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Reduced Lung Function and Cerebral Small Vessel Disease in Japanese Men: the Shiga Epidemiological Study of Subclinical Atherosclerosis (SESSA)

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Aim: We aimed to investigate the association between reduced lung function and cerebral small vessel diseases via cranial magnetic resonance imaging (MRI) in the cross-sectional study of the general Japanese population.

Methods: We recruited participants aged ≥40 years from the general population of a single city in Japan. We clarified the comorbidities and treatments, smoking habits, second-hand smoke exposure, current alcohol consumption, education level, exercise habits, and occupation. The pulmonary function test was performed to assess the forced expiratory volume in 1 second (FEV_1) % predicted and forced vital capacity (FVC) % predicted values. Cranial MRI was performed to evaluate the white matter lesions (WMLs) and lacunar infarcts. We examined the association of the WMLs and lacunar infarcts with a 1-standard deviation (SD) lower in the FEV_1 % predicted and FVC % predicted, on the basis of the smoking status.

Results: A total of 473 men were examined. The association of WMLs and lacunar infarcts with the spirometry-based indices were significant only in never smokers. The association between lung function impairment and cerebral small vessel disease did not change after further adjusting for second-hand smoke exposure.

Conclusion: In a community-based sample of Japanese men, we found an association between reduced lung function and WMLs and lacunar infarcts in never smokers.

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Key words: Lacunar infarcts, MRI, Reduced lung function, White matter lesions, Smoking status

Introduction

Cerebral small vessel diseases, including white matter lesions (WMLs) and lacunar infarcts, are frequently observed on cranial magnetic resonance imaging (MRI) in elderly subjects. These asymptomatic lesions usually develop as precursors of clinical stroke[1)], gait disorder, and dementia[2)]. The pathogenesis of these lesions is considered to involve age-related and hypertension-related ischemic small vessel disease as well as cerebral amyloid formation[3)]. Advancing age and hypertension induce endothelial dysfunction[4)] in the cerebral small

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vessels and may lead to hypoperfusion.

Although smoking is known to accelerate forced expiratory volume in 1 second (FEV_1) decline[5-7], some population-based studies have shown that reduced lung function was associated with the presence of subclinical cerebrovascular abnormalities, independent of the smoking status[8-10]. The mechanism underlying this phenomenon remains unclear, although reduced lung function may play an important role in the development of atherosclerosis[11] by inducing inflammation[12, 13].

However, these previous studies did not consider the cumulative smoking exposure, including pack-years in smokers and second-hand smoke exposure in never smokers. Moreover, the association between reduced lung function and the presence of subclinical cerebrovascular abnormalities has not been confirmed in the Asian population, including Japanese individuals, in whom stroke is dominant among the various cardiovascular diseases and the smoking prevalence is still high[14]. Furthermore, lacunar infarct is the dominant type of ischemic stroke in Japan, in contrast with that observed in western countries[15].

Aim

In the present cross-sectional study of the general Japanese population, we aimed to investigate the association between reduced lung function and cerebral small vessel diseases via cranial MRI.

Methods

Study Participants and Measurements

The Shiga Epidemiological Study of Subclinical Atherosclerosis (SESSA) is an ongoing, prospective study of a random sample from the general population residing in Kusatsu City in Shiga, Japan, as described elsewhere[16, 17]. For participant recruitment, we directly contacted (via phone) the SESSA male participants aged ≥40 years from February 2014 to November 2015. Among the 853 SESSA participants, 549 agreed to participate in the present study. A total of 76 subjects were excluded because of the lack of MRI data (n=23); presence of self-reported asthma (n=25) and other lung diseases (n=13) such as prior tuberculosis, lung cancer, and interstitial pneumonia; history of stroke (n=11); and the use of long-acting β agonist inhaler (n=4) (**Supplementary Fig. 1**). Thus, a total of 473 men were examined in the present study (**Table 1**). The protocols were approved by the ethics committee of Shiga University of Medical Science, and written informed consent was obtained from all subjects prior to the study.

A brief and self-administered questionnaire was provided to the participants. The questionnaire recorded data on comorbidities, treatment, smoking habits, second-hand smoke exposure (exposure to smoking in the indoor workplace or at home), current alcohol consumption (yes/no), education level (years of education <10 years, junior high school or below), exercise habits (exercise <1 h, once a week), and occupation. After the participants completed the questionnaire, trained nurses confirmed the responses with the participants. The smoking status was classified as current, former, and never. Participants who smoked in the last 30 days were defined as current smokers, whereas participants who had never smoked or smoked <100 cigarettes in their lifetime[18] were defined as never smokers. On the basis of this information, daily cigarette consumption was estimated in former and current smokers. The pack-years were estimated by multiplying the average number of packs of cigarettes smoked daily by the number of smoking years. We evaluated the long-term (>6 years) exposure to high-risk occupations that are reportedly associated with the development of chronic obstructive pulmonary disease (COPD), including asbestos workers, building destroyers, carpenters, chemical workers, cotton ginners, farmers, mechanics, miners, and welders[19, 20]. We also administrated the Modified British Medical Research Council (mMRC) questionnaire for dyspnea[21], and the COPD assessment test (CAT)[22] to the patients.

