Pulmonary function is associated with cognitive decline and structural brain differences

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Abstract
The association of poor pulmonary function (PF) with cognitive trajectories and structural brain differences remains unclear. Within the Rush Memory and Aging Project, 1377 dementia-free subjects were followed up to 21 years. PF was assessed with a composite score measured at baseline. Global and domain-specific cognitive function was assessed annually constructed from 19 cognitive tests. A subsample of 351 participants underwent brain magnetic resonance imaging to investigate the cross-sectional association between PF and structural brain volumes. We found that low PF was related to faster decline in global cognition, and domain-specific function including episodic memory, semantic memory, working memory, visuospatial ability, and perceptual speed. In addition, low PF was associated with smaller volumes of total brain, white matter and gray matter, and larger white matter hyperintensities volume. Our results suggest that low PF is associated with faster cognitive decline, and both neurodegeneration and vascular brain lesions may underlie the association.

Keywords
cognitive decline, cohort study, magnetic resonance imaging, pulmonary function

1 | NARRATIVE

1.1 | Contextual background

Tests of pulmonary function (PF) are used to assess lung capacity and the potency of the respiratory tract in people with respiratory diseases. PF decreases with age due to modifications in elastic recoil and thorax compliance,1 which slowly lead to a decline in the body’s oxygen supply.2 In general, the prevalence of pulmonary hypofunction increases sharply with age.3 Decreased PF has been used in the clinical diagnosis of airway dysfunction and chronic respiratory diseases.4,5 Further, poor PF has been associated with lower quality
of life and all-cause mortality in older adults, making it a public health priority.5,7

PF is an important parameter for complete evaluation of the respiratory system and can be measured by a spirometer. PF is assessed by peak expiratory flow (PEF; i.e., the maximum speed of expiration), forced expiratory volume in 1 second (FEV1; i.e., the volume of air exhaled with force for 1 second), and forced vital capacity (FVC; i.e., the maximum amount of air that can be exhaled after a maximum inhalation).8 This composite measure reflects not only lung capacity but also the resistance encountered during breathing.8

Growing evidence suggests that compromised lung health may be linked to faster cognitive decline and greater risk of dementia. Several epidemiological studies have demonstrated the association between indicators of PF (including FEV1, FVC, and PEF) and global cognitive decline in older individuals.2,9–11 However, the relationship between PF indicators and domain-specific cognitive function has been less consistent.12–18 One study reported an association between poor PF and faster decline in working memory, episodic memory, and semantic memory.12 However, other studies have suggested that low FEV1 is associated with declines in spatial ability, processing speed, semantic memory, and working memory.13–16 In addition, several studies have reported no association between FEV1 or FVC and episodic memory or semantic memory.17,18 In light of these conflicting results, the impact of lung function on long-term trajectories of cognitive function remains unclear, particularly because prior studies often used a single PF indicator and had relatively short follow-up (3–19 years).

There are several mechanisms by which PF could impact cognition. Low PF may result in reduced brain oxygenation, leading to vascular endothelial dysfunction, enhanced blood clotting activity, or reduced cerebral blood flow, ultimately exacerbating ischemia in some brain regions or contributing to the development of white matter lesions and lacunar infarctions.19–21 Impaired lung function could also affect cognition indirectly by increasing the risk of cardiovascular events,18 which could contribute to cerebral hypoperfusion, hypoxia, emboli, or infarcts, causing cognitive decline by accelerating vascular damage and degenerative lesions.22 Furthermore, PF is also related to general physical health, which could influence cognitive function by affecting factors such as physical activity level.23

Of course, these candidate mechanisms are not mutually exclusive. Indeed, vascular and neurodegenerative brain damage can overlap and develop in parallel, leading to more severe impacts on cognition than would have resulted from either pathological process alone.24 Mixed pathologies are very common in the aging brain,24 and the presence of vascular lesions can accelerate the progression of neurodegeneration.25

Brain magnetic resonance imaging (MRI) can be used to investigate structural alterations in the brain, offering an opportunity to evaluate the possible mechanisms underlying cognitive changes associated with PF.26 MRI measures the volume of different brain regions, which reflect different brain pathological changes. A reduction in total brain volume or white matter volume may be reflective of vascular brain changes,25,27 whereas a reduction in gray matter volume is indicative of neurodegeneration.28 White matter hyperintensities (WMH) have a multifactorial pathogenesis, but are strongly associated with cerebrovascular disease and vascular risk factors and thus could reflect microvascular lesions.25 So far, only a few studies have addressed the association between PF and structural brain differences, and with mixed results.29–31 Two studies have shown that lower FEV1 is related to smaller volumes of gray and white matter and a greater volume of WMH.30,31 However, another study has indicated that poor FVC, but not FEV1, is associated with increased WMH.29 To date, no prior studies have addressed the association between PF and cognitive trajectories in different cognitive domains with supporting results from brain MRI data.

