

The association of pulmonary function with carotid atherosclerosis in older Chinese: Guangzhou Biobank Cohort Study-CVD Subcohort

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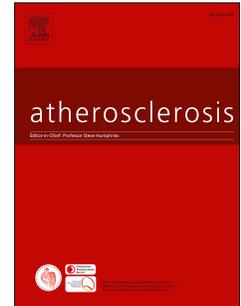
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**The association of pulmonary function with carotid atherosclerosis in older Chinese:
Guangzhou Biobank Cohort Study-CVD Subcohort**

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Abstract

Background Evidence describing the association between pulmonary function and carotid atherosclerosis has been inconclusive and the role of smoking in this association is unclear. We therefore examined this association in the Guangzhou Biobank Cohort Study-CVD Subcohort.

Methods Common carotid artery (CCA) intima-media thickness (IMT) and carotid plaques were measured by B-mode ultrasonography and lung function by spirometry using a turbine flowmeter. Chronic obstructive pulmonary disease (COPD) was defined as the ratio of forced expiratory volume in 1 second (FEV₁) to forced vital capacity (FVC) of less than 0.70. Predicted FEV₁ and FVC were derived using equations for Chinese.

Results Of 1625 participants aged 50+ years, 382 (23.5%) had evidence of carotid plaque. The mean CCA-IMT was higher in those with COPD than those without (0.82±0.29mm versus 0.76±0.31mm, P=0.02). We found no evidence that the association of pulmonary function with CCA-IMT varied by smoking status (P values interaction: 0.23-0.83). After adjustment for a wide range of potential confounders, the increased risks of thickened CCA-IMT (CCA-IMT ≥1.0mm) in those with COPD became marginally nonsignificant (adjusted odds ratio (OR) 1.45, 95% confidence interval (CI) 0.91-2.29; P=0.12). Compared to those in the highest tertile, participants in the lowest tertile of FEV₁ observed to predicted ratio had increased risk of thickened CCA-IMT (adjusted OR 2.18, 95% CI 1.42-3.34) and carotid plaque (adjusted OR 1.50, 95% CI 1.08-2.09), while participants in the lowest tertile of FVC observed to predicted ratio had increased risk of thickened CCA-IMT (adjusted OR 2.29, 95% CI 1.46-3.58), but the adjusted OR for carotid plaque was marginally nonsignificant (adjusted OR 1.29, 95% CI 0.93-1.80; P =0.13).

Conclusion: Independent of smoking status, poor pulmonary function was dose-dependently associated with carotid atherosclerosis in older Chinese. (281 words)

Keywords

Pulmonary function, chronic obstructive pulmonary disease, intimal-medial thickness, carotid

atherosclerosis

ACCEPTED MANUSCRIPT

Introduction

Cardiovascular disease (CVD) is one of the leading causes of death globally, and the associated morbidity and mortality is rapidly increasing in China.¹ Poor pulmonary function has been linked to a higher risk of CVD in previous studies.²⁻⁴ This may result from an induced systemic inflammatory response, leading to endothelial dysfunction or vascular alterations that are characterized by increase in vascular permeability and formation of plaques.² Common carotid artery (CCA) intima-medial thickness (IMT) and the presence of carotid plaques are well accepted surrogate markers for atherosclerosis. However, the results describing the association of poor pulmonary function with thicker carotid IMT are inconsistent.⁵⁻¹¹

As smoking causes both chronic obstructive pulmonary disease (COPD)¹² and atherosclerosis,^{13, 14} some studies showed that the association between pulmonary function and atherosclerosis varied by smoking status.^{5, 15-17} For example, the Atherosclerosis Risk in Communities (ARIC) Study showed that poor pulmonary function was significantly associated with atherosclerosis in smokers but not in never smokers.⁵ Other studies, such as the Etude sur le Vieillissement Artériel study⁶ and the Multi-Ethnic Study of Atherosclerosis Study (MESA),¹⁸ reported a significant association of poor pulmonary function with atherosclerosis in both smokers and never smokers. Whether the association between pulmonary function and atherosclerosis varies by smoking status is unclear.

Few studies have assessed the association of pulmonary function with carotid atherosclerosis in Chinese populations. We found only one study from China showing a significant association of poor pulmonary function and higher IMT.¹⁹ In that study, low forced expiratory volume in 1 second (FEV₁) but not low forced vital capacity (FVC) was associated with a thicker carotid IMT in smokers.¹⁹ However, whether the association of pulmonary function with carotid plaque varies by smoking status was not assessed.¹⁹ Hence, we examined the association of poor pulmonary function with

carotid atherosclerosis in an older Chinese sample from the Guangzhou Biobank Cohort Study-CVD Subcohort.