The body mass index (BMI) was calculated as the weight (kg) divided by height squared (m^2). As the self-measured home blood pressure (BP) has been shown to have a stronger predictive power for cardiovascular risk as compared with office BP screening[23], we evaluated the home BP using a HEM-7051T (Omron Healthcare Co., Ltd., Kyoto, Japan). Hypertension was defined as an average home systolic BP of ≥135 mmHg, average home diastolic BP of ≥85 mmHg[24], and/or the use of medication for hypertension in this study. Blood samples were drawn from the participants after a 12 h fast and were centrifuged immediately after coagulation. The blood glucose and hemoglobin A1c levels were measured using an enzymatic assay and latex agglutination inhibition assay, respectively. The total cholesterol and triglyceride levels were measured using enzymatic methods, whereas high-density lipoprotein cholesterol levels were measured using a direct method. The lipid measurements were standardized according to the protocol for the Center for Disease Control and Prevention/Cholesterol Reference Method Laboratory Network. Hyperlipidemia was defined as total cholesterol ≥220 mg/dL[25], and/or the use of medication for hyperlipidemia. Diabetes mellitus was defined as a fasting glucose level of ≥126 mg/dL, hemoglobin A1c value of ≥6.1% (per the Japan Diabetes Society protocol;

Table 1. Characteristics of the participants stratified by the smoking status ($n=473$)

	All ($n=473$)	Never smoker ($n=123$)	Former smoker ($n=252$)	Current smoker ($n=98$)
Age, years	69.0 ± 7.9	68.3 ± 8.8	70.4 ± 6.6	66.1 ± 8.9 †‡
BMI, kg/m^2	23.3 ± 2.9	23.4 ± 2.6	23.4 ± 2.9	23.2 ± 3.1
Pack-years	26.5 ± 25.3	–	35.3 ± 23.9	36.7 ± 21.5
Second-hand smoke exposure, %	24.1	15.4	–	–
Exercise habits, %	41.0	32.5	37.7	60.2 †‡
Current alcohol consumption, %	81.4	82.9	81.7	78.6
Occupation*, %	22.8	22.8	25.0	17.3
Education*, %	11.0	7.3	11.9	13.3
mMRC dyspnoea scale 0/1/2/3/4, %	78.6/18.6/2.5/0.2/0	86.2/13.0/0/0.8/0	82.1/16.7/0.1/0/0	60.2/30.6/9.2/0/0 †‡
CAT	3.5 ± 3.3	2.7 ± 2.5	3.3 ± 2.8	5.1 ± 4.5 †‡
FEV_1, L	2.5 ± 0.5	2.6 ± 0.5	2.5 ± 0.5	2.5 ± 0.6
FEV_1 % predicted, %	87.2 ± 14.1	90.2 ± 14.0	87.7 ± 13.6	82.0 ± 14.2 †‡
FVC, L	3.4 ± 0.6	3.4 ± 0.6	3.4 ± 0.6	3.5 ± 0.8
FVC % predicted, %	95.0 ± 14.2	95.9 ± 14.1	95.1 ± 13.7	93.5 ± 15.6
Hypertension, %	67.2	65.0	69.0	65.3
Hyperlipidemia, %	53.5	51.2	58.3	43.9 ‡
Diabetes, %	19.5	14.6	19.4	25.5 †
WMLs, %	21.4	21.1	20.6	23.5
PVWM, %	0.3	0.8	2.8	5.1
DWM, %	21.4	21.1	20.6	23.5
Lacunar infarcts, %	13.1	10.6	14.3	13.3

BMI, body mass index; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; WMLs, white matter lesions; PVWM, periventricular white matter; DWM, deep white matter.

Pack-years were calculated in former and current smokers. Second-hand smoke exposure was evaluated in never smokers. Second-hand smoke exposure (exposure to smoking in the indoor workplace or at home), exercise habits (exercise for < 1 hour, once a week), current alcohol consumption (yes/no), *occupation (high-risk occupational history for > 6 years), *education (years of education < 10 years, junior high school or below), hypertension (average home systolic blood pressure of ≥ 135 mmHg, average home diastolic blood pressure of ≥ 85 mmHg, and/or the use of medication for hypertension), hyperlipidemia (total cholesterol ≥ 220 mg/dL, and/or the use of medication for hyperlipidemia), diabetes (fasting glucose level of ≥ 126 mg/dL, hemoglobin A1c value of ≥ 6.1%, and/or the use of medication for diabetes), WMLs (grade 3 according to the Fazekas classification), PVWM (grade 3 according to the Fazekas classification), DWM (grade 3 according to the Fazekas classification), and lacunar infarcts (≥ 2 silent infarcts) were assessed.