### RESEARCH IN CONTEXT

1. **Systematic review:** We have reviewed the literature on pulmonary function (PF), cognitive function, and structural brain volumes by accessing PubMed and Web of Science databases. Several studies examining the association of PF with domain-specific cognitive decline have shown inconsistent findings. Moreover, studies examining the association of PF with structural brain differences were sparse. The impact of poor PF on cognitive trajectories and structural brain changes remains unclear.

2. **Interpretation:** In this community-based cohort study, we found that poor PF was associated with faster decline in episodic memory, semantic memory, working memory, visuospatial ability, and perceptual speed, as well as global cognition. Both neurodegeneration and vascular brain lesions may underlie the association. Our findings underscore the detrimental impact of poor pulmonary health on the brain, and suggest that interventions designed to maintain pulmonary health may represent significant opportunities for preventing cognitive decline in late life.

3. **Future directions:** Further longitudinal studies are warranted to examine the effect of PF on cognitive decline and explore the mechanisms linking PF, structural brain differences, and cognitive trajectories.

### HIGHLIGHTS

- Poor pulmonary function (PF) is associated with faster decline in global cognition and domain-specific cognitive functions.
- Low PF is further related to both neurodegeneration and vascular lesions in the brain.
- Interventions designed to maintain pulmonary health may represent significant opportunities for maintaining cognitive health in late life.
Based on this emerging evidence, we hypothesize that low PF accelerates cognitive decline. We further hypothesize that this is related to both neurodegeneration and the accumulation of vascular lesions in the brain.

We tested our novel hypothesis using 21-year follow-up data from the Rush Memory and Aging Project (MAP). We first analyzed the association between baseline PF and cognitive function using a composite measure of PF that included FEV1, FVC, and PEF to assess PF comprehensively from different dimensions. In addition to pure PF, this measure also reflects the contribution of some respiratory muscles, capturing even more aspects of lung health to evaluate the PF–cognition association more globally. We assessed cognitive function in terms of five specific cognitive domains: episodic memory, semantic memory, working memory, visuospatial ability, and perceptual speed. These were operationalized as composite scores calculated from the raw scores of 19 individual cognitive tests, an approach that reduces random variability and the impact of floor and ceiling artifacts. We found that low PF significantly accelerated the decline in global cognitive function as well as function in all five specific cognitive domains. To our knowledge, this is the first study to examine the impact of comprehensive PF on long-term cognitive trajectories among older adults.

Because apolipoprotein E (APOE) ε4, sex, smoking, and physical activity may affect cognitive function, we also explored whether these factors interacted with PF to impact cognitive decline. We did not uncover any statistically significant interactions, but this may reflect the small sample size in joint effect analysis. Further research is required to clarify the interaction between PF and these factors on cognitive decline.

Additionally, to evaluate possible mechanisms underlying the association between PF and cognitive decline, we analyzed the relationship between baseline PF and structural brain differences in a subsample of Rush MAP participants who underwent MRI. We assessed the volumes of total brain, total gray matter (including cerebellar, cortical, and subcortical gray matter), white matter (including cerebellar and cortical white matter), WMH, and hippocampus. We found that poor PF was related to smaller total brain, gray matter, and white matter volume and a greater volume of WMHs. Together, our results indicate that poor PF might contribute to cognitive decline through both neurodegenerative and vascular pathologies.

Furthermore, specific structural brain changes may affect cognitive performance in different domains. Gray matter atrophy may underlie deterioration of episodic memory, processing speed, and semantic memory. White matter lesions, that is, a greater volume of WMH, have been linked to impairments in working memory, semantic memory, visuospatial ability, and processing speed. Finally, white matter atrophy is related to the decline of working memory and processing speed. Thus, the connection between domain-specific cognitive decline and regional brain volumes suggests that neurodegeneration and vascular changes in the brain may underlie the association between low PF and cognitive decline.

