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# Associations of Pulmonary Function with MRI Brain Volumes: A Coordinated Multi-Study Analysis

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## Abstract.

**Background:** Previous studies suggest poor pulmonary function is associated with increased burden of cerebral white matter hyperintensities and brain atrophy among elderly individuals, but the results are inconsistent.

**Objective:** To study the cross-sectional associations of pulmonary function with structural brain variables.

**Methods:** Data from six large community-based samples (N=11,091) were analyzed. Spirometric measurements were standardized with respect to age, sex, height, and ethnicity using reference equations of the Global Lung Function Initiative. Associations of forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and their ratio FEV1/FVC with brain volume, gray matter volume, hippocampal volume, and volume of white matter hyperintensities were investigated using multivariable linear regressions for each study separately and then combined using random-effect meta-analyses.

**Results:** FEV1 and FVC were positively associated with brain volume, gray matter volume, and hippocampal volume, and negatively associated with white matter hyperintensities volume after multiple testing correction, with little heterogeneity present between the studies. For instance, an increase of FVC by one unit was associated with 3.5 ml higher brain volume (95% CI: [2.2, 4.9]). In contrast, results for FEV1/FVC were more heterogeneous across studies, with significant positive associations with brain volume, gray matter volume, and hippocampal volume, but not white matter hyperintensities volume. Associations of brain variables with both FEV1 and FVC were consistently stronger than with FEV1/FVC, specifically with brain volume and white matter hyperintensities volume.

**Conclusion:** In cross-sectional analyses, worse pulmonary function is associated with smaller brain volumes and higher white matter hyperintensities burden.

Keywords: Dementia, epidemiology, magnetic resonance imaging, respiratory function tests

## INTRODUCTION

Both clinical and epidemiological studies suggest pulmonary diseases are related to increased risk of vascular brain injury and neurodegeneration in older individuals. For instance, chronic obstructive pulmonary disease (COPD) has been identified as a risk factor for cerebral small vessel disease, stroke, and cognitive impairment [1–3]. COPD is associated with structural brain abnormalities, including impaired white matter integrity [4], white matter hyperintensities [3, 5], and gray matter atrophy [6]. Chronic hypoxemia is a major driver of COPD-related pathology and has been found to be associated with increased risk of cognitive impairment [7]. COPD is characterized by an obstructive spirometry pattern, i.e., difficulties in exhaling quickly, with abnormally low forced expiratory volume in 1 second (FEV1) but preserved or proportionally less reduced forced vital capacity (FVC), resulting in reduced FEV1/FVC. Impaired vital capacity on the other hand is characterized by preserved FEV1/FVC with reduced FVC. It is as prevalent as COPD in the general population (about 10% in western countries) and may be an underappreciated cause of mild cognitive impairment and dementia [2, 8, 9].

The few studies investigating associations of impaired pulmonary function with structural brain variables in community samples have identified cerebellar abnormalities [10], overall brain atrophy [11], and increased burden of white matter hyperintensities [12–14]. However, they relied on relatively small samples and pulmonary function was assessed with only a single spirometry variable in some of these studies. We expanded on this literature by performing a coordinated multi-study analysis of associations of cross-sectional pulmonary function, assessed by FEV1, FVC, and FEV1/FVC, with structural brain variables in 11,091 individuals aged 21 to 97 years using six large community samples within the neurology working group of the Cross-Cohort Collaboration Consortium.

The main objective of our study was to gain insight into the brain structural underpinning of the previously reported association of impaired pulmonary function with increased dementia risk [2, 15]. Structural changes such as brain atrophy are known to precede cognitive decline and dementia by several years [16–18]. We hypothesized that reduced lung function (i.e., lower FEV1 or FVC) is associated with smaller brain volumes and higher burden of white matter hyperintensities.

## MATERIALS AND METHODS

### *Study cohorts*

Analyses were performed within the neurology working group of the Cross-Cohort Collaboration Consortium and were based on data from six large-scale community-based studies, namely: Age, Gene/Environment Susceptibility Study (AGES) [19], Atherosclerosis Risk in Communities Study (ARIC) [20], Cardiovascular Health Study (CHS) [21], Framingham Heart Study [22], the Rotterdam Study (RS) [23], and the Study of Health in Pomerania (SHIP) [24]. Participants who underwent both spirometry and brain magnetic resonance imaging (MRI) within 3 years were included. Details on data collection and the analytic samples can be found in the Supplementary Material.