Values are presented as unadjusted means ± standard deviation or number of subjects (%).

†$p<0.05$, versus never. ‡$p<0.05$, versus former.

equivalent to ≥ 6.5% as per the National Glycohemoglobin Standardization Program)[26], and/or the use of antidiabetic medication. We used self-reported disease history for comparison of the characteristics between the participants and non-participants from the SESSA study.

Pulmonary Function Tests

Spirometry was performed using a CHEST graph HI-105T spirometer (CHEST M.I., Inc., Tokyo, Japan) according to the recommendations of the American Thoracic Society/European Respiratory Society[27]. The predicted values for spirometry were calculated in accordance with the guidelines of the Japanese Respiratory Society[28].

Assessment of Cerebral Small Vessel Disease

We assessed for the presence of cerebral small vessel disease by using axial T1, T2-weighted and fluid-attenuated inversion-recovery sequences (FLAIR) images from 1.5 Tesla MRI scanners (GE Healthcare Bio-Sciences, Pittsburgh, PA, USA) at a slice thickness of 4 mm. We defined WML, which was further subdivided as periventricular white matter (PVWM) and deep white matter (DWM) by using FLAIR images. PVWM was graded according to the Fazekas classification[29] as follows: absent (grade 0), periventricular caps or pencil-thin lining (grade 1), smooth halo (grade 2), and irregular periventricular signal extending into the DWM (grade 3). In addition, DWM was graded according to the Fazekas classification[29] as follows: absent (grade 0), punctate foci (grade 1), early confluence (grade 2), and large confluent areas (grade 3). Because we focused on

the future risk factors for lacunar infarcts, only asymptomatic infarcts were considered for the cases. Lacunar lesions were defined as areas of low signal intensity, with a size of ≥3 mm measured on high-resolution three-dimensional T1-weighted images (SPGR), which were visible as hyperintense lesions on T2-weighted images. The shape of the lacunar lesions and its surrounding gliosis were also considered when differentiating these lesions from large perivascular space. As the risk of subsequent stroke increases in the presence of severe WMLs and multiple infarcts[1, 30], we considered those with PVWM grade 3 and/or DWM grade 3 as participants with WMLs[3, 31, 32] and those with multiple lacunar infarcts (≥2 silent infarcts) as participants with lacunar infarcts in the present study. We also considered those with WMLs (grade 3 according to the Fazekas classification) and/or lacunar infarcts (≥2 silent infarcts) as participants with cerebral small vessel disease. Two neurosurgeons, who were blinded to the clinical information, independently evaluated the MRI findings. In the case of disagreement, consensus was achieved by a panel of two neurosurgeons and two epidemiologists.

Statistical Analyses

The differences in the baseline characteristics, stratified by smoking status, were evaluated by using analyses of variance, Kruskal−Wallis tests, and chi-square tests. We examined the association of WMLs and lacunar infarcts with a 1-standard deviation (SD) lower in the FEV_1 % predicted and forced vital capacity (FVC) % predicted values according to the smoking status. Multivariate logistic regression analyses were performed after adjusting for age, BMI, exercise habits, current alcohol consumption, and average home systolic BP as well as the use of medication for hypertension, hyperlipidemia, diabetes mellitus, occupation, and education level (Model 1). Further adjustments were made for pack-years in ever smokers (Model 2) and for second-hand smoke exposure in never smokers (Model 3). All the statistical analyses were performed using JMP 9 software (SAS Institute; Cary, NC, USA). A two-tailed P value <0.05 was considered to be significant. We also evaluated interaction P-values between smoking status and WMLs or lacunar infarcts on lung function in Model 2 of **Tables 2** and **3**.