Our findings raise the possibility that PF could play a role in the development and progression of dementia. To assess this, future studies should clarify whether poor PF is associated with the development of mild cognitive impairment (MCI) and its progression to dementia. Furthermore, PF’s relationship to other relevant brain pathology—including biomarkers from cerebrospinal fluid and brain autopsy (e.g., total tau, amyloid beta [Aβ], neurofibrillary tangles, and plaques)—should be analyzed in large cohort studies with long-term follow-up to better understand the mechanisms linking PF and cognitive function. Furthermore, future studies investigating the underlying pathological mechanisms of the PF–cognitive function association should include a larger sample size that enables the assessment of the mediating role of structural brain differences. Finally, clinical or community trials should be conducted to determine whether improving lung health in older adults through lifestyle interventions (e.g., smoking cessation, healthy diet, exercise, management of chronic conditions, adequate sleep) can improve cognitive function and prevent or delay the onset of dementia.

### 1.2 Strengths and limitations

Strengths of this study include the community-based cohort study design with a relatively large sample and long follow-up, the comprehensive assessment of PF and domain-specific cognitive function, and the use of brain MRI data to assess the mechanisms underlying the association between PF and cognitive function. However, some limitations must be acknowledged. First, the Rush MAP participants were volunteers who were not randomly selected from the community. Compared to the general population, they were well educated and had high scores on cognitive tests. This may have contributed to an underestimation of the magnitude of the association between PF and cognitive function. Furthermore, our findings may only be generalizable to demographically similar cohorts, and this limitation precludes the generalization of these findings to the general population. Second, the association between PF and structural brain markers was assessed based on cross-sectional data, thus the temporality of the observed association is unclear. Third, given the small sample size of MRI data available, we could not assess the mediating role of brain MRI changes in the PF–cognitive function association. Fourth, selection bias may have occurred due to missing data. However, we addressed this by repeating the analysis after multiple imputations, and the results were largely unchanged. Fifth, because PF was measured at baseline, there may be a reverse causality between cognitive function and PF. However, we addressed this by repeating the analysis after excluding participants with baseline MCI, and the PF–cognitive decline association remained significant. Thus, the temporality of the observed association is clear. Finally, potential confounding caused by unmeasured factors (such as an unhealthy diet) could not be completely ruled out.

### 1.3 Study conclusions

Our study provides further evidence that poor PF is associated with faster decline in global cognition and several domain-specific cognitive function.
functions including episodic memory, working memory, semantic memory, visuospatial ability, and perceptual speed. Both neurodegeneration and vascular lesions in the brain may underlie this association. Our results underscore the importance of maintaining pulmonary health to prevent cognitive decline and subsequent dementia among older adults.

2 | DETAILED METHODS AND RESULTS

2.1 | Study design, setting, and participants

The Rush MAP is an ongoing community-based prospective study with an emphasis on investigating the risk factors for common chronic neurodegenerative conditions in older adults. Details regarding the MAP study design and the evaluation protocol have been described previously. Briefly, 2155 participants were followed up annually from 1997 until 2019, for a maximum of 21 years. Beginning in 2009, 401 participants were invited to undergo brain MRI scans. As MAP is an ongoing longitudinal cohort study, the baseline MRI scans used in these analyses could be conducted at study entry or any follow-up examination. We excluded 115 participants with prevalent dementia as well as those with missing data on baseline PF (n = 591) or cognitive function during the follow-up (n = 282). Therefore, the present study included 1377 participants, 351 of whom had MRI data available (Figure 1).

All participants provided written informed consent as well as repository consent to allow their data to be shared. MAP was approved by the Institutional Review Board of Rush University Medical Center and was performed in accordance with the ethical standards outlined in the 1964 Declaration of Helsinki and its later amendments.

2.2 | Assessment of PF

At baseline, measures of FVC, FEV1, and PEF were collected using a hand-held spirometer to assess PF (MicroPlus Spirometer MS03, MicroMedical LTC). Two measurements were collected and averaged for each parameter. Raw scores from the three averaged measures were then converted to z-scores based on the means and standard deviations for the entire cohort. As previously reported, a composite PF score was created by averaging the z-scores for FVC, FEV1, and PEF. Composite PF scores were then tertiled into three categories: lowest PF (tertile 1), middle PF (tertile 2), and highest PF (tertile 3). Participants with an FEV1/FVC ratio less than or equal to 0.7 were considered to have possible chronic obstructive pulmonary disease (COPD).