### *Standardization of spirometric measurements*

Forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) were measured by spirometry in accordance with guidelines of the American Thoracic Society and the European Respiratory Society. At least two acceptable maneuvers were required. For more details, we refer to the Supplementary Material.

As spirometric measurements are known to decrease with age, airflow obstruction is underestimated in young and overestimated in elderly individuals when relying on unadjusted measurements (e.g., when using the Global Initiative for Chronic Obstructive Lung Disease criterion of  $FEV1/FVC < 70\%$ ) [25]. The measurements were therefore standardized with respect to age, sex, body height, and ethnicity (if applicable) by means of the Global Lung Function Initiative (GLI) 2012 reference equations, which are based on data of more than 70,000 healthy lifelong non-smokers [26]. Using these reference equations, each individual measurement was transformed to a z-score which indicates how many standard deviations it is from the expected value of a healthy non-smoker with the same age, sex, body height, and ethnicity (see [26] Fig. 8 on page 1337 for an illustration). All association analyses were performed with the resulting z-scores. Some studies found small but significant biases of these z-scores in specific populations [27, 28]. Therefore, we additionally included age, sex, and height in the regression models to account for any residual correlations with these important confounders (see below).

### Brain imaging

Brain volume, gray matter volume, hippocampal volume (sum of left and right), and white matter hyperintensities volume were determined from T1-weighted and fluid attenuated inversion recovery (FLAIR) images via automated image-processing pipelines in all studies except AGES. In AGES, brain volumes were derived using multispectral MRI based on T1, T2, FLAIR, and proton density images. For details we refer to the Supplementary Material.

### Statistical analyses

The main rationale behind the standardization of spirometry measurements based on GLI-2012 reference equations was to remove nuisance variation related to age, sex, and body height. We checked this by comparing the fraction of variance in spirometry measurements explained by these variables in the SHIP sample before and after standardization.

Associations of brain volume, gray matter volume, hippocampal volume, and log-transformed white matter hyperintensities volume (outcomes) with standardized FEV1, FVC, and FEV1/FVC (exposures) were analyzed by multivariable linear regressions in each study sample separately. Analyses were adjusted for age, sex, the interaction of age with sex, intracranial volume, body height, smoking status (never/former/current), and diabetes mellitus. Age was modelled using restricted cubic splines with five knots located study-specifically at the 5%, 27.5%, 50%, 72.5%, and 95% quantiles to account for acceleration of atrophy rates with increasing age [29, 30]. Diagnostic plots were inspected for outliers, which were excluded from the analyses. Results from each study were combined using a random-effects meta-analysis [31]. Heterogeneity was assessed using Cochran's  $Q$  and  $I^2$  according to Higgins and Thompson [32]. We used the Benjamini-Hochberg procedure with false discovery rate (FDR)  $\leq 5\%$  to account for multiple testing of associations between 4 outcomes and 3 exposures (12 tests) [33]. Statistical analyses were performed with R version 4.0 and the meta package [31]. For standardization of spirometric measurements, the rspirometry package was used.

## RESULTS

In total, cross-sectional data from 11,091 individuals aged 21 to 97 years were analyzed. Sample

characteristics are shown in Table 1. All participants from AGES, ARIC, and CHS were older than 60 years. In total, 8,870 individuals (81%) were older than 60 years of age. Median age was lowest in SHIP (52 years) and highest in CHS (77 years). Prevalence of diabetes was considerably higher in ARIC (28%) compared to the other samples (about 10%).

Overall, medians and quartiles of standardized spirometry measurements in SHIP and RS showed reasonable agreement with theoretical values of the normal distribution. Values were slightly smaller in the other samples comprising older individuals.

