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Reduced forced vital capacity is associated with cerebral small vessel disease burden in cognitively normal individuals

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ABSTRACT

Background: Pulmonary dysfunction is associated with elevated risk of cognitive decline. However, the mechanism underlying this relationship has not been fully investigated. In this study, we investigate the relationships between pulmonary function, cerebral small vessel disease (CSVD) markers, cortical thickness, and the Mini-Mental Status Examination (MMSE) scores in cognitively normal individuals.

Methods: We used a cross-sectional study design. We identified 1924 patients who underwent pulmonary function testing, three-dimensional brain magnetic resonance imaging (MRI), and the MMSE. Pulmonary function was analyzed according to the quintiles of percentage predicted values (% pred) for forced vital capacity (FVC) or forced expiratory volume in 1 s (FEV_1). Regarding CSVD markers, we visually rated white matter hyperintensities (WMH) and manually counted lacunes and microbleeds. Cortical thickness was measured by surface-based methods.

Results: Compared with the highest quintile of FVC, the lowest quintile of FVC (% pred) showed a higher risk of WMH (OR 1.98, 95% CI: 1.21–3.24) and lacunes (OR 1.86, 95% CI: 1.12–3.08). There were no associations between FVC or FEV_1 and cortical thickness. Low FVC, but not FEV_1, was associated with low MMSE scores. Path analyses showed that WMH partially mediated the positive relationship between FVC (% pred) and MMSE score.

Conclusions: Our findings suggested that decreased pulmonary function was associated with increased CSVD burdens, which in turn wass associated with decreased cognition, even in cognitively normal subjects.

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1. Introduction

Deteriorating pulmonary function contributes to adverse clinical outcomes in patients with respiratory disease. It is also associated with extra-pulmonary manifestations and comorbidities, including metabolic syndrome and cardiovascular disease. Due to shared contributing factors such as aging and smoking, or as a direct result of respiratory difficulty, pulmonary function impairment is thought to be associated with increased risk of cognitive decline. Indeed, there is increasing evidence that impaired lung function, such as reduced forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC), is associated with cognitive decline or dementia (Pathan et al., 2011, Dodd, 2015). In particular, chronic obstructive pulmonary disease, represented by reduced FEV_1, has been shown to be associated with increases in the risk of cognitive impairment, cognitive decline, and dementia (Dodd, 2015).

Cerebral small vessel disease (CSVD) refers to pathological processes that affect the small vessels, including small arteries, arterioles, capillaries, and small veins of the brain (Pantoni, 2010). Recently, the term CSVD has more commonly been used to denote a syndrome of clinical, neuropathologic, and neuroimaging findings (Wardlaw et al., 2013). CSVD markers include lacunes (Vermeer et al., 2007), white matter hyperintensities (WMH) (Rost et al., 2010), microbleeds (Doubal et al., 2010), and brain atrophy (Aribisala et al., 2013). CSVD is strongly associated with incident ischemic and hemorrhagic stroke (Debette and Markus, 2010), progressive cognitive dysfunction (Gorelick et al., 2011), and vascular risk factors (Jackson et al., 2010). Previous studies have shown that impaired lung function is associated with increased WMH (Longstreth et al., 1996, Liao et al., 1999, Spilling et al., 2017), but few studies have shown the relationship between other CSVD markers such as lacunes and microbleeds and pulmonary function.

Another important biomarker for predicting cognitive impairment in cognitively normal individuals is cortical thickness. It is widely accepted that cortical thinning precedes the onset of cognitive decline (Jack et al., 2009). However, only a few studies have investigated the relationship between pulmonary function and brain atrophy (Spilling et al., 2017, Sachdev et al., 2006). Furthermore, the topography of brain atrophy related to lung function has not been fully investigated.

In the present study, we examined the relationships between lung function and CSVD burden, cortical thickness, and Mini-Mental Status Examination (MMSE) scores in a large sample of cognitively normal individuals.

2. Materials and methods

2.1. Participants

We studied 3996 participants who attended medical check-ups, which included assessments of cognitive function and dementia status (Kang et al., 2019), at the Health Promotion Center of the Samsung Medical Center (Seoul, Korea) from October 2009 to December 2014. Among them, 2682 participants were 45 years or older and underwent pulmonary function testing and brain magnetic resonance imaging (MRI). We excluded the following participants from this study: 502 subjects with missing data for demographic and anthropometric variables, Korean MMSE (K-MMSE) score, or CSVD markers, and 256 subjects with significant cognitive impairment, brain lesions, or unreliable analyses of cortical thickness. The final sample was composed of 1924 participants.