Methods

Study participants

Details of the Guangzhou Biobank Cohort Study (GBCS) have been described elsewhere.²⁰ Briefly, it is a three-way collaboration among the Guangzhou Number 12 Hospital, the Universities of Hong Kong and Birmingham. A total of 30518 older Chinese in Guangzhou were recruited at baseline from 2003 to 2008. The Cardiovascular Disease Subcohort (GBCS-CVD) included 1996 participants from phase 3 of GBCS.²¹ A standardized computer-based questionnaire was used by trained interviewers to collect information on the demographic characteristics, family and personal disease history and lifestyle, including smoking, alcohol drinking and physical activity according to the International Physical Activity Questionnaire (IPAQ). Physical examination included height, weight, waist circumference and blood pressure. Blood glucose, lipids and high-sensitivity C-reactive protein (hs-CRP) were assayed after an overnight (>8 hours) fast. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or self-reported use of antihypertensive medication. Diabetes was defined as fasting glucose >7.0 mmol/L or 2 hours oral glucose tolerance test (OGTT) >11.1 mmol/L or previous diagnosis of diabetes or use of antidiabetic medication. Ethical approval was obtained from the Guangzhou Medical Ethics Committee of the Chinese Medical Association, Guangzhou, China. All participants gave written, informed consent before participating in the study.

Exposures

Spirometry was done by a turbine flowmeter (Cosmed microQuark, Rome, Italy), and we had described the details elsewhere.²² The pulmonary function test was conducted in a standing position

following standard procedures, with at least three maneuvers and the best measure of FEV₁ and FVC were recorded. Predicted values for FEV₁ and FVC were derived using the equations of Ip and colleagues for Chinese.²³ COPD was defined by FEV₁/FVC <0.70 according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines without the use of a bronchodilator. The cutoff points of the tertiles of the FEV₁ observed to predicted ratio were as follows: tertile 1, <91.2%; tertile 2, 91.2%–104.4%; and tertile 3, >104.4%. The cutoff points of the tertiles of FVC observed to predicted ratio were as follows: tertile 1, <90.5%; tertile 2, 90.5%–102.8%; and tertile 3, >102.8%.

Study outcomes

CCA-IMT and carotid artery plaque, measured by B-mode ultrasonography, are non-invasive quantitative measures of the presence and severity of carotid atherosclerosis.²⁴ We had reported the details of these measures elsewhere.^{21, 25, 26} Briefly, the participants had carotid B-mode ultrasonographic examination using ALT HDI 3000 mainframe with a high-resolution, linear array scanner (medium frequency 7.5 MHz), performed by a registered specialist physician. All scans were performed following a predetermined, standardized scanning protocol for the right and left carotid arteries using images of the far wall of the distal 10 mm of the common carotid arteries. Three scanning angles, with the image focused on the posterior wall, were recorded from the angle showing the greatest distance between the lumen-intima interface and the media-adventitia interface. All scans were analyzed by the same physician, blinded to subjects' information. When thicker CCA-IMT or carotid plaque were observed, at least two physicians, including one chief physician, discussed and made the final decision by consensus.

The thickest measures of the left and right bilateral CCA-IMT were obtained, and the means used in the analyses. The presence of thickened CCA-IMT was diagnosed when one or both of the left or right CCA-IMT was ≥ 1.0 mm.²⁷ A plaque was defined as a distinct area protruding ≥ 1.2 mm into the

vascular lumen of the carotid artery.²⁸ Participants with one or more plaques in the CCA, internal carotid arteries or bifurcations of carotid arteries, on the right or left side were categorized as having carotid plaque. The pulmonary function tests and the measurements of vascular morphological parameters were conducted during the same visit.

Statistical analysis

Continuous variables were analyzed using independent sample t-test and categorical variables using χ^2 test. Multivariable logistic regression was used to calculate odds ratio (OR) of presence of thickened CCA-IMT and carotid plaque for (a) COPD status, (b) FEV₁ observed to predicted ratio tertiles, and (c) FVC observed to predicted ratio tertiles with and without adjustment for multiple potential confounders. Model 1 adjusted for the following potential confounders: age (years), education (primary or below, middle school, college or above), occupation (manual, non-manual and others), smoking (never smokers, ex-smokers, current smokers with 0-29 pack-years and current smokers with 30+ pack-years), alcohol drinking (never drinkers, ex-drinkers and current drinkers), occupational dust exposure, self-rated health and IPAQ physical activity (physically active, moderate and inactive) and model 2 additionally adjusted for body mass index (BMI) (kg/m²), hs-CRP, low-density lipoprotein (LDL)-cholesterol (mmol/l), triglycerides (mmol/l), systolic blood pressure (mmHg) and diabetes.