Among never-smokers from SHIP, about 75% of the variance of raw values of FEV1 and FVC could be explained by age, sex, and body height. After standardization according to the GLI-2012 reference equations, the explained variance dropped to 2% for FEV1 and 1% for FVC, and the model fit remained significant for FEV1 only ( $n=685$ ,  $F_{3,681}=5.2$ ,  $p=0.002$ ). However, standardized FEV1 and FVC were still highly correlated ( $r^2 \approx 0.85$ ). Histograms of the spirometry measurements in SHIP are shown in Supplementary Figure 1, and all subsequent associations analyses were performed with the standardized z-scores.

Results of the association analyses in each study are shown in Fig. 1 and Supplementary Tables 1 and 2. Cohort-specific inspection of regression diagnostic plots led to the exclusion of up to 18 cases per cohort (proportions  $< 1.1\%$ ). Overall effects are shown in Table 2. After correction for multiple testing, FEV1 and FVC were significantly and positively associated with brain volume, gray matter volume, hippocampal volume, and negatively associated with white matter hyperintensities volume with little or no heterogeneity between the studies ( $I^2 < 30\%$ ). For instance, an increase of FEV1 by one unit, which corresponds to about one standard deviation of raw FEV1 values, was associated with 3.4 ml higher brain volume (95% CI: [2.1, 4.7]). An increase of FVC by one unit was associated with 3.5 ml higher brain volume (95% CI: [2.2, 4.9]). This is approximately twice the one-year decrease in brain volume (about 1.7 ml) in the SHIP sample. FEV1/FVC was also significantly positively associated with brain volume, gray matter volume, and hippocampal volume, albeit with smaller effect estimates. An increase in FEV1/FVC by one unit was associated with 1.8 ml higher brain volume (95% CI: [0.6, 3.1]). FEV1/FVC was not associated with white matter hyperintensities volume. In contrast to the results for FEV1 and FVC, substantial heterogeneity was present in associations of FEV1/FVC

Table 1

Sample characteristics. Values are given as numbers with percentages, or medians with interquartile ranges. All associations analyses were performed with z-scores of spirometry measurements according to the Global Lung Function Initiative 2012 reference equations. In total, data of 11,091 individuals from six community-based studies were analyzed

