that small samples increase the variance of indirect effect calculations, leading to unstable confidence intervals.⁴⁹ Second, bilirubin may not be a strong mediator in this Chinese community-dwelling older adult population: Bilirubin's antioxidant role in the “pulmonary-brain axis” often synergizes with other antioxidants (eg, superoxide dismutase, glutathione),⁵⁰ and measuring only total bilirubin (without fractionated bilirubin or other antioxidant markers) may incompletely capture its biological role. Additionally, in this population, vascular factors (eg, cerebral microangiopathy) may be more dominant mediators between PF and cognition, overriding bilirubin's potential mediating effect. Though bilirubin counteracts oxidative stress via mechanisms like ROS scavenging and antioxidant enzyme induction, in complex in vivo environments, total bilirubin may incompletely reflect its role in the “lung-brain axis”.

This study has limitations: first and foremost, its cross-sectional design severely limits causal inference—prospective cohort studies are urgently needed to confirm whether a temporal relationship exists; while collinearity was managed via simplified models, potential complex inter-indicator interactions may remain unaccounted for; the sample, from an urban Hubei community cohort, restricts generalizability to other regions; lack of air pollutant data may omit key confounders; and the small sample size of APOE ϵ 4 carriers necessitates further validation of their interaction with PF.

Conclusion

This study confirms that abnormal PF and reduced RMS in Chinese community-dwelling older adults are significantly associated with cognitive impairment risk and cognitive decline. It underscores that better preserved RMS is linked to better performance in language, executive function, and attention, with total bilirubin identified as a potential biological mediator.

Notably, the cross-sectional design of this study precludes any conclusions about causality or directionality between PF/RMS and cognitive function—this limitation must be emphasized, as temporal relationships remain unaddressed. These findings shed new light on the “pulmonary-cognition axis” and suggest that respiratory muscle training to improve PF could be a hypothesis worth testing in future trials for preventing cognitive impairment in older adults. Future prospective cohort studies with long-term follow-up, diverse populations, and mechanistic research are needed to clarify causal relationships and regulatory pathways between PF and cognition.

Abbreviations

PF, pulmonary function; RMS, respiratory muscle strength; APOE ϵ 4, apolipoprotein ϵ 4; PEF, peak expiratory flow; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; MIP, maximal inspiratory pressure; MEP, maximum expiratory pressure; c-PF, comprehensive pulmonary function; c-RMS, comprehensive respiratory muscle strength; HMAACS, Hubei Memory and Aging Cohort Study; OR, odd ratio; CI, confidence interval; SD, standard deviation; PET, Positron Emission Tomography; MRI, Magnetic Resonance Imaging; EVs, Extracellular Vesicles; ICC, Intraclass Correlation Coefficient; GLI-2012, Global Lung Initiative 2012; MoCA-B, Basic Montreal Cognitive Assessment; ADL, Activities of

Daily Living; MCI, Mild Cognitive Impairment; PCR, Polymerase Chain Reaction; SAP, Alkaline Phosphatase; MICE, Multiple Imputation by Chained Equations; BMI, Body Mass Index; ANOVA, Analysis of Variance; LSD, Least Significant Difference; VIF, Variance Inflation Factor; Q1, Quartile 1; Q2, Quartile 2; Q3, Quartile 3; Q4, Quartile 4.

Data Sharing Statement

The datasets used in the current study are not publicly available because of privacy and ethical restrictions but are available from the corresponding author, Guirong Cheng, upon reasonable request.

Ethics Approval and Consent to Participate

The Hubei Memory and Aging Cohort Study (HMACS) (ChiCTR, <https://www.chictr.org.cn>; registration number: ChiCTR1800019164) was approved by the Ethics Committee of Wuhan University of Science and Technology (protocol code: 201845; approved on October 22, 2018), Wuhan, China. Written informed consent was obtained from all participants or, in the case of cognitively impaired individuals, from a proxy (usually a guardian or family member).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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