We tested for interaction between pulmonary function and sex/smoking using likelihood ratio test to test for the fitness of models with or without the interaction terms. Models with a lower Akaike information criterion (AIC) value indicate better fitness. We also performed analysis examining the association of pulmonary function with atherosclerosis by sex or smoking status as sensitivity analysis. All tests of significance were 2-tailed, with $p < 0.05$ as statistically significant. All analyses were performed using SPSS version 19.0 (SPSS Inc., Chicago, Illinois, USA).

Results

Of 1996 participants in the GBCS-CVD Subcohort, 1625 (81%) participants with all the information of interest were included in the current analyses. The mean age was 59.4 years (standard deviation, 6.8). Half of the participants were women (49.5%) and 9.7% had COPD. Table 1 shows that compared to those without COPD, those with COPD were older, had lower socioeconomic position (lower education and more manual occupation), were less physically active, and more likely to be men and smokers, and tended to have poor self-rated health and hypertension. They also had higher hs-CRP, systolic blood pressure, CCA-IMT levels and a higher prevalence of carotid plaque, but had lower BMI and lipids (all $P < 0.05$ except for HDL-cholesterol).

We found no evidence that the association of pulmonary function with carotid atherosclerosis (presence of carotid plaque or thickened CCA-IMT) varied by sex or smoking status (P values for sex interaction: 0.17-0.57, and for smoking interaction: 0.23-0.83). Hence, all analyses were conducted in men and women together with adjustment for sex and smoking. Table 2 model 2 shows that, compared to those without COPD, the increased risk of thickened CCA-IMT in participants who had COPD became marginally non-significant (adjusted odds ratio (OR) 1.45, 95% CI 0.91-2.29; $P = 0.12$) after adjustment for age, sex, BMI, occupation, education, occupational dust exposure, self-rated health, physical activity, smoking, alcohol drinking, hs-CRP, LDL-cholesterol, triglycerides, systolic blood pressure and diabetes. However, the association of COPD with the presence of carotid plaque became non-significant after adjustment for the multiple potential confounders (adjusted OR 1.06, 95% CI 0.71-1.59).

Compared with participants in the highest tertile, those in the lowest tertile of FEV_1 observed to predicted ratio had increased risk of thickened CCA-IMT (adjusted OR 2.18, 95% CI 1.42-3.34) and

the presence of carotid plaque (adjusted OR 1.50, 95% CI 1.08-2.09) (Table 3 model 2), while those in the lowest tertile of FVC observed to predicted ratio had increased risk of thickened CCA-IMT (adjusted OR 2.29, 95% CI 1.46-3.58) (Table 4 model 2). The association of lower FVC with the presence of carotid plaque became marginally non-significant after adjustment for multiple potential confounders (adjusted OR 1.29, 95% CI 0.93-1.80; $P=0.12$) (Table 4). Generally, the association of poorer pulmonary function with carotid atherosclerosis showed dose-response relationships (P values for trend ranged from <0.001 to 0.005).

Stratified analysis by smoking status (Appendix Tables 1 and 2) and sex (Appendix Tables 3 and 4) showed similar results. Compared to participants in the highest tertile of FEV₁ observed to predicted ratio, the adjusted OR of thickened CCA-IMT for those in the lowest tertile of FEV₁ observed to predicted ratio was 3.00 (95% CI 1.58-5.71) in ever smokers and 1.47 (95% CI 0.83-2.59; $P=0.18$) in never smokers (Appendix Table 1), and 2.16 (95% CI 1.32-3.55) in men and 3.34 (95% CI 1.19-9.39) in women (Appendix Table 3). The adjusted ORs of thickened CCA-IMT by FVC observed to predicted ratio were similar in ever smokers (OR 1.77, 95% CI 0.95-3.29, $P=0.07$) and never smokers (OR 1.98, 95% CI 1.07-3.65, $P=0.03$), but seemed to be higher in women than men (3.41, 95% CI 1.22-9.55, and 1.52, 95% CI 0.93-2.49, $P=0.10$, respectively) (Appendix Tables 2 and 4).

Discussion

Our study showed that poorer pulmonary function, indicated by COPD, lower FEV₁ and FVC, was dose-dependently associated with thickened CCA-IMT and carotid plaque. Furthermore, we found no evidence that the associations varied by sex or smoking status with significant associations being found in both never and ever smokers as well as in both sexes. Poor pulmonary function was associated with a higher risk of carotid atherosclerosis in most,^{10, 29-31} but not all, of the earlier

cross-sectional^{5-10, 15-19, 29-31} or prospective^{6, 7} studies.