2.3 | Assessment of cognitive function, mild cognitive impairment, and dementia

Cognitive function was assessed at baseline and each follow-up using a comprehensive battery of cognitive tests. Cognitive assessments have been described in detail in a previous study. Briefly, a composite score for global cognitive function was derived by averaging the z-scores from 19 cognitive tests in the battery. Scores were also derived for domain-specific cognitive functions including episodic
memory, semantic memory, working memory, visuospatial ability, and perceptual speed (Methods A in supporting information).

Dementia and MCI were diagnosed based on a combination of cognitive test scores, clinical judgment by a neuropsychologist, and diagnostic classification by a clinician (Methods A).48,49

2.4 | Assessment of structural brain volumes

The MAP MRI protocol is described in Methods B in supporting information. Volumetric measurements (in mm³) of total brain, total gray matter (including cerebellar, cortical, and subcortical gray matter), total white matter (including cerebellar and cortical white matter), WMH, and hippocampus were derived. Values for WMH volume had a skewed distribution and were therefore log-transformed. All MRI data used in the present study came from stroke-free participants to exclude brain damage caused by stroke.

2.5 | Assessment of other variables

Information on demographic characteristics, socioeconomic status, and lifestyle factors was collected at baseline.50 Data on race was based on self-report and was classified as White or non-White. Education was represented as the number of years of formal schooling. Body mass index (BMI) was calculated as weight (kg) divided by squared height (m²). Alcohol consumption was measured as the average amount of alcohol (g) consumed per day over the past year. Smoking status was categorized as never, former, or current smoker. Physical activity was operationalized as participants’ total number of hours of physical activity per week (according to the National Health Interview Survey) and further classified as high or low according to whether this value fell above or below the median weekly physical activity in the study population.47

Blood pressure was measured using a mercury sphygmomanometer at baseline and each follow-up examination. Two consecutive readings were taken from the right arm while participants were in a seated position with the arm resting at heart level. A third reading was taken from a standing position after 1 minute. The mean of the three values was recorded. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or the use of antihypertensive drugs. Heart disease and congestive heart failure were assessed based on self-reported medical history. Stroke was diagnosed by a clinician through a review of self-reported information on medical history, neurological exams, cognitive testing, and participant interviews. Diabetes was defined as hemoglobin A1c ≥6.5%, fasting plasma glucose ≥126 mg/dL, random blood glucose ≥200 mg/dL, a history of diabetes, or the use of glucose-lowering medications.51 Depression was diagnosed based on the use of aluminum-containing or the use of antidepressive medication.

Blood samples were taken from all participants at study entry. APOE was genotyped by Polymorphic DNA Technologies and genotypes were dichotomized as ε4 carriers versus non-carriers in the present analysis. Additional details about the MAP data collection protocol can be found at the Rush Alzheimer’s Disease Center Research Resource Sharing Hub (https://www.radc.rush.edu/).

2.6 | Statistical analysis

Baseline characteristics of the study population by PF category were compared using Chi-square tests for categorical variables and one-way analysis of variance or Wilcoxon rank sum tests for continuous variables.

The associations between PF (as both a continuous and a categorical variable) and annual changes in global cognition and domain-specific cognitive function were analyzed using linear mixed-effects models to estimate the β-coefficients and 95% confidence intervals (CIs). The fixed effect included PF, follow-up time (year), and their interaction. The random effect included random intercept and slope, allowing us to assess individual differences at baseline and across follow-up. Linear regression models were used to estimate the cross-sectional relationship between PF and structural brain volumes. The basic models were adjusted for age, sex, and education. Multivariable-adjusted models were further adjusted for race, BMI, stroke, hypertension, diabetes, depression, heart disease, congestive heart failure, COPD, alcohol consumption, smoking, physical activity, and APOE ε4. Statistical interactions were examined by creating indicator variables containing the cross-product of PF and other variables (APOE ε4, sex, smoking, and physical activity).