Results

The characteristics of the study participants are shown in **Table 1**. The mean age (±SD) of all subjects was 69.0±7.9 years. Among the subjects, 53.3% were former smokers and 20.7% were current smokers. The prevalence of high-risk occupational history over 6 years was 22.8%. The prevalence of WMLs and multiple lacunar infarcts was 21.4% and 13.1%, respectively; the prevalence of these conditions has been stratified by smoking status and described in **Table 1**. We compared the prevalence of each condition according to the smoking status. Although current smokers were younger, they had lower FEV_1 % predicted and worse respiratory symptoms evaluated by mMRC and CAT than never smokers and former smokers. The prevalence of WMLs and multiple lacunar infarcts were not different in spite of the smoking status. The differences between the participants' characteristics based on the status of cerebral small vessel disease (WMLs and/or lacunar infarcts) are shown in **Supplementary Table 1**. The participants with cerebral small vessel disease were older, had higher prevalence of hypertension and diabetes mellitus, and showed lower FVC % predicted than those without cerebral small vessel disease. There was no statistical difference in the severity of airflow obstruction between the two groups ($P=0.242$). However, these lesions were significantly increased in the group with cerebral small vessel disease who had restrictive ventilatory impairment ($P=0.0033$). For evaluating the distribution of lung function impairments, the 473 participants were assigned to four different groups: normal; obstructive; restrictive; or obstructive and restrictive (mixed) ventilatory impairment based on the results of pulmonary function tests. These results were pre-bronchodilator values. The prevalence of obstructive ventilatory impairment (VC % predicted ≥80% and FEV_1/FVC <70%) was 18.8%, restrictive ventilatory impairment (VC % predicted <80% and FEV_1/FVC ≥70%) was 9.7% and mixed ventilatory impairment (VC % predicted <80% and FEV_1/FVC <70%) was 3.2% (**Supplementary Fig. 2**). In the participants with FEV_1/FVC <70%, the prevalence of FEV_1 % predicted ≥80% was 44.2%, 80%>FEV_1 % predicted ≥50% was 52.9%, and FEV_1 % predicted <50% was 2.9%; thus, the distribution of airflow limitation tended to be mild in our study.

We evaluated the multivariable adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of cerebral small vessel disease (WMLs and/or lacunar infarcts) for every 1-SD lower in the FEV_1 % predicted and FVC % predicted values, stratified by smoking status in **Supplementary Table 2**. The association of cerebral small vessel disease with these spirometry-based indices was significant only in never smokers (FEV_1 % predicted: OR, 2.11; FVC % predicted: OR, 2.09), but not in former and current smokers. These results did not change after adjusting for second-hand smoke exposure in never smokers (Model 3).

Then we evaluated WMLs and lacunar infarcts individually. The multivariable adjusted ORs and 95%

Table 2. Odds ratios of WMLs for per 1-standard deviation lower in the FEV_1 and FVC, stratified by the smoking status, in 473 Japanese men aged 40−79 years (Shiga Epidemiological Study of Subclinical Atherosclerosis, Shiga, Japan, 2014−2015)

	Model	All (n=473)	Never smoker (n=123)	Former smoker (n=252)	Current smoker (n=98)
FEV_1 % predicted, %	1	1.33 (1.06−1.68)*	1.99 (1.13−3.76)*	1.03 (0.73−1.45)	1.58 (0.91−2.90)
	2	1.37 (1.08−1.75)*		1.07 (0.74−1.51)	1.50 (0.84−2.80)
	3		1.97 (1.13−3.73)*		
FVC % predicted, %	1	1.37 (1.08−1.74)*	2.11 (1.22−3.94)*	1.08 (0.75−1.55)	1.52 (0.89−2.72)
	2	1.38 (1.09−1.76)*		1.09 (0.76−1.57)	1.50 (0.87−2.68)
	3		2.09 (1.20−3.91)*		

WMLs, white matter lesions; BMI, body mass index; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.
Data represent the results of multiple logistic regression analysis.
Model 1: adjusted for age, BMI, exercise habits (exercise for <1 hour, once a week), current alcohol consumption (yes/no), average home systolic blood pressure, the use of medication for hypertension (yes/no), hyperlipidemia (yes/no), diabetes (yes/no), education (years of education <10 years, junior high school or below), occupation (high-risk occupational history for >6 years)
Model 2: Model 1 + pack-years
Model 3: Model 1 + second-hand smoke exposure (exposure to smoking in the indoor workplace or at home)
*p values <0.05 were considered significant.

Table 3. Odds ratios of lacunar infarcts per 1-standard deviation lower in the FEV_1 and FVC, stratified by the smoking status, in 473 Japanese men aged 40−79 years (Shiga Epidemiological Study of Subclinical Atherosclerosis, Shiga, Japan, 2014−2015)

	Model	All (n=473)	Never smoker (n=123)	Former smoker (n=252)	Current smoker (n=98)
FEV_1 % predicted, %	1	1.21 (0.91−1.60)	2.04 (1.02−4.58)*	1.13 (0.75−1.68)	1.20 (0.59−2.47)
	2	1.22 (0.91−1.63)		1.13 (0.74−1.71)	1.16 (0.56−2.50)
	3		2.39 (1.10−6.08)*		
FVC % predicted, %	1	1.26 (0.95−1.70)	1.91 (0.97−4.04)	1.21 (0.77−1.91)	1.28 (0.66−2.62)
	2	1.26 (0.95−1.70)		1.21 (0.77−1.92)	1.26 (0.65−2.59)
	3		2.21 (1.04−5.30)*		