Most of earlier studies showed lower FEV₁ was associated with thicker IMT^{3, 5, 8, 15, 18} and the presence of subclinical atherosclerosis,^{3, 7, 10, 15} However, a small study by Pike *et al.* of 61 subjects without airflow limitation found that FEV₁ was not associated with IMT.¹⁷ Similarly, most of the previous studies reported significant association of lower FVC observed to predicted ratio and FEV₁/FVC ratio with carotid IMT.^{18, 19} Whether the association varied by smoking status was unclear. One study of 3642 participants showed that, when stratified by smoking status, no association of FVC with CCA or ICA-IMT in smokers was found.¹⁸ The major limitation of this study was the lack of concurrent measures with the lung function being assessed about 4 years after the measures of carotid atherosclerosis.

Few studies have assessed the association between pulmonary function and carotid IMT in Chinese populations. We found only one study by Ma *et al.* which showed that lower FVC observed to predicted ratio and FEV₁ observed to predicted ratio were significantly associated with thicker IMT in all participants and in never smokers after adjustment for potential confounders.¹⁹ Only FEV₁ observed to predicted ratio, but not FVC observed to predicted ratio, was associated with carotid IMT in smokers, probably because of the small number of smokers (n=74 in the 4th quartile). Moreover, due to the limited sample size, the authors did not assess the interaction of smoking categories with lung function. Our findings extended the observations from Ma's study and further showed dose-response relationships of poorer pulmonary function with thickened CCA-IMT in both never smokers and ever smokers.

In our study, we found no evidence that the association between pulmonary function and carotid atherosclerosis varied by sex. Few studies examined sex interaction, and for those that did, the results

were mixed.^{5,6} A study of 656 older French people found significant associations between lung function and atherosclerosis in both men and women, and the associations did not vary by sex ($P=0.91$).⁶ However, another study of 14000 American participants found that the association was stronger in women than in men among never smokers (P for sex interaction <0.001).⁵ Taken together, whether the association of lung function and atherosclerosis varies by sex or depends on some sex-specific factors remains unclear.

Lung inflammation due to COPD may lead to a systemic inflammatory response with increase in circulating leukocytes, platelets, cytokines, and acute-phase proteins.² These mediators activate the vascular endothelium, causing endothelial dysfunction which is characterized by reduced vasodilatation with decreased nitric oxide (NO) and increased endothelin (ET) expression; increased vascular permeability and the uptake of oxidized low-density lipoproteins (LDL) promoting the development of atherosclerotic plaque.² A ventilation/perfusion mismatch associated with impaired pulmonary function and a systemic inflammatory response have been proposed as the mechanisms for this association.² A lower ventilation/perfusion ratio due to impaired lung function may result in chronic arterial wall hypoxia.² Arterial medial hypoxia stimulates release of a cascade of growth factors and cytokines that promote macrophage migration and activation, increased endothelial permeability, and platelet adherence and degranulation, completing an atherogenic positive feedback loop as intimal and adventitial proliferation further decreases trans-intimal oxygen delivery.³² Moreover, Sabater-Lleal *et al.* described genetic factors (i.e., rs9978142 and rs3995090 located in the HTR4 gene) that were implicated in determining human lung function also influenced carotid IMT supporting a molecular basis of the co-localization of these co-morbidities.³³ Common genetic pathways existing between impaired lung function and atherosclerosis which may be independent of common vascular risk factors, could be the fundamental to this association.³³ Ventilation/perfusion mismatch and systemic inflammation might thus exacerbate this association on the background of a

permissive genetic makeup.

There were several limitations in our study. Common to all such cohorts, as our participants being older and therefore survivors, healthy volunteer bias could not be fully ruled out. The number of participants with airflow limitation and smokers was relatively small and we did not perform post-bronchodilator spirometry. However, all earlier population-based studies on pulmonary function and cardiovascular risk were similarly based on pre-bronchodilator spirometry measurements.³⁴ We also could not ascertain the time sequences between changes in pulmonary function and the vascular morphological parameters. Some of the potential confounders could also be mediators, and the multivariate adjustment could have led to an underestimation of the true effect, although that would have been more of an issue had we not observed such associations. Similarly, our sample size could be insufficient to test small interaction effects, but again given the associations in the sex-specific analyses and in never and ever smokers were similar, this is unlikely to be a major issue. Finally, residual confounding could not be fully ruled out. For instance, non-occupational environmental dust exposure might adversely contribute to both vascular and pulmonary function.³⁵ Renal function (estimated glomerular filtration rate) and other determinants of IMT (e.g. serum uric acid) might also confound the observed association.³⁶ Further studies need to consider these factors to clarify the most important factors directly involved in the disease aetiology. The causal association between pulmonary function and carotid atherosclerosis could not be confirmed in this cross-sectional analysis.