2.2. Standard protocol approvals, registrations, and patient consent

The Institutional Review Board at Samsung Medical Center approved this study. All methods were carried out in accordance with approved guidelines. The requirement for informed consent was waived, as we collected retrospective de-identified data.

2.3. Measurements

Health screening exams were performed by trained personnel according to a standard protocol. This health screening program has been described in detail previously (Park et al., 2010). Demographic characteristics, medical history including medication, and smoking status were collected using a standardized self-report questionnaire at each visit. Smoking status was classified as never, past, or current smoker. A trained nurse measured height and weight with each participant wearing a lightweight hospital gown and no shoes. Body mass index (BMI) was calculated by dividing body weight in kilograms by height in meters squared. Blood pressure was measured in a sitting position by trained nurses. Hypertension was defined as systolic blood pressure greater than 140 mm Hg, diastolic blood pressure greater than 90 mm Hg, a self-reported history of hypertension, or current antihypertensive use. Serum total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol were measured by the enzymatic colorimetric method. Glucose was measured using fasting blood samples collected after at least 10 h of fasting. Diabetes was defined as fasting serum glucose level greater than 126 mg/dL, self-reported diabetes history, or use of diabetes medications. Laboratory tests were conducted at the Department of Laboratory Medicine and Genetics at Samsung Medical Center.

2.4. Measurement of pulmonary function

Spirometry was performed as recommended by the American Thoracic Society/European Respiratory Society using Vmax 22 (SensorMedics, OH, USA) (Pellegrino et al., 2005). We obtained the absolute values of FVC and FEV1 and calculated percentage predicted values (% pred) for FVC and FEV1 using equations for reference values regarding age, sex, height, and weight obtained from a representative Korean sample (Choi et al., 2005).

2.5. Acquisition of MRI data

All subjects underwent 3D volumetric brain MRI scans. 3D T1 Turbo Field Echo (TFE) MRI data were acquired using an Achieva 3.0-Tesla MRI scanner (Philips, Best, the Netherlands), with a sagittal slice thickness of 1.0 mm, over-contiguous slices with 50% overlap and no gap, a repetition time of 9.9 ms, an echo time of 4.6 ms, a flip angle of 8°, and a matrix size of 240 × 240 pixels reconstructed to 480 × 480 over a field of view of 240 mm. Radiologists reviewed all MRI data for evidence of brain tumors, major infarctions (excluding lacunar infarctions), and hemorrhages (which are observed as low-intensity areas on T2-weighted images). The following parameters were used for the 3D FLAIR images: axial slice thickness of 2 mm; no gap; repetition time of 11,000 ms; echo time of 125 ms; flip angle of 90; and matrix size of 512 × 512 pixels.

2.6. WMH visual rating scale

A modified Fazekas scale was used for the visual rating of WMH (Fazekas et al., 1987). We classified periventricular WMH (PWMH) into P1 (maximum diameter of cap and band < 5 mm), P2 (5 mm ≤ cap or band < 10 mm), or P3 (cap or band ≥ 10 mm); deep WMH (DWMH) was classified as D1 (maximum diameter of deep white matter lesion < 10 mm), D2 (10 mm ≤ lesion < 25 mm), and D3 (≥ 25 mm). The inter-rater reliability of the WMH visual rating scale was excellent (intraclass correlation coefficient between 0.726 and 0.905), as shown in a previous study (Moon et al., 2011). The WMH visual rating scale was well correlated with an automated measure of WMH volume in a previous study (Noh et al., 2014). The ratings were combined to determine an ischemia classification: minimal, moderate, or severe. A combination of

D1 with P1 (D1P1) and D1P2 was defined as 'minimal'. The combination of D1P3, D2P1, D2P2, D2P3, D3P1, and D3P2 was defined as 'moderate'. D3P3 was defined as 'severe'. This ischemia classification system was previously reported to distinguish the presence of vascular risk factors and the severity of CSVD markers (Noh et al., 2014). We then dichotomously classified WMH into negative and positive, with negative defined as minimal and positive defined as moderate to severe WMH.