In sensitivity analysis, we repeated the original analyses after (1) excluding participants with MCI (n = 352) and COPD (n = 65) and (2) using multiple imputation to estimate missing values for PF and other covariates (n = 413). P-values less than 0.05 were considered statistically significant. All statistical analyses were performed using Stata SE 16.0 for Windows (StataCorp).

3 | RESULTS

3.1 | Baseline characteristics

Among the 1377 dementia-free participants in the study (mean age = 79.41 ± 7.71 years, 75.74% female), baseline PF score ranged from −2.36 to 3.47. Compared to participants with the highest PF (PF > 0.33), those with middle (−0.46 < PF ≤ 0.33) or lowest (PF ≤ −0.46) PF were more likely to be older; female; have fewer years of education, poorer cognitive performance, less alcohol consumption, lower levels of physical activity, and higher BMI; and have hypertension, COPD, stroke, congestive heart failure, or depression (Table 1). Subjects who did not undergo tests of PF at baseline had better global cognitive function (Table S1 in supporting information).

3.2 | Association between PF and cognitive decline

The median follow-up time was 7 years (range: 1–21 years). Better PF (as a continuous variable) was related to slower decline in global
TABLE 1 Characteristics of the Rush MAP population by tertiles of PF at baseline (N = 1377)

| Characteristics          | PFa                        | Lowest (n = 457) | Middle (n = 464) | Highest (n = 456) | P   |
|--------------------------|----------------------------|------------------|------------------|-------------------|-----|
| Age (y), mean (SD)       |                            | 82.61 (6.78)     | 79.24 (7.22)     | 76.35 (7.99)      | <0.001 |
| Female                   |                            | 422 (92.34)      | 404 (87.07)      | 217 (47.59)       | <0.001 |
| Race-White               |                            | 419 (91.68)      | 426 (91.81)      | 430 (92.73)       | 0.199 |
| Education (y), mean (SD) |                            | 14.12 (3.26)     | 14.49 (2.99)     | 15.40 (3.36)      | <0.001 |
| BMI (kg/m²), mean (SD)   |                            | 27.51 (5.29)     | 27.40 (5.28)     | 27.38 (5.45)      | <0.001 |
| Alcohol consumption (g), median (IQR) | | 0.00 (0.00-4.32) | 0.00 (0.00-4.32) | 2.16 (1.84-10.80) | <0.001 |
| Smoking status           |                            |                  |                  |                   | 0.267 |
| Never                    |                            | 256 (56.26)      | 288 (62.07)      | 252 (55.26)       |      |
| Former smoker            |                            | 184 (40.44)      | 164 (35.34)      | 190 (41.67)       |      |
| Current smoker           |                            | 15 (3.30)        | 12 (2.59)        | 14 (3.07)         |      |
| Physical activity (h/week), median (IQR) | | 1.83 (0.50-4.00) | 2.33 (0.75-4.60) | 3.02 (1.50-5.50) | <0.001 |
| Hypertension             |                            | 367 (80.31)      | 342 (73.71)      | 309 (67.76)       | <0.001 |
| Diabetes                 |                            | 64 (14.00)       | 58 (12.50)       | 73 (16.01)        | 0.306 |
| COPD                     |                            | 46 (10.07)       | 13 (2.80)        | 6 (1.32)          | <0.001 |
| Stroke                   |                            | 54 (12.77)       | 28 (6.76)        | 26 (6.44)         | 0.001 |
| Congestive heart failure |                            | 30 (6.56)        | 17 (3.66)        | 11 (2.41)         | 0.006 |
| Heart disease            |                            | 44 (9.63)        | 43 (9.29)        | 39 (8.55)         | 0.847 |
| Depression               |                            | 102 (22.32)      | 81 (17.46)       | 60 (13.16)        | 0.001 |
| APOE ε4 carrier          |                            | 95 (21.16)       | 89 (19.52)       | 119 (26.50)       | 0.031 |
| MMSE, median (IQR)       |                            | 28.00 (27.00-29.00) | 29.00 (27.00-29.00) | 29.00 (27.50-30.00) | <.001 |
| Global cognition, mean (SD) |                        | −0.11 (0.53)    | 0.11 (0.51)      | 0.22 (0.56)       | <0.001 |
| Episodic memory, mean (SD) |                        | −0.01 (0.64)    | 0.16 (0.66)      | 0.17 (0.67)       | <0.001 |
| Visuospatial ability, mean (SD) |                    | −0.23 (0.76)    | −0.00 (0.77)     | 0.34 (0.78)       | <0.001 |
| Perceptual speed, mean (SD) |                        | −0.22 (0.76)    | 0.11 (0.70)      | 0.29 (0.75)       | <0.001 |
| Semantic memory, mean (SD) |                        | −0.12 (0.67)    | 0.12 (0.60)      | 0.20 (0.67)       | <0.001 |
| Working memory, mean (SD) |                        | −0.12 (0.73)    | 0.07 (0.74)      | 0.20 (0.79)       | <0.001 |