In conclusion, we found that poorer pulmonary function was associated with higher risk of carotid atherosclerosis after adjusting for multiple potential confounders including smoking, and the association did not vary by sex or smoking status. Given the relatively small sample and cross-sectional nature of our study, further large prospective studies are warranted. If our results were

confirmed, subclinical atherosclerosis screening in people with poor pulmonary function may identify those at high risk of atherosclerosis and measures to prevent further progress and complications would be needed.

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Conflict of interest statement: We declare no conflict of interests.

Ethics approval: The Guangzhou Medical Ethics Committee of the Chinese Medical Association approved the study and all participants gave written, informed consent before participation.

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Table 1.Characteristics of the study sample by pulmonary function status

	Normal FEV ₁ /FVC \geq 0.70	COPD FEV ₁ /FVC <0.70	P value
Number	1467	158	
Men, n (%)	697 (47.5)	124 (78.5)	<0.001
Age (y)	58.7 \pm 6.4	65.0 \pm 7.7	<0.001
Occupation, n (%)			<0.001
Manual	338 (23.0)	60(38.0)	
Non-manual	741 (50.5)	68 (43.0)	
Others	388 (26.4)	30 (19.0)	
Education, n (%)			<0.001
\leq Primary	376 (25.6)	69 (43.7)	
Middle school	900 (61.3)	70 (44.3)	
\geq College	191 (13.0)	19 (12.0)	
Smoking, n (%)			<0.001
Never	1062 (72.4)	60 (38.0)	
Former	182 (12.4)	41 (25.9)	
Current(0-29 pack-years)	116 (7.9)	20(12.7)	
Current(\geq 30 pack-years)	107 (7.3)	37 (23.4)	
Drinking, n (%)			0.26
Never	549 (37.4)	57 (36.1)	
Former	40 (2.7)	8 (5.1)	
Current	878 (59.9)	93 (58.9)	
Occupational dust exposure, n (%)	51 (3.5)	8 (5.1)	0.31
IPAQ Physical activity, n (%)			0.03
High	880 (60.0)	83 (52.5)	
Moderate	429 (29.2)	62 (39.2)	
Low	158 (10.8)	13 (8.2)	
Self-rated poor health status, n (%)	233(15.9)	41(25.9)	0.001
Body mass index, kg/m ²	23.9 \pm 3.0	22.8 \pm 2.9	<0.001
Waist circumference, cm	78.5 \pm 8.9	78.8 \pm 8.3	0.72
Hypertension, n (%)	487 (33.2)	68 (43.0)	0.01
Diabetes, n (%)	137 (9.3)	18 (11.4)	0.40
Systolic blood pressure, mmHg	127 \pm 20	132 \pm 21	0.005
Diastolic blood pressure, mmHg	74 \pm 11	75 \pm 10	0.63
Total cholesterol, mmol/l	5.87 \pm 1.09	5.69 \pm 1.09	0.04
HDL-cholesterol, mmol/l	1.57 \pm 0.40	1.60 \pm 0.37	0.53
LDL-cholesterol, mmol/l	3.39 \pm 0.68	3.26 \pm 0.65	0.03
Triglycerides, mmol/l	1.87 \pm 1.48	1.60 \pm 0.91	0.001
Fasting plasma glucose, mmol/l	5.59 \pm 1.41	5.54 \pm 1.10	0.70
hs-CRP, mg/l	2.44 \pm 2.83	3.13 \pm 3.59	0.02
Mean CCA-IMT, mm	0.76 \pm 0.31	0.82 \pm 0.29	0.02
Thickened CCA-IMT, n (%)	158 (10.8)	41 (25.9)	<0.001

Carotid plaque, n (%)	316 (21.5)	66 (41.8)	<0.001
Number of carotid plaque, n (%)			
0	1151 (78.5)	92 (58.2)	<0.001
1	208 (14.2)	26 (16.5)	
2+	108 (7.4)	40 (25.3)	

FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; COPD, chronic obstructive pulmonary disease; IPAQ, International Physical Activity Questionnaire; hs-CRP, high-sensitivity C-reactive protein; CCA-IMT, common carotid artery-intima-media; Thickened CCA-IMT: CCA-IMT \geq 1.0mm