BMI, body mass index; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.
Data represent the results of multiple logistic regression analysis.
Model 1: adjusted for age, BMI, exercise habits (exercise for <1 hour, once a week), current alcohol consumption (yes/no), average home systolic blood pressure, the use of medication for hypertension (yes/no), hyperlipidemia (yes/no), diabetes (yes/no), education (years of education <10 years, junior high school or below), occupation (high-risk occupational history for >6 years)
Model 2: Model 1 + pack-years
Model 3: Model 1 + second-hand smoke exposure (exposure to smoking in the indoor workplace or at home)
*p values <0.05 were considered significant.

CI of WMLs for every 1-SD lower in the FEV_1 % predicted and FVC % predicted values, stratified by smoking status, are shown in **Table 2**. The adjusted ORs of WMLs were 1.33 for FEV_1 % predicted and 1.37 for FVC % predicted in all the participants (Model 1). The association of WMLs with these spirometry-based indices was significant only in never smokers (FEV_1 % predicted: OR, 1.99; FVC % predicted: OR, 2.11), but not in former smokers and current smokers. These results did not change after adjusting for second-hand smoke exposure in never smokers (Model 3).

The multivariable adjusted ORs and 95% CI of lacunar infarcts for every 1-SD lower in the FEV_1 % predicted and FVC % predicted values, stratified by smoking status, are shown in **Table 3**. The association of lacunar infarcts with these spirometry-based indices was not significant in former smokers and current smokers. However, in never smokers, lacunar infarcts were significantly associated with FEV_1 % predicted (OR, 2.04; Model 1); this finding did not change after adjusting for second-hand smoke exposure (Model 3). In never smokers, after adjusting for second-hand smoke exposure, the association between lacunar infarcts and FVC % predicted became significant (OR, 2.21; Model 3)

In Model 2 of **Tables 2** and **3**, interaction *P*-values between smoking status and WMLs or lacunar infarcts on lung function were not statistically significant (data were not shown).

Discussion

In this community-based cross-sectional study of Japanese men without apparent stroke, we found that reduced FVC % predicted and FEV_1 % predicted values were associated with a high prevalence of WMLs in never smokers, independent of the presence of smoking exposure. In contrast, in former and current smokers, reduced FVC % predicted and FEV_1 % predicted values were not associated with WMLs. We also found the associations between FEV_1 % predicted values and lacunar infarcts in never smokers. Furthermore, significant associations were observed between FVC % predicted values and lacunar infarcts in never smokers after adjusting for second-hand smoke exposure. To our knowledge, this is the first study to examine the association between lung function impairment and cerebral small vessel disease while considering pack-years and second-hand smoke exposure.

Previous findings showed a significant association between FVC, FEV_1 decline, and cerebral small vessel disease after adjusting for the smoking status[8-10]. Liao *et al.* indicated an association between reduced lung function and the presence of WMLs and lacunar infarcts only in nonsmokers[9], consistent with the present results.

The Atherosclerosis Risk in Communities Study[33] and Multi-Ethnic Study of Atherosclerosis Lung Study[34] showed that the decline in FEV_1 was associated with an increase in the intima media thickness and decreases in the ankle brachial index, independent of the smoking status. Among smokers, those with airflow limitation have shown exaggerated subclinical atherosclerosis as compared with those without any airflow limitation[35]. These reports suggest that the FEV_1 decline was associated with subclinical atherosclerosis, independent of smoking. Smoking is an important risk factor for both FEV_1 decline[5-7] and endothelial dysfunction[36, 37] that leads to atherosclerosis[17]; and hence, the association between reduced lung function and atherosclerosis may be weaker in former and current smokers in our study. In never smokers, the association between FVC % predicted values and lacunar infarcts became significant after adjusting for second-hand smoke exposure. It might also suggest that interaction of second-hand smoke weakened the association between reduced lung function and atherosclerosis. Furthermore, as interaction *P*-values between smoking status and WMLs or lacunar infarcts on lung function were not statistically significant, former smokers and current smokers were also considered to have the same association with never smokers. There might be the lack of statistical power in former and current smokers according to the sample size.

Our findings in the current Japanese population and the results from previous western studies indicate that reduced lung function is associated with silent cerebrovascular disease, such as WML and lacunar infarcts, particularly in never smokers.

The mechanism underlying the association between reduced lung function and atherosclerosis in never smokers is unclear, although one possible explanation is that systemic inflammation is associated with both reduced lung function and atherosclerosis. Some longitudinal studies showed that an increase in systemic inflammation, including C-reactive protein levels, is associated with a decline in lung function (decline in FVC and FEV_1), independent of the smoking status[38, 39]. Systemic inflammation is also an important factor for atherosclerosis[11]. Hence, lung function impairment in never smokers might be attributed to an exaggerated inflammatory response to factors such as age[40, 41] and the environment[42] because of a genetic predisposition[43].