2.7. Number of lacunes

A lacune was defined as a small lesion (3 mm ≤lesion≤15 mm in diameter) with low signal on T1-weighted images, high signal on T2-weighted images, and a perilesional halo on FLAIR images following the consensus criteria (Wardlaw et al., 2013). Two neurologists manually counted the number of lacunes. The rate of agreement between the two neurologists was 83.0%, and a consensus was reached for any case of discrepancy. Lacunes were dichotomized into categories of absent or present.

2.8. Number of microbleeds

Cerebral microbleeds were defined as <10 mm in diameter and the following consensus criteria (Wardlaw et al., 2013). Two experienced neurologists, who were blinded to patient data, reviewed the number and locations of cerebral microbleeds on 20 axial slices of T2 FFE-MRI. The rate of agreement between the two neurologists was 92.3%, and consensus was reached in any case of discrepancy. Microbleeds were dichotomized into categories as absent or present.

2.9. Image processing for cortical thickness measurement

Using the standard Montreal Neurological Institute image processing tool CIVET, T1-weighted images were processed to measure the thickness of the cortex. This software has been shown to be valid and has been described previously (Lerch and Evans, 2005). Native MRI images were registered into a standardized stereotaxic space using an affine transformation (Collins et al., 1994). Using the N3 algorithm, non-uniformity artifacts were corrected. Using an artificial neural net classifier, the registered and corrected volumes were classified into white matter (WM), gray matter (GM), cerebrospinal fluid (CSF) and background (Sled et al., 1998). Using the Laplacian-Based Automated Segmentation with Proximities Algorithm, we extracted the inner and outer cortical surfaces by deforming the spherical mesh onto the gray-white boundaries of each hemisphere (Im et al., 2006, Kim et al., 2005).

The thickness of the cortex was calculated using the Euclidean distance between the connected vertices of the inner and outer surfaces, after applying an inverse transformation matrix to the surfaces of the cortex and reconstructing them in the native space (Kim et al., 2005). We used classified tissue information and a skull mask acquired from the T1-weighted image and computed ICV to control for brain size (Smith, 2002). ICV was defined as the sum of the volume of GM, WM, and CSF, considering voxel dimensions. GM, WM, CSF, and background within the mask were transformed back into individual native space.

The thicknesses were registered spatially on an unbiased iterative group template by matching sulcal folding patterns using surface-based registration involving sphere-to-sphere warping to compare the thicknesses of corresponding regions between subjects (Lyttelton et al., 2007). We used the lobe parcellated group template, which was divided into frontal, temporal, parietal, and occipital lobes using SUMA (http://afni.nimh.nih.gov) for global and lobar regional analyses (Im et al., 2006). For global analysis, we used average values of the thickness of all vertices in each hemisphere and lobar region.

2.10. Statistical analyses

We performed multivariable linear regression analysis to explore the relationships between pulmonary function and CSVD markers. Predictors were pulmonary functions measured by the quintiles of FVC or FEV_1 (% pred) using the highest quintile group as the reference group. We determined the presence of CSVD markers, measured by moderate to severe WMH and the presence of lacunes or microbleeds. We adjusted for age (< 65 vs. ≥ 65), years of education, presence of hypertension, diabetes, and hyperlipidemia, and smoking status. To minimize collinearity problems between age and pulmonary function, we classified age as less than 65, and 65 years or older, following the definition of elderly status.

To explore the relationships between FVC or FEV_1 (% pred) and global and regional cortical thickness, we also performed multivariable linear regression analyses after controlling for age (< 65 vs. ≥ 65), years of education, smoking status, presence of hypertension, diabetes, hyperlipidemia, and ICV. To explore the relationships between FVC or FEV_1 (% pred) and MMSE, we performed multivariable linear regression analyses after controlling for age (< 65 vs. ≥ 65), years of education, smoking status, presence of hypertension, diabetes and hyperlipidemia.

Statistical analyses were performed with STATA version 14 (StataCorp LP, College Station, TX, USA). Two-tailed p-values less than 0.05 were considered statistically significant. We applied the Bonferroni correction in cases of multiple comparisons between quintile groups, and p-values less than 0.0125 were considered statistically significant.