Table 2. Odds ratios (ORs) for the presence of carotid atherosclerosis by COPD status

	COPD		P value
	No (n=1467)	Yes (n=158)	
Presence of thickened CCA-IMT, n (%)	158 (10.8)	41 (25.9)	
Crude OR (95%CI)	1.00	2.90 (1.96-4.30)**	<0.001
Model 1, OR (95%CI)	1.00	1.32 (0.84-2.06)	0.23
Model 2, OR (95%CI)	1.00	1.45 (0.91-2.29)	0.12
Presence of carotid plaque, n (%)	316 (21.5)	66 (41.8)	
Crude OR (95%CI)	1.00	2.61 (1.86-3.67)**	<0.001
Model 1, OR (95%CI)	1.00	1.08 (0.72-1.60)	0.72
Model 2, OR (95%CI)	1.00	1.06(0.71-1.59)	0.77

COPD, chronic obstructive pulmonary disease; CCA-IMT, common carotid artery intima-media thickness;

Model 1: Adjusted for sex, age, education, occupation, smoking, drinking, occupational dust exposure, self-rated health and physical activity.

Model 2: Additionally adjusted for body mass index, high-sensitivity C-reactive protein, LDL-cholesterol, triglycerides, systolic blood pressure and diabetes.

Thickened CCA-IMT: CCA-IMT \geq 1.0mm

*P<0.05; **P<0.01

Table 3. Odds ratios (ORs) for the presence of carotid atherosclerotic by tertiles of FEV₁ observed to predicted ratio

	FEV ₁ observed to predicted ratio (%)			P for trend
	Tertile 1	Tertile 2	Tertile 3	
Range, %	<91.2	91.2-104.4	>104.4	
Number of participants	541	543	541	
Presence of thickened CCA-IMT, n (%)	103 (19.0)	58 (10.7)	38 (7.0)	
Crude OR (95% CI)	3.11 (2.10-4.61)**	1.58 (1.03-2.43)*	1.00	<0.001
Model 1, OR (95% CI)	2.27 (1.49-3.45)**	1.55 (0.99-2.42)	1.00	0.001
Model 2, OR (95% CI)	2.18 (1.42-3.34)**	1.49 (0.94-2.34)	1.00	0.001
Presence of carotid plaque, n (%)	159 (29.4)	134 (24.7)	89 (16.5)	
Crude OR (95% CI)	2.11 (1.58-2.83)**	1.66 (1.23-2.25)**	1.00	<0.001
Model 1, OR (95% CI)	1.51 (1.09-2.10)*	1.76 (1.27-2.44)**	1.00	0.003
Model 2, OR (95% CI)	1.50 (1.08-2.09)*	1.71 (1.23-2.39)**	1.00	0.005

FEV₁, forced expiratory volume in 1 second; CCA-IMT, common carotid artery intima-median thickness;

Model 1: Adjusted for sex, age, education, occupation, smoking, drinking, occupational dust exposure, self-rated health and physical activity.

Model 2: Additionally adjusted for body mass index, high-sensitivity C-reactive protein, LDL-cholesterol, triglycerides, systolic blood pressure and diabetes.

Thickened CCA-IMT: CCA-IMT \geq 1.0mm

*P<0.05; **P<0.01

Table 4 Odds ratios (ORs) for the presence of carotid atherosclerotic by tertiles of FVC observed to predicted ratio

	FVC observed to predicted ratio(%)			P for trend
	Tertile 1	Tertile 2	Tertile 3	
Range, %	<90.5	90.5-102.8	>102.8	
Number of participants	541	542	542	
Presence of thickened CCA-IMT, n (%)	99 (18.3)	67 (12.4)	33 (6.1)	
Crude OR (95%CI)	3.46 (2.28-5.23)**	2.18 (1.41-3.36)**	1.00	<0.001
Model 1, OR (95%CI)	2.48 (1.60-3.85)**	2.27 (1.44-3.57)**	1.00	<0.001
Model 2, OR (95%CI)	2.29 (1.46-3.58)**	2.20 (1.39-3.49)**	1.00	0.001
Presence of carotid plaque, n(%)	161 (29.8)	125 (23.1)	96(17.7)	
Crude OR (95%CI)	1.97 (1.48-2.62)**	1.39 (1.03-1.88)*	1.00	<0.001
Model 1, OR (95%CI)	1.33 (0.96-1.83)	1.45 (1.05-2.01)*	1.00	0.07
Model 2, OR (95%CI)	1.29 (0.93-1.80)	1.44 (1.03-2.00)*	1.00	0.09

FVC, forced vital capacity; CCA-IMT, common carotid artery intima-media thickness;

Model 1: Adjusted for sex, age, education, occupation, smoking, drinking, occupational dust exposure, self-rated health and physical activity.