The present study has certain limitations. First, the study design was cross-sectional. Hence, we could not evaluate the longitudinal relationships between lower pulmonary function and subclinical cerebrovascular disease. Second, as only Japanese men were included for analyses, our results were restricted to men of a single ethnic group. However, the population homogeneity reduces possible confounding from cultural and environmental variation. Third, the participants who participated in this study ($n=549$) were significantly younger than those who did not participate ($n=304$) (**Supplementary Table 3**). This may lead to an underestimation of the relationship between cerebral vascular disease and reduced lung function in this study. Fourth, because most of our participants showed the relatively mild airflow limitation and we used pre-bronchodilator values, it might be difficult to evaluate the difference of the prevalence of cerebral vascular disease according to the severity of obstructive ventilatory impairment. Meanwhile, we did not evaluate lung images such as CT scan, so we could not know the causes of restrictive ventilatory impairment. Finally, it was difficult to fully eliminate asthma, other lung diseases, and history of stroke, as these components were self-reported.

Conclusion

In conclusion, in a community-based sample of

Japanese men without clinical stroke, we found an association between reduced lung function and WMLs and lacunar infarcts in never smokers.

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Conflict of Interest Disclosures

None.

Appendix
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Footnotes

Abbreviations list:

BMI, body mass index; BP, blood pressure; COPD, chronic obstructive pulmonary disease; CAT, COPD assessment test; CI, confidence interval; DWM, deep white matter; FEV_1, forced expiratory volume in 1 second; FLAIR, fluid-attenuated inversion-recovery sequences; FVC, forced vital capacity; LABA, long-acting β agonist inhaler; mMRC, Modified British Medical Research Council; MRI, magnetic resonance imaging; OR, odds ratio; PVWM, periventricular white matter; SESSA, Shiga Epidemiological Study of Subclinical Atherosclerosis; SD, standard deviation; VC, vital capacity; WML, white matter lesion.

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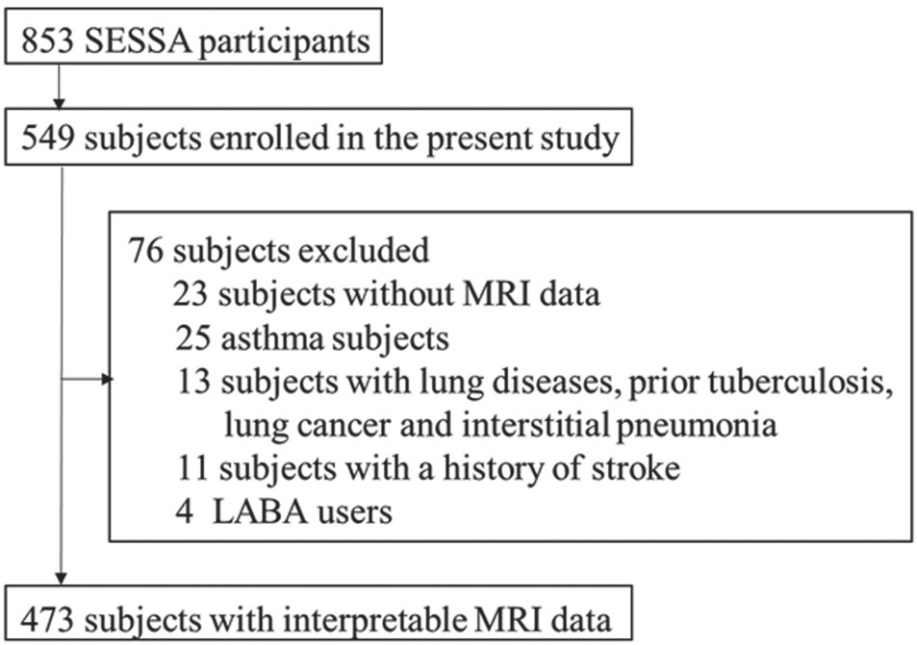


Supplementary Fig. 1. Study population

Of the 853 participants of the SESSA, 549 agreed to participate in the present study. A total of 76 subjects were excluded for the lack of MRI data ($n=23$); presence of self-reported asthma ($n=25$) and lung diseases ($n=13$) such as prior tuberculosis, lung cancer, and interstitial pneumonia; history of stroke ($n=11$); and the use of medication with long-acting β agonist inhaler (LABA) ($n=4$). A total of 473 men were finally examined in the present study.
SESSA, Shiga Epidemiological Study of Subclinical Atherosclerosis; MRI, magnetic resonance imaging; LABA, long-acting β agonist inhaler.