Using path analyses, we evaluated whether CSVD burden mediated the relationship between pulmonary function and MMSE score after controlling for age (< 65 vs. ≥ 65), years of education, the presence of hypertension, diabetes, and hyperlipidemia, and smoking status. We simultaneously considered the direct, indirect, and total effects of predictors on outcomes through mediators. We used bootstrapping to verify the significance of indirect effects. The path analysis was conducted using Amos Version 18.0 software (SPSS, Chicago, IL, USA).

3. Results

3.1. Baseline characteristics of the participants

Table 1 shows the clinical characteristics of the participants. The total number of participants was 1924, the mean age was 63.9 years, and 48.3% of the participants were female. Current or ex-smokers comprised 41.4% of the participants. The clinical characteristics of the participants based on quintiles of FVC and FEV_1 % of predicted value are shown in Supplementary Tables 1 and 2.

3.2. Pulmonary function and CSVD burden

Regarding the relationship between FVC (% pred) and CSVD burden, multivariable logistic regression analyses found that the lowest quintile group of FVC (% pred) exhibited higher risk of WMH (OR 1.98, 95% CI: 1.21–3.24) and lacunes (OR 1.86, 95% CI: 1.12–3.08) compared to the highest quintile group. There was a significant trend between low FVC (% pred) and risk of WMH (p for trend = 0.027) and lacunes (p for trend = 0.018). (Fig. 1A, Supplementary Table 3) There were no correlations between FEV_1 (% pred) and WMH, lacunes, or microbleeds (Fig. 1B, Supplementary Table 3).

3.3. Pulmonary function and cortical thickness

In terms of the relationship between FVC (% pred) and cortical thickness, FVC (% pred) was positively associated with cortical thickness in the global (p for trend = 0.007), frontal (p for trend = 0.023), parietal (p for trend = 0.001) and occipital regions (p for

Table 1
Clinical characteristics of the participants

	Total
Number (%)	1924 (100)
Age, years	63.9 (7.2)
Female, N (%)	901 (46.8)
Education, years	12.8 (4.3)
Hypertension, N (%)	930 (48.3)
Diabetes mellitus, N (%)	328 (17.1)
Hyperlipidemia, N (%)	603 (31.3)
Smoking status	
Never smoker, N (%)	1127 (58.6)
Ex-smoker, N (%)	622 (32.3)
Current smoker, N (%)	175 (9.1)
BMI, kg/m2	23.3 (2.1)
Stroke	56 (2.9)
Cardiovascular disease	121 (6.3)
ICV, cm3	1367.1 (123.1)
K-MMSE, points	28.0 (1.9)
Pulmonary function test	
FEV1, (% pred)	89.3 (13.4)
FVC, (% pred)	86.6 (12.3)
FEV1/FVC ratio, (%)	77.3 (6.5)
CSVD markers	
Moderate to severe WMH, N (%)	235 (12.2)
Presence of lacunes, N (%)	182 (9.5)
Presence of microbleeds, N (%)	174 (9.0)
Cortical thickness (mm)	
Global	3.05 (0.11)
Frontal	3.09 (0.12)
Temporal	3.20 (0.17)
Parietal	2.91 (0.14)
Occipital	2.69 (0.13)

Values are mean (SD) or number (%).
N, number; SD, standard deviation; BMI, body mass index; ICV, intracranial volume; K-MMSE, Korean mini-mental status examination

trend = 0.016) in model 1, after controlling for years of education, smoking status, presence of hypertension, diabetes, and hyperlipidemia. However, this association disappeared after additional adjustments for related factors, especially age (< 65 vs. ≥ 65) (model 2). There was no significant relationship between FEV_1 (% pred) and cortical thickness (Supplementary Table 4).

3.4. Pulmonary function and MMSE

In terms of the relationship between FVC (% pred) and MMSE, the lowest FVC (% pred) group had a lower MMSE score compared to the highest group. FVC (% pred) was positively associated with MMSE (mean difference −0.47, p for trend = 0.001). By contrast, there was no relationship between FEV_1 (% pred) and MMSE (Table 2).