	AGES	ARIC	CHS	FHS	RS	SHIP
Year	2002 – 2006	2011 – 2013	1997 – 1999	1998 – 2001	2009 – 2013	2008 – 2011
n	1655	1365	774	1720	3857	1720
Age at spirometry, y	76 (71, 81)	76 (72, 80)	77 (74, 80)	61 (54, 68)	67 (62, 74)	52 (42, 62)
Time between spirometry and MRI (absolute value), d	14 (8, 27)	284 (128, 460)	407 (371, 448)	207 (110, 349)	23 (13, 43)	18 (4, 39)
Females (%)	956 (58)	823 (60.3)	455 (59)	945 (55)	2131 (55)	877 (51)
Smoking (%)						
never	711 (43)	603 (44.2)	373 (48)	629 (37)	1241 (32)	686 (40)
former	736 (45)	692 (50.7)	351 (45)	894 (52)	2154 (56)	648 (38)
current	208 (12)	70 (5.1)	50 (7)	197 (11)	450 (12)	386 (22)
missing	0	0	0	0	12	0
Height, m	1.68 (1.59, 1.74)	1.64 (1.58, 1.72)	1.63 (1.56, 1.70)	1.67 (1.61, 1.75)	1.69 (1.62, 1.76)	1.70 (1.63, 1.77)
missing	0	0	0	0	1	0
Diabetes (%)	189 (11)	381 (28)	81 (10)	167 (10)	548 (14)	150 (9)
missing	0	0	0	5	57	0
Forced expiratory volume in 1 s (FEV <sub>1</sub> ), l	2.06 (1.65, 2.59)	2.04 (1.65, 2.47)	1.88 (1.52, 2.34)	2.63 (2.17, 3.19)	2.59 (2.11, 3.17)	3.22 (2.64, 3.90)
missing	0 (0)	0	0	0	0	1
Forced vital capacity (FVC), l	2.86 (2.35, 3.52)	2.76 (2.27, 3.49)	2.47 (1.98, 3.06)	3.56 (3.01, 4.31)	3.38 (2.77, 4.15)	4.06 (3.37, 4.88)
missing	0	0	0	0	0	6
FEV <sub>1</sub> /FVC	0.73 (0.68, 0.77)	0.74 (0.68, 0.79)	0.78 (0.73, 0.82)	0.74 (0.69, 0.78)	0.77 (0.73, 0.81)	0.80 (0.76, 0.83)
missing	0	0	0	0	0	4
FEV <sub>1</sub> GLI-2012 z-score	-0.62 (-1.39, 0.10)	-0.27 (-0.98, 0.41)	-0.49 (-1.32, 0.19)	-0.46 (-1.20, 0.18)	-0.04 (-0.78, 0.65)	0.15 (-0.57, 0.84)
missing	0	0	0	0	0	1
FVC GLI-2012 z-score	-0.34 (-1.00, 0.24)	-0.03 (-0.72, 0.59)	-0.57 (-1.38, -0.00)	-0.06 (-0.69, 0.57)	-0.05 (-0.66, 0.57)	0.11 (-0.51, 0.72)
missing	0	0	0	0	0	6
FEV <sub>1</sub> /FVC GLI-2012 z-score	-0.44 (-1.14, 0.06)	-0.41 (-1.07, 0.18)	0.15 (-0.44, 0.60)	-0.74 (-1.32, -0.19)	-0.03 (-0.63, 0.50)	0.01 (-0.58, 0.53)
missing	0	0	0	0	0	4
Intracranial volume, ml	1490.7 (1398.0, 1608.4)	1366.9 (1268.5, 1484.8)	1415.1 (1322.4, 1517.4)	1227.2 (1145.3, 1313.8)	1132.4 (1053.9, 1216.1)	1584.1 (1470.6, 1703.8)
missing	0	0	0	37	0	0
Brain volume, ml	1076.3 (1008.2, 1151.1)	1008.9 (940.1, 1088.3)	956.5 (887.2, 1022.4)	950.6 (883.3, 1023.4)	925.0 (860.6, 990.7)	1139.7 (1057.9, 1223.4)
missing	0	3	0	37	0	0
Gray matter volume, ml	672.9 (631.9, 716.3)	439.1 (409.8, 472.0)	523.3 (485.7, 558.9)	497.3 (461.6, 530.3)	525.0 (490.0, 562.6)	630.8 (588.0, 676.8)
missing	0	0	0	37	0	0
Total hippocampal volume, ml	5.60 (5.17, 5.99)	6.90 (6.30, 7.56)	6.80 (6.21, 7.45)	6.66 (6.64, 7.13)	6.66 (6.21, 7.13)	7.94 (7.37, 8.49)
missing	0	7	0	37	299	0
White matter hyperintensities volume, ml	13.87 (7.65, 24.59)	10.99 (6.18, 19.72)	4.25 (2.56, 7.79)	0.57 (0.32, 1.05)	3.45 (1.83, 7.08)	0.16 (0.06, 0.46)
missing	0	4	0	51	0	4

AGES, Age, Gene/Environment Susceptibility Study; ARIC, Atherosclerosis Risk in Communities Study; CHS, Cardiovascular Health Study; FHS, Framingham Heart Study; RS, Rotterdam Study; SHIP, Study of Health in Pomerania.