Model 2: Additionally adjusted for body mass index, high-sensitivity C-reactive protein, LDL-cholesterol, triglycerides, systolic blood pressure and diabetes.

Thickened CCA-IMT: CCA-IMT \geq 1.0mm

*P<0.05; **P<0.01

Appendix Table 1. Odds ratios (ORs) for the presence of carotid atherosclerotic by tertiles of FEV₁ observed to predicted ratio and by smoking status

	FEV ₁ observed to predicted ratio (%)			P for trend
	Tertile 1	Tertile 2	Tertile 3	
Ever smokers				
Range, %	<85.4	85.4-99.6	>99.6	
Number	167	168	168	
Presence of thickened CCA-IMT, n (%)	51 (30.5)	35 (20.8)	18 (10.7)	
Crude OR (95%CI)	3.66 (2.03-6.61)**	2.19 (1.19-4.05)*	1.00	<0.001
Model 1, OR (95%CI)	3.08 (1.64-5.80)**	2.27 (1.18-4.34)*	1.00	0.002
Model 2, OR (95%CI)	3.00 (1.58-5.71)**	2.04 (1.05-3.95)*	1.00	0.004
Presence of carotid plaque n (%)	72 (43.1)	68 (40.5)	43 (25.6)	
Crude OR (95%CI)	2.20 (1.39-3.50)**	1.98 (1.24-3.14)**	1.00	0.002
Model 1, OR (95%CI)	1.67 (1.00-2.78)	2.18 (1.32-3.63)**	1.00	0.01
Model 2, OR (95%CI)	1.76 (1.04-2.98)*	2.39 (1.42-4.03)**	1.00	0.004
Never smokers				
Range, %	<93.7	93.7-105.9	>105.9	
Number	374	374	374	
Presence of thickened CCA-IMT, n (%)	41 (11.0)	30 (8.0)	24 (6.4)	
Crude OR (95%CI)	1.80 (1.06-3.04)*	1.27 (0.73-2.22)	1.00	0.08
Model 1, OR (95%CI)	1.53 (0.88-2.64)*	1.26 (0.70-2.25)	1.00	0.31
Model 2, OR (95%CI)	1.47 (0.83-2.59)	1.25 (0.69-2.27)	1.00	0.41
Presence of carotid plaque, n (%)	78 (20.9)	65 (17.4)	56 (15.0)	
Crude OR (95%CI)	1.50 (1.03-2.18)*	1.20 (0.81-1.77)	1.00	0.11
Model 1, OR (95%CI)	1.32 (0.88-2.00)	1.34 (0.88-2.05)	1.00	0.31
Model 2, OR (95%CI)	1.26 (0.82-1.92)	1.29 (0.83-1.98)	1.00	0.46

FEV₁, forced expiratory volume in 1 second; CCA-IMT; common carotid artery intima-median thickness;

Model 1: Adjusted for sex, age, education, occupation, drinking, occupational dust exposure, self-rated health and physical activity.

Model 2: Additionally adjusted for body mass index, high-sensitivity C-reactive protein, LDL-cholesterol, triglycerides, systolic blood pressure and diabetes.

Thickened CCA-IMT: CCA-IMT \geq 1.0mm

P for smoking interaction (ever smokers vs. never smokers): (1) thickened CCA-IMT: 0.23; (2) carotid plaque: 0.53

*P<0.05; **P<0.01

Appendix Table 2. Odds ratios (ORs) for the presence of carotid atherosclerotic by tertiles of FVC observed to predicted ratio and smoking status