Table 2
Relationships between FVC % of predicted value and FEV_1 % of predicted value and MMSE

	MMSE	
	Mean difference (SD)	*P*
FVC (% pred)		
Q1 (n = 385)	−0.47 (0.12)	< 0.001
Q2 (n = 385)	−0.13 (0.12)	0.280
Q3 (n = 385)	−0.17 (0.12)	0.147
Q4 (n = 385)	−0.17 (0.12)	0.145
Q5 (n = 384)	Ref	
p for trend		0.001
FEV_1 (% pred)		
Q1 (n = 385)	−0.12 (0.12)	0.322
Q2 (n = 385)	−0.01 (0.12)	0.955
Q3 (n = 385)	−0.01 (0.12)	0.939
Q4 (n = 385)	0.01 (0.12)	0.913
Q5 (n = 384)	Ref	
p for trend		0.341

Adjusted for age (< 65 vs. ≥ 65), years of education, presence of hypertension, diabetes, hyperlipidemia, and smoking status

MMSE, mini-mental state examination; Coef., coefficient; SD, standard deviation; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity

3.5. Path analysis for MMSE

We constructed a hypothetical model of relationships among FVC (% pred), the presence of CSVD markers, and MMSE. Our results indicated that WMH partially mediated the relationship between FVC (% pred) and MMSE (Fig. 2, Table 3). The path analysis model showed high goodness of fit to the data (goodness of fit index = 0.948). Models of the relationships among FVC (% pred), the presence of microbleeds or lacunes, and MMSE did not show mediation effects of microbleeds or lacunes on the relationship between FVC (% pred) and MMSE (Supplementary Tables 5, 6).

FVC, forced vital capacity; % pred, percentage predicted values; WMH, white matter hyperintensities

MMSE, mini-mental state examination; WMH, white matter hyperintensities; FVC (% pred), forced vital capacity; β, standardized beta coefficient; SE, standard error

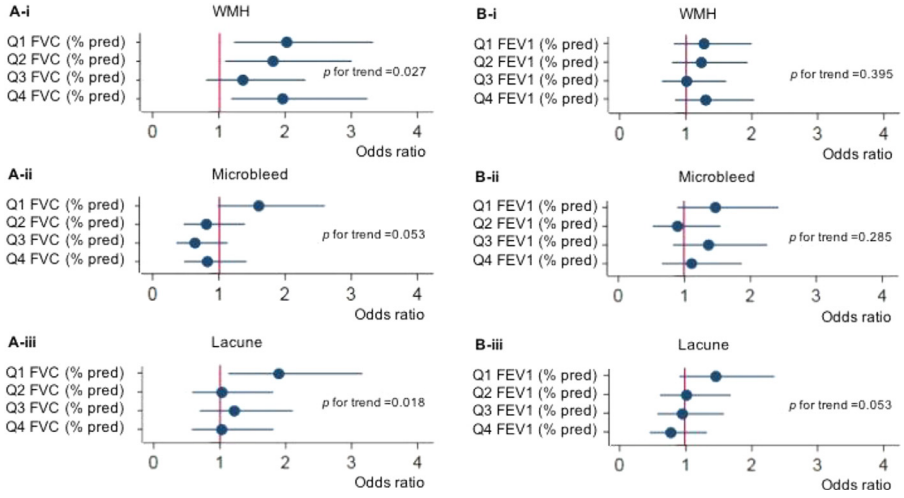

Fig. 1. Relationships between pulmonary function and CSVD markers. Compared with the highest quintile group of FVC % of predicted value (Q5 FVC (% pred), left), the lowest quintile group FVC % of predicted value (Q1 FVC (% pred)) had higher risk of A-i) WMH (adjusted OR 1.98, 95% CI: 1.21–3.24, *p* for trend = 0.027) and A-iii) lacunes (adjusted OR 1.86, 95% CI: 1.12–3.08, *p* for trend = 0.018) after controlling for age (< 65 vs. ≥ 65), years of education, presence of hypertension, diabetes, and hyperlipidemia, and smoking status. Microbleeds showed a trend of higher risk (A-ii, adjusted OR 1.57, 95% CI: 0.98–2.54, *p* for trend = 0.053). There was no relationship between FEV1 (% pred) and CSVD markers (B-i though B-iii).
Q, quintile; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second;
% pred, percentage predicted values; WMH, white matter hyperintensities; CSVD, cerebral small vessel disease.