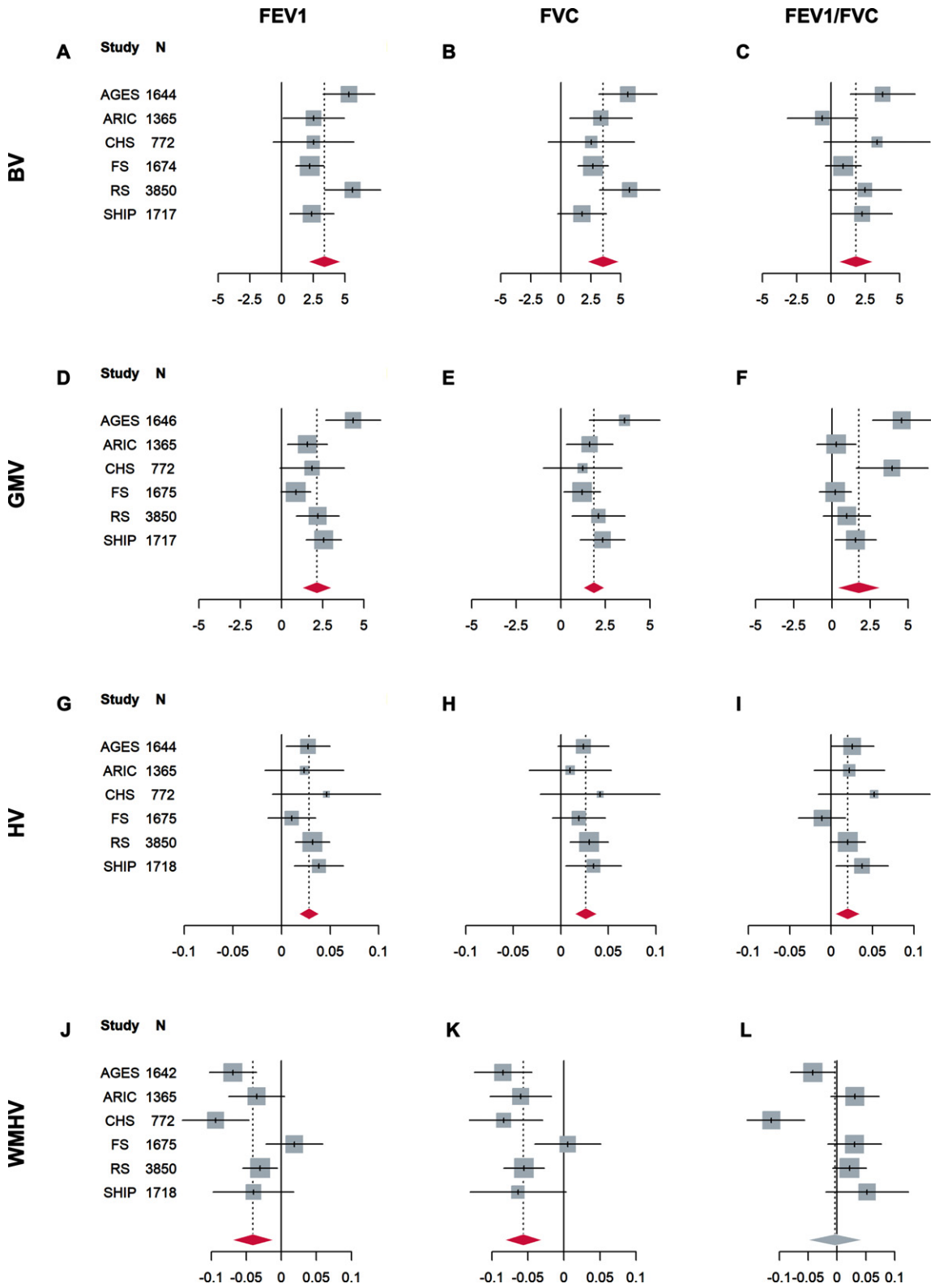


Fig. 1. (Continued)

with gray matter volume ( $I^2 = 52\%$ ) and white matter hyperintensities volume ( $I^2 = 61\%$ ).

## DISCUSSION

In our coordinated meta-analyses of six large-scale community-based samples comprising 11,091 individuals, we found statistically significant associations of both lower values of FEV1 and FVC with lower values of brain volume, gray matter volume, hippocampal volume, and higher volume of white matter hyperintensities. FEV1/FVC was also statistically significantly, albeit less strongly, associated with brain volume, gray matter volume, and hippocampal volume, but not with white matter hyperintensities volume.

Our findings are in line with the general consensus of previous smaller studies. For instance, Sachdev et al. reported associations of FEV1 and FVC, but not FEV1/FVC, with subcortical brain atrophy in a community sample of 469 individuals aged 60–64 years [11]. In contrast to our study, they did not find an association with white matter hyperintensities volume, which may be attributed to the smaller sample size and, on average, younger participants. However, two larger studies did find associations of FEV1 and FVC with markers of cerebral small vessel disease, including lacunes and white matter hyperintensities, which is in line with our results [13, 14].