Abbreviations: APOE ε4, apolipoprotein E epsilon 4; BMI, body mass index; COPD, chronic obstructive pulmonary disease; IQR, interquartile ratio; MAP, Memory and Aging Project; MMSE, Mini-Mental State Examination; PF, pulmonary function; SD, standard deviation. Missing data: Race = 2; Alcohol consumption = 2; APOE ε4 genotype = 23; BMI = 26; Heart disease = 1; Stroke = 136; Smoking status = 2.

The results from the basic-adjusted models were similar to those from multivariable-adjusted models (Table S2 in supporting information).

While APOE ε4 is associated with both cognitive decline and PF decline in aging,52,53 we did not detect any significant interactions between PF and APOE ε4 carrier status with respect to global or domain-specific cognitive decline (all P > 0.05). This may be due to the small sample size of APOE ε4 carriers in the study. Additionally, APOE ε4 carriers are more likely to develop dementia and therefore may have been excluded from the study population at baseline. Moreover, no significant interactions were identified between PF and sex, smoking, or physical activity on cognitive decline. While sex, smoking, and physical activity may affect both PF54–56 and brain function57–59 simultaneously, we attribute the lack of interaction to the small sample size in this joint effect analysis.
# TABLE 2  Association between baseline PF and changes in global cognition and domain-specific cognitive functions

| PF               | Global cognition $\beta$ (95% CI)$^a$ | Episodic memory $\beta$ (95% CI)$^a$ | Semantic memory $\beta$ (95% CI)$^a$ | Working memory $\beta$ (95% CI)$^a$ | Visuospatial ability $\beta$ (95% CI)$^a$ | Perceptual speed $\beta$ (95% CI)$^a$ |
|------------------|----------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|-------------------------------------------|-----------------------------------------|
| **Baseline**     |                                        |                                       |                                       |                                       |                                           |                                         |
| Continuous PF    | 0.12 $^*$ (0.08–0.16)                  | 0.06 $^*$ (0.01–0.11)                 | 0.13 $^*$ (0.08–0.18)                 | 0.12 $^*$ (0.07–0.18)                 | 0.14 $^*$ (0.08–0.19)                     | 0.22 $^*$ (0.16–0.27)                   |
| Categories PF    |                                        |                                       |                                       |                                       |                                           |                                         |
| Highest          | Reference                              | Reference                             | Reference                             | Reference                             | Reference                                 | Reference                               |
| Middle           | −0.06 (−0.13–−0.02)                    | −0.01 (−0.08–−0.10)                  | −0.02 (−0.11–−0.06)                  | −0.07 (−0.18–−0.03)                  | −0.07 (−0.17–−0.03)                       | −0.13 (−0.24–−0.03)                     |
| Lowest           | −0.21 $^*$ (−0.29–−0.13)               | −0.09 $^*$ (−0.19–−0.01)             | −0.23 $^*$ (−0.32–−0.13)             | −0.19 $^*$ (−0.30–−0.08)             | −0.21 $^*$ (−0.32–−0.10)                  | −0.36 (−0.47–−0.25)                     |
| **Longitudinal** |                                        |                                       |                                       |                                       |                                           |                                         |
| Continuous PF× time | 0.02 (0.01–0.03)                           | 0.02 (0.01–0.03)                           | 0.02 (0.01–0.02)                           | 0.01 (0.01–0.02)                           | 0.01 (0.01–0.02)                           | 0.02 (0.01–0.02)                           |
| Categories PF× time |                                          |                                       |                                       |                                       |                                           |                                         |
| Highest          | Reference                              | Reference                             | Reference                             | Reference                             | Reference                                 | Reference                               |
| Middle           | −0.01 (−0.03–0.00)                     | −0.01 (−0.03–0.01)                  | −0.01 (−0.02–0.01)                  | −0.00 (−0.02–0.01)                  | −0.01 (−0.03–0.00)                       | −0.02 (−0.03–0.00)                     |
| Lowest           | −0.05 (−0.06–−0.04)                    | −0.05 (−0.07–−0.03)                  | −0.03 (−0.05–−0.02)                  | −0.03 (−0.04–−0.01)                  | −0.03 (−0.04–−0.01)                       | −0.04 (−0.05–−0.02)                     |

Abbreviations: CI, confidence interval; PF, pulmonary function.