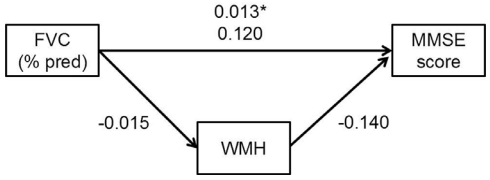

Fig. 2. Schematic diagram of path analyses for MMSE scores. The lowest and the highest quintiles of FVC (% pred) were entered as predictors. Presence of moderate to severe WMH was entered as a mediator. We adjusted for age (< 65 vs. ≥ 65), years of education, presence of hypertension, diabetes, and hyperlipidemia, and smoking status. Numbers on the paths are standardized direct effects that were statistically significant. Starred numbers (*) on the path between FVC (% pred) and MMSE score indicate standardized indirect effects.

4. Discussion

In this study, we assessed the relationships between pulmonary function and CSVD markers, cortical thickness, and MMSE score in cognitively normal subjects. First, pulmonary function, especially low FVC (% pred), was associated with the presence of CSVD markers. Second, there was no significant association between low FVC (% pred) and cortical thickness. Third, low FVC (% pred) was related to low MMSE scores even in cognitively normal subjects. Fourth, among CSVD markers, the WMH burden partially mediated the relationship between FVC (% pred) and MMSE score. However, we did not observe associations between decreased FEV_1 (% pred) and CSVD markers, cortical thickness, or MMSE scores. Taken together, our findings suggested that restrictive pulmonary dysfunction was associated with increased CSVD burden, which was in turn associated with decreased cognition in cognitively normal subjects. In this regard, clinicians should be attentive to signs in patients with restrictive patterns to ensure brain health, even when they are cognitively normal.

In agreement with the findings of previous studies, in the present study we demonstrated that low FVC (% pred) was associated with increased CSVD burden as indicated by variables such as WMH (Longstreth et al., 1996, Liao et al., 1999, Sachdev et al., 2006) and lacunes (Liao et al., 1999). We further showed a trend towards low FVC with the presence of microbleeds, which was not revealed by previous research. However, we did not observe any relationship between FVC (% pred) and cortical thickness, which is in line with the results of a previous study showing a lack of association between pulmonary function and subcortical atrophy (Sachdev et al., 2006). In particular, cortical thickness was strongly affected by aging in our results, which diminished the association between cortical thickness and FVC (% pred). Thus, our conclusions suggest that there is an association between CSVD burden and low FVC (% pred), but that there is no association of cortical thickness with low FVC (% pred) beyond aging in subjects with normal cognitive function. Further prospective longitudinal studies are required to explain the sequential mechanism linking CSVD burden and cortical thickness with FVC (% pred).

In terms of the relationship between cognitive function and pulmonary function, previous studies reported a correlation between decreased pulmonary function and impaired cognitive function in COPD patients, and these studies mostly targeted FEV_1 as a predictor (Dodd et al., 2010, Wang et al., 2019). Community-based studies also reported a correlation between pulmonary function and cognitive function (Emery et al., 2012, Richards et al., 2005). In the present study, as dementia can be caused by various factors, our subjects were restricted to those with a normal cognitive function of 16 percentiles or more according to MMSE scores. Even in cognitively normal subjects, we observed a positive correlation between FVC (% pred) and MMSE score. This suggests that cognitively normal subjects with low FVC (% pred) may require continuous follow-up for cognitive function.

It is generally recognized that low FVC is related to lung and thoracic diseases, including interstitial lung disease, neuromuscular disorders, and space-occupying lesions (Pellegrino et al., 2005). However, accumulating evidence has demonstrated that restrictive pulmonary function, represented by low FVC, is not only associated with cardiovascular disease itself (Kang et al., 2015), but also associated with a multitude of clinical conditions beyond the lungs and thorax, such as aging (Vaz Fragoso et al., 2016), smoking (Lederer et al., 2009), obesity, metabolic syndrome, and diabetes mellitus (Leone et al., 2009, Lee et al., 2009), which eventually increases the risk of cerebrovascular diseases. In terms of the measurement value of pulmonary function, in our study, FVC showed significant relationships with CSVD markers and MMSE score, while FEV_1 did not. In a previous study evaluating patients with chronic obstructive pulmonary disease (COPD), there was a significant association between FEV_1 and WMH (Spilling et al., 2017). Studies conducted in a community cohort also showed significant correlations between both FVC and FEV_1 and WMH (Longstreth et al., 1996, Liao et al., 1999, Sachdev et al., 2006). However, the significance disappeared after controlling for smoking status in some of these studies. (Longstreth et al., 1996, Sachdev et al., 2006) Given that cognitively normal subjects at a health checkup were included in this study, FVC, rather than FEV_1, might be associated with CSVD and MMSE score. Further prospective studies should be performed to confirm our findings.