COPD has long been recognized as an important risk factor for reduced white matter integrity, increased white matter hyperintensities burden, and cognitive decline [4, 5]. It is characterized by an obstructive spirometry pattern, i.e., decreased FEV1 but relatively preserved FVC resulting in reduced FEV1/FVC. Impaired vital capacity on the other hand, characterized by simultaneously decreased FEV1 and FVC but preserved FEV1/FVC, is as prevalent in the general population (about 10% in western countries) and has been found to be associated with diabetes, metabolic syndrome, and systemic inflammation [8, 9]. Besides genetic and developmental factors (e.g., low birth weight, childhood socio-economic status) [34–37], exposure to air pollutants such as particulate matter or nitrogen

dioxides is believed to be a major risk factor for the development of restrictive dysfunction, potentially explaining the high prevalence in countries with high usage of biomass fuels for cooking [38–41]. Impaired vital capacity is associated with chronic respiratory symptoms, higher rates of cardiovascular disease, and increased mortality [8]. Two studies conducted within ARIC found impaired pulmonary function, in particular impaired vital capacity, to be associated with worse cognitive function and increased risk of dementia and mild cognitive impairment later in life [2, 42]. While some heterogeneity was present in our study, the overall associations for FVC were consistently stronger than for FEV1/FVC, specifically with brain volume and white matter hyperintensities volume. This might explain the more pronounced association of impaired vital capacity with increased risk of dementia and lower cognitive function found in previous studies. However, reduced FVC can be both due to lung restriction and hyperinflation (sometimes seen in COPD with predominant emphysema) and differentiation requires full pulmonary testing (body plethysmography). This is also reflected in current guidelines which only distinguish between obstruction and non-obstruction [43]. Further studies relying on body plethysmography data are required to assess the differential associations of restrictive and obstructive lung disease with brain aging and dementia.

### *Pathophysiological mechanisms*

Pulmonary function is linked to advanced brain ageing by several pathophysiological mechanisms. For instance, poor pulmonary function is associated with reduced cerebral blood flow, which may lead to hypoxia and ischemic brain injury [3, 44]. Second, a close link also exists with diabetes [45, 46], which itself is associated with cognitive dysfunction and advanced brain ageing [47]. Hypoxemia-induced insulin resistance, and alterations in organogenesis and metabolic pathway programming due to adverse early-life conditions have been suggested as potential mechanisms, among others [45]. Nevertheless, associations in the current study persisted after accounting

Fig. 1. Forest plots of associations of standardized FEV1 (left column), FVC (middle column), and FEV1/FVC (right column) with brain volume (BV, in ml, A-C), gray matter volume (GMV, in ml, D-F), hippocampal volume (HV, in ml, G-I), and white matter hyperintensities volume (WMHV, in mm<sup>3</sup>, natural log-transformed, J-L). Regression coefficients (lines) and overall effects (diamonds) are shown. All analyses were adjusted for age, sex, intracranial volume, body height, smoking status, and diabetes mellitus. Red diamonds indicate significant overall effects after correction for multiple testing with the Benjamini-Hochberg method ( $FDR \leq 5\%$ ). FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity. Abbreviations for the studies are defined in the footnote to Table 1.



Table 2

Overall effects in linear ordinary regressions of structural brain variables on standardized FEV1, FVC, and FEV1/FVC. Analyses were adjusted for age, sex, intracranial volume, body height, smoking status, and presence of diabetes

Outcome	Exposure	No. of Studies	Heterogeneity Test		I <sup>2</sup> [%]	Overall effect (95% CI)	p-value	P <sub>FDR</sub>	
			Cochran's Q	p-value					
BV	FEV1	6	12.23	0.02	5	3.388 (2.086, 4.691)	3.4E-07	1.0E-06	***
BV	FVC	6	8.67	0.07	0	3.525 (2.176, 4.873)	3.0E-07	1.0E-06	***
BV	FEV1/FVC	6	8.73	0.11	0	1.811 (0.549, 3.072)	0.00	0.01	**
GMV	FEV1	6	16.42	0.01	21	2.136 (1.224, 3.049)	4.5E-06	1.1E-05	***
GMV	FVC	6	6.16	0.34	0	1.860 (1.256, 2.463)	1.6E-09	1.9E-08	***
GMV	FEV1/FVC	6	23.80	3.6E-4	52	1.755 (0.322, 3.187)	0.02	0.02	*
HV	FEV1	6	3.56	0.66	0	0.028 (0.018, 0.039)	9.3E-08	5.6E-07	***
HV	FVC	6	1.23	0.91	0	0.026 (0.014, 0.038)	1.3E-05	2.6E-05	***
HV	FEV1/FVC	6	6.87	0.24	0	0.020 (0.005, 0.035)	0.01	0.01	*
WMHV	FEV1	6	17.09	0.01	29	-0.041 (-0.071, -0.011)	0.01	0.01	**
WMHV	FVC	6	11.72	0.08	0	-0.056 (-0.082, -0.031)	1.9E-05	3.2E-05	***
WMHV	FEV1/FVC	6	29.74	5.3E-5	61	-0.003 (-0.051, 0.044)	0.89	0.89	

FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; BV, brain volume (in ml); GMV, gray matter volume (in ml); HV, hippocampal volume (in ml); WMHV, volume of white matter hyperintensities (in mm<sup>3</sup>, natural log-transformed); I<sup>2</sup>, heterogeneity index; FDR, false discovery rate. \*\*\*P<sub>FDR</sub> < 0.001, \*\*P<sub>FDR</sub> < 0.01, \*P<sub>FDR</sub> < 0.05.

for comorbid diabetes. Third, systemic inflammation has been found to be related to both advanced brain aging [48] and reduced pulmonary function independent from smoking and obesity [49, 50]. Systemic inflammation may be due to local inflammation within the lungs as part of a defense reaction against environmental toxins or infection agents [50].

### Strengths and limitations

In addition to the large sample size, one of the strengths of our study is the standardization of spirometry measurements based on GLI-2012 reference equations [26]. These are based on data from 74,187 life-long non-smokers without lung disease and allow for separating pathological changes from those related to normal ageing, sex, body size, and ethnicity. As shown in the SHIP sample, variance in spirometry measurements related to age, sex, and body height was greatly reduced by this procedure, with the explained variance decreasing from about 75% to 2% for FEV1 and 1% for FVC, respectively. This is of great importance, since these variables are major confounders in association analyses with structural brain variables [26, 30, 51, 52]. The resulting standardized spirometry measurements should be approximately normally distributed, which was seen in our study samples.

While the assessment of airway restriction is based on forced expiratory maneuvers in most studies it can also be measured by maximal inspiration after complete expiration. The so-obtained inspiratory vital capacity (IVC) is generally larger than FVC with the difference being more pronounced in individuals with

obstructive impairment due to narrowing of peripheral airways. As a consequence, FVC underestimates the actual vital capacity and FEV1/FVC is spuriously high when being indexed to FVC compared to IVC in those individuals [53, 54]. Future studies should therefore also consider the IVC in addition to FVC. However, reference equations for IVC based different ethnicities and ages ranges are still lacking to date. Another possibility is the measurement of vital capacity during slow (non-forced) exhalation, which also reduces its underestimation compared to forced exhalation. Our study has several additional limitations. First, the cross-sectional nature of the analyses hampers causal inference. Second, selecting participants who underwent both spirometry and MRI may have led to somewhat healthier analytic samples. This might have introduced bias, most likely causing an underestimation of the true effect, for instance when current smokers with worse brain health and lower pulmonary function are less willing to participate. Third, there is the possibility of reverse causality, with subjects performing worse in the spirometric testing due to their cognitive impairment. Fourth, although we considered important potential confounders such as age, body height, smoking, and diabetes, residual confounding cannot be ruled out. For instance, dietary factors (e.g., intake of foods rich in anti-oxidants and vitamins) have been associated with pulmonary function, brain structure, and cognition [55–57]. Finally, as the inspiratory vital capacity exceeds the FVC in particular in individuals with obstructive impairment, overestimations of FEV1/FVC in our study may have attenuated the corresponding effect estimates.

## CONCLUSIONS

In summary, impaired pulmonary function is associated with lower brain volumes and increased burden of white matter hyperintensities in six large community-based samples. Our results provide further evidence to the notion that lung function plays an important but underappreciated role in cognitive decline and dementia pathophysiology.

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Authors' disclosures available online (<https://www.j-alz.com/manuscript-disclosures/22-0667r1>).

## SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: <https://dx.doi.org/10.3233/JAD-220667>.

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