$^a$Model adjusted for age, sex, education, race, body mass index, stroke, hypertension, diabetes, depression, heart disease, congestive heart failure, chronic obstructive pulmonary disease, alcohol consumption, smoking, physical activity, and apolipoprotein E ε4.

*P < 0.05.
3.3  Association between PF and structural brain differences

Participants with the lowest PF had smaller volumes of total brain, gray matter, white matter, and greater WMH (Table S3 in supporting information). In linear regression analysis, compared to participants with the highest PF, those with the lowest PF showed smaller volumes of total brain, gray matter, and white matter as well as greater WMH volume after adjustment for age, sex, education, race, BMI, stroke, hypertension, diabetes, depression, heart disease, congestive heart failure, COPD, alcohol consumption, smoking, physical activity, and APOE ε4 (Table 3, Figure S1 in supporting information). There was no significant difference in hippocampus volume between participants with the lowest versus highest levels of PF. Results from the basic-adjusted models were similar to those from the multivariable-adjusted models (Table S4 in supporting information).

3.4  Sensitivity analysis

Similar results were obtained after we repeated the main analyses after (1) excluding participants with MCI (n = 352; Table S5 in supporting information) or COPD (n = 65; Table S6 in supporting information) and (2) using multiple imputation to estimate missing values for PF and some covariates (n = 413; Table S7 in supporting information).

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TABLE 3  Association between PF and regional brain volumes on MRI

| Regional brain volumes (mm³) | Continuous PF | Middle vs. highest | Lowest vs. highest |
|-----------------------------|--------------|-------------------|-------------------|
|                             | β (95% CI)² | β (95% CI)² | β (95% CI)² |
| Total brain                 | 15.06 (7.23–22.89) | −20.49 (−33.87–−7.11) | −30.28 (−45.92–−14.64) |
| Total gray matter           | 9.67 (3.69–15.66) | −9.01 (−19.28–1.27) | −17.17 (−29.19–−5.16) |
| Cerebellar gray matter      | 1.54 (0.48–2.59) | −1.48 (−3.29–0.33) | −2.78 (−4.90–0.67) |
| Cortical gray matter        | 5.80 (1.43–10.17) | −4.78 (−12.27–2.71) | −10.54 (−19.29–1.79) |
| Subcortical gray matter     | 2.34 (0.85–3.83) | −2.75 (−5.31–0.19) | −3.86 (−6.85–0.86) |
| Hippocampal                 | 0.03 (−0.07–0.14) | −0.11 (−0.29–0.06) | −0.05 (−0.26–0.15) |
| Total white matter          | 6.92 (0.51–13.34) | −12.96 (−23.90–2.02) | −15.89 (−28.67–3.10) |
| Cerebellar white matter     | 0.04 (−0.34–0.42) | −0.27 (−0.91–0.37) | 0.10 (−0.66–0.85) |
| Cortical white matter       | 6.88 (0.59–13.18) | −12.69 (−23.42–1.96) | −15.98 (−28.52–3.44) |
| White matter hyperintensitiesb | −0.12 (−0.18–0.06) | 0.11 (0.00–0.21) | 0.22 (0.10–0.34) |

Abbreviations: CI, confidence interval; MRI, magnetic resonance imaging; PF, pulmonary function.
²Model adjusted for age, sex, education, race, body mass index, hypertension, diabetes, depression, heart disease, congestive heart failure, chronic obstructive pulmonary disease, alcohol consumption, smoking, physical activity, and apolipoprotein E 4.
³The volume of white matter hyperintensities was transformed by taking the logarithm.
*P < 0.05.

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CONFLICTS OF INTEREST
The authors report no disclosures relevant to the manuscript.

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