Supplementary Table 1. Characteristics of the 473 Japanese men aged 40−79 years (Shiga Epidemiological Study of Subclinical Atherosclerosis, Shiga, Japan, 2014−2015) based on the status of cerebral small vessel disease

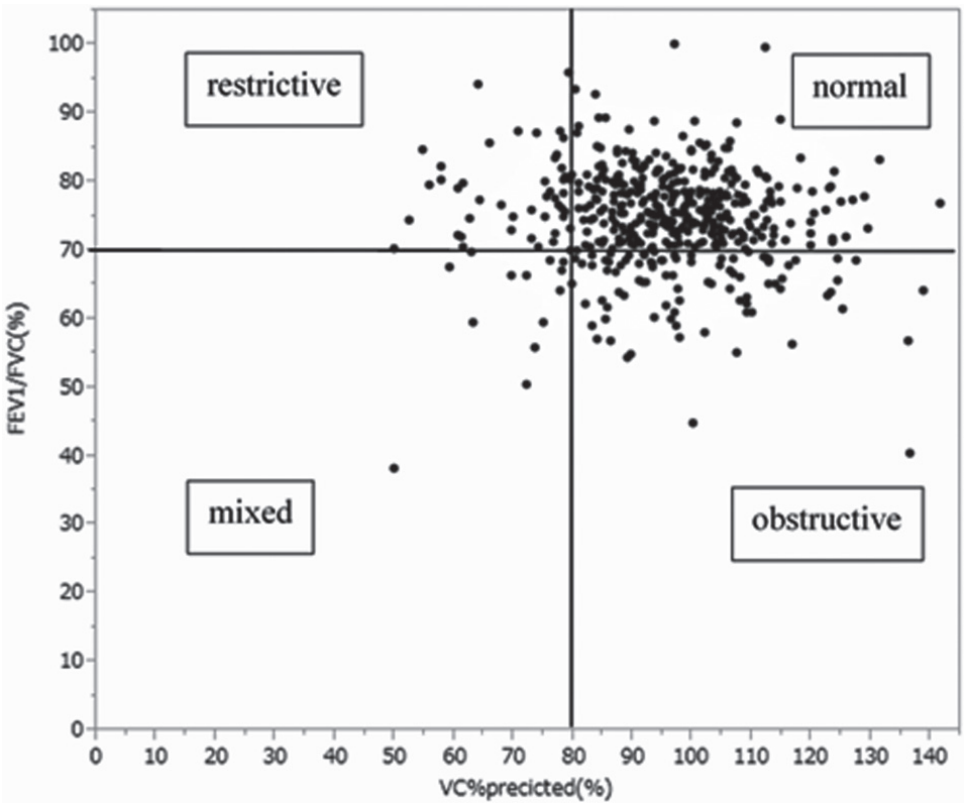
	cerebral small vessel disease		
	+ (n=131)	− (n=342)	p
Age, years	71.7±5.5	67.9±8.5	<0.0001*
BMI, kg/m^2	23.5±2.8	23.3±2.9	0.198
Smoking status			
Never/Former/Current, %	23.7/55.7/20.6	26.9/52.3/20.8	0.746
Pack-years	27.6±24.2	26.1±25.7	0.386
Second-hand smoke exposure, %	22.1	24.9	0.631
Exercise habits, %	42.7	40.4	0.676
Current alcohol consumption, %	80.9	81.6	0.895
Occupation*, %	24.4	22.2	0.823
Education*, %	10.7	11.1	1.0
FEV_1, L	2.4±0.5	2.6±0.5	<0.0001*
FEV_1 % predicted, %	84.8±16.0	88.1±13.2	0.154
FVC, L	3.2±0.7	3.5±0.6	<0.0001*
FVC % predicted, %	91.8±15.6	96.2±13.4	0.013*
FEV_1/FVC, %	74.2±7.7	74.7±7.6	0.428
FEV_1/FVC <70% and			0.242
FEV_1 % predicted ≥80%, %	34.5	48.0	
FEV_1 % predicted 50≤, <80%, %	58.6	50.7	
FEV_1 % predicted 30≤, <50%, %	3.4	1.3	
FEV_1 % predicted <30%, %	3.4	0	
VC % predicted <80%, %	20.6	9.9	0.0033*
Hypertension, %	78.6	62.9	0.001*
Hyperlipidemia, %	53.4	53.5	1.0
Diabetes, %	26.7	16.7	0.019*

SESSA, Shiga Epidemiological Study of Subclinical Atherosclerosis; BMI, body mass index; mMRC, Modified British Medical Research Council; CAT, COPD assessment test; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; VC, vital capacity; WMLs, white matter lesions.