Our conclusion, that the correlation between pulmonary function and cognition might be driven by vascular pathways rather than neurodegenerative pathways, is supported by the following observations: (1) WMH was associated with both FVC and MMSE; (2) FVC was not correlated with cortical thickness; and (3) WMH partially mediated the relationship between low FVC and low MMSE score. Our vascular hypothesis might be related to brain network disruption. In fact, previous studies have shown that WMH was associated with imbalances in large-scale brain networks, including decreased network integration and increased network segregation (Kim et al., 2015, Kim et al., 2015). Furthermore, altered structural networks induced by WMH were associated with poor neuropsychological performance in variable domains including attention, language, visuospatial, memory, and frontal-executive functions. Alternatively, it is possible that lower FVC might contribute to the development of ischemic processes, which in turn leads to decreased perfusion or metabolism of the brain, eventually resulting in cognitive impairment. To test our hypotheses, further studies with other modalities of brain imaging are needed. We did not observe significant mediation effects of microbleeds or lacunes on the relationship between FVC (% pred) and MMSE score, perhaps because most of our subjects were healthy participants and did not have microbleeds or lacunes.

The strengths of this study include high-quality clinical

Table 3
Effects of pulmonary function (quintiles of FVC (% pred)) on MMSE score through the presence of WMH

	Direct						Indirect		
	WMH			MMSE			MMSE		
	β	SE	*p*	β	SE	*p*	β	SE	*p*
FVC (% pred)	−0.015	0.038	0.038	0.120	0.031	0.010	0.013	0.006	0.038
WMH				−0.140	0.036	0.010			

measurements and the availability of information on multiple covariates to control for pulmonary function in a large sample size. However, this study has some limitations. First, participants did not undergo amyloid PET scans, and we were not able to further investigate the effects of Alzheimer's disease on the relationships between low FVC and cortical thickness. Second, our study was designed to be cross-sectional, therefore, causality cannot be established. To compensate for this limitation, we performed path analysis, and suggested a possible association between low FVC (% pred), WMH and MMSE score. Third, regarding ratings of WMH and counting microbleeds and lacunes, we reported only inter-rater reliability. We could not assess intra-rater variability, and therefore could not additionally evaluate the accuracy of CSVD marker measurements. Finally, the sample was composed of people who came to the hospital of their own volition for preventive health checkups, which are not covered by national medical insurance. Therefore, the generalizability of our results might be limited, and these results should be cautiously applied to target groups with the disease. Nevertheless, it is noteworthy that this is the first study showing the complex relationships among pulmonary function, CSVD, and cognition in a large sample of cognitively normal individuals. In this regard, attempts to maintain pulmonary function have important implications for brain health, especially considering the paucity of known protective factors for cognitive impairments.

In conclusion, in this study we showed that low FVC is associated with CSVD burden and MMSE, even in cognitively normal subjects. Further longitudinal studies are required to explain the relationship between cognitive decline and decreased pulmonary function.

CRediT authorship contribution statement

Yeshin Kim: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft. **Hyun Lee:** Writing - review & editing. **Tea Ok Son:** Conceptualization, Resources. **Hyemin Jang:** Investigation, Data curation. **Soo Hyun Cho:** Investigation, Data curation. **Si Eun Kim:** Investigation, Data curation. **Seung Joo Kim:** Investigation, Data curation. **Jin San Lee:** Investigation, Data curation. **Jun Pyo Kim:** Investigation, Data curation. **Young Hee Jung:** Investigation, Data curation. **Samuel N. Lockhart:** Writing - review & editing. **Hee Jin Kim:** Investigation, Data curation. **Duk L. Na:** Investigation, Data curation. **Hye Yun Park:** Conceptualization, Methodology, Investigation, Writing - original draft, Writing - review & editing, Supervision. **Sang Won Seo:** Conceptualization, Methodology, Investigation, Writing - original draft, Writing - review & editing, Supervision, Project administration.

Declaration of Competing Interest

The authors declare no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nicl.2019.102140.

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