We considered those with WML (grade 3 according to the Fazekas classification), and/or lacunar infarcts (≥2 silent infarcts) as patients with cerebral small vessel disease. Pack-years were calculated in former and current smokers. Second-hand smoke exposure was evaluated in never smokers. Second-hand smoke exposure (exposure to smoking in the indoor workplace or at home), exercise habits (exercise for <1 hour, once a week), current alcohol consumption (yes/no), *occupation (high-risk occupational history for >6 years), *education (years of education <10 years, junior high school or below), hypertension (average home systolic blood pressure of ≥135 mmHg, average home diastolic blood pressure of ≥85 mmHg, and/or the use of medication for hypertension), hyperlipidemia (total cholesterol ≥220 mg/dL, and/or the use of medication for hyperlipidemia), diabetes (fasting glucose level of ≥126 mg/dL, hemoglobin A1c value of ≥6.1%, and/or the use of medication for diabetes), WML (grade 3 according to the Fazekas classification), and lacunar infarcts (≥2 silent infarcts) were assessed.

Values are presented as unadjusted means±standard deviation or number of subjects (%).

*p values <0.05 were considered significant.



Supplementary Fig. 2. The distribution of four phenotype groups

The 473 participants were assigned to four different groups: normal (VC % predicted ≥80% and FEV_1/FVC ≥70%); obstructive (VC % predicted ≥80% and FEV_1/FVC <70%); restrictive (VC % predicted <80% and FEV_1/FVC ≥70%); or mixed (VC % predicted <80% and FEV_1/FVC <70%) ventilatory impairment based on the results of pulmonary function tests. These results were pre-bronchodilator values.

Supplementary Table 2. Odds ratios of cerebral small vessel diseases per 1-standard deviation lower in the FEV_1 and FVC, stratified by the smoking status, in 473 Japanese men aged 40−79 years (Shiga Epidemiological Study of Subclinical Atherosclerosis, Shiga, Japan, 2014−2015)

	Model	All (n=473)	Never smoker (n=123)	Former smoker (n=252)	Current smoker (n=98)
FEV_1 % predicted, %	1	1.27 (1.03−1.57)*	2.11 (1.24−3.91)*	1.01 (0.74−1.37)	1.30 (0.76−2.29)
	2	1.30 (1.04−1.63)*		1.05 (0.76−1.44)	1.26 (0.72−2.27)
	3		2.11 (1.24−3.91)*		
FVC % predicted, %	1	1.27 (1.02−1.58)*	2.09 (1.25−3.74)*	1.03 (0.75−1.43)	1.21 (0.72−2.07)
	2	1.27 (1.02−1.59)*		1.05 (0.76−1.46)	1.19 (0.70−2.05)
	3		2.09 (1.25−3.75)*		

BMI, body mass index; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; WMLs, white matter lesions.
We considered those with WML (grade 3 according to the Fazekas classification), and/or lacunar infarcts (≥2 silent infarcts) as patients with cerebral small vessel disease. Data represent the results of multiple logistic regression analysis.
Model 1: adjusted for age, BMI, exercise habits (exercise for <1 hour, once a week), current alcohol consumption (yes/no), average home systolic blood pressure, the use of medication for hypertension (yes/no), hyperlipidemia (yes/no), diabetes (yes/no), education (years of education <10 years, junior high school or below), occupation (high-risk occupational history for >6 years)
Model 2: Model 1 + pack-years
Model 3: Model 1 + second-hand smoke exposure (exposure to smoking in the indoor workplace or at home)
*p values <0.05 were considered significant.

Supplementary Table 3. Comparison of the characteristics between the participants and non-participants from SESSA study

	SESSA study (n=853)		
	Participants (n=549)	Non-participants (n=304)	p
Age, years	69.2±7.8	72.4±9.4	<0.0001*
BMI, kg/m^2	23.4±2.9	23.2±3.0	0.392
Smoking status			
Never/Former/Current, %	24.6/54.5/21.0	20.7/56.3/23.0	0.414
Pack-years	27.0±26.0	27.8±23.0	0.202
Exercise habit, %	41.2	46.4	0.149
Current alcohol consumption, %	80.9	74.9	0.045*
Hypertension, %	47.0	54.9	0.027*
Hyperlipidemia, %	36.6	34.2	0.503
Diabetes, %	19.7	24.0	0.138

SESSA, Shiga Epidemiological Study of Subclinical Atherosclerosis; BMI, body mass index.
Pack-years were calculated in former and current smokers. Exercise habits (exercise for <1 hour, once a week), current alcohol consumption (yes/no), hypertension (yes/no), hyperlipidemia (yes/no), and diabetes (yes/no) were assessed.
Values are presented as unadjusted means±standard deviation or number of subjects (%).
*p values <0.05 were considered significant.