	FVC observed to predicted ratio (%)			P for trend
	Tertile 1	Tertile 2	Tertile 3	
Ever smokers				
Range, %	<86.1	86.1-99.9	>99.9	
Number	167	168	168	
Presence of thickened CCA-IMT, n (%)	46 (27.5)	36 (21.4)	22 (13.1)	
Crude OR (95%CI)	2.52 (1.44-4.43)**	1.81 (1.01-3.23)*	1.00	0.006
Model 1, OR (95%CI)	1.94 (1.06-3.57)*	1.89 (1.02-3.49)*	1.00	0.07
Model 2, OR (95%CI)	1.77 (0.95-3.29)	1.69 (0.90-3.16)	1.00	0.15
Presence of carotid plaque, n (%)	72 (43.1)	64 (38.1)	47 (28.0)	
Crude OR (95%CI)	1.95 (1.24-3.08)**	1.58 (1.001-2.51)*	1.00	0.01
Model 1, OR (95%CI)	1.42 (0.86-2.36)	1.79(1.09-2.95)*	1.00	0.07
Model 2, OR (95%CI)	1.51 (0.90-2.54)	1.88 (1.12-3.13)*	1.00	0.05
Never smokers				
Range, %	<92.6	92.6-103.7	>103.7	
Number	374	374	374	
Presence of thickened CCA-IMT, n (%)	45 (12.0)	32 (8.6)	18 (4.8)	
Crude OR (95%CI)	2.71 (1.54-4.77)**	1.85 (1.02-3.36)*	1.00	0.003
Model 1, OR (95%CI)	2.16 (1.19-3.90)*	1.93 (1.04-3.58)*	1.00	0.03
Model 2, OR (95%CI)	1.98 (1.07-3.65)*	1.95 (1.04-3.68)*	1.00	0.07
Presence of carotid plaque, n (%)	81 (21.7)	60 (16.0)	58 (15.5)	
Crude OR (95%CI)	1.51 (1.04-2.19)*	1.04 (0.70-1.54)	1.00	0.05
Model 1, OR (95%CI)	1.16 (0.77-1.75)	1.08 (0.71-1.65)	1.00	0.78
Model 2, OR (95%CI)	1.04 (0.68-1.60)	1.04 (0.67-1.60)	1.00	0.98

FVC, forced vital capacity; CCA-IMT, common carotid artery intima-median thickness;

Model 1: Adjusted for sex, age, education, occupation, drinking, occupational dust exposure, self-rated health and physical activity.

Model 2: Additionally adjusted for body mass index, high-sensitivity C-reactive protein, LDL-cholesterol, triglycerides, systolic blood pressure and diabetes.

Thickened CCA-IMT: CCA-IMT \geq 1.0mm

P for smoking interaction (ever smokers vs. never smokers): (1) thickened CCA-IMT: 0.83; (2) carotid plaque: 0.57

*P<0.05; **P<0.01

Appendix Table 3. Odds ratios (ORs) for the presence of carotid atherosclerosis by tertiles of FEV₁ observed to predicted ratio and by sex

	FEV ₁ observed to predicted ratio (%)			P for trend
	Tertile 1	Tertile 2	Tertile 3	
Men				
Range, %	<88.2	88.2-102.3	>102.3	
Number	274	273	274	
Presence of thickened CCA-IMT, n (%)	71 (25.9)	48 (17.6)	32 (11.7)	
Crude OR (95% CI)	2.65 (1.68-4.18)**	1.61 (1.00-2.61)	1.00	<0.001
Model 1, OR (95% CI)	2.18 (1.34-3.53)**	1.53 (0.93-2.52)	1.00	0.007
Model 2, OR (95% CI)	2.16 (1.32-3.55)**	1.50 (0.90-2.51)	1.00	0.009
Presence of carotid plaque, n (%)	103 (37.6)	109 (39.9)	68 (24.8)	
Crude OR (95% CI)	1.83 (1.26-2.64)**	2.01 (1.40-2.90)**	1.00	<0.001
Model 1, OR (95% CI)	1.41 (0.94-2.10)	2.03 (1.37-3.01)**	1.00	0.002
Model 2, OR (95% CI)	1.41 (0.94-2.12)	2.04 (1.37-3.05)**	1.00	0.002
Women				
Range, %	<94.0	94.0-105.7	>105.7	
Number	268	268	268	
Presence of thickened CCA-IMT, n (%)	24 (9.0)	19 (7.1)	5 (1.9)	
Crude OR (95% CI)	5.17 (1.94-13.77)**	4.01 (1.48-10.91)**	1.00	0.004
Model 1, OR (95% CI)	3.96 (1.43-10.94)**	3.81 (1.36-10.70)*	1.00	0.02
Model 2, OR (95% CI)	3.34 (1.19-9.39)*	3.39 (1.20-9.62)*	1.00	0.05
Presence of carotid plaque, n (%)	48 (17.9)	29 (10.8)	25 (9.3)	
Crude OR (95% CI)	2.12 (1.27-3.56)**	1.18 (0.67-2.07)	1.00	0.007
Model 1, OR (95% CI)	1.90 (1.08-3.32)*	1.23 (0.68-2.25)	1.00	0.06
Model 2, OR (95% CI)	1.80 (1.01-3.22)*	1.14 (0.61-2.10)	1.00	0.09

FEV₁, forced expiratory volume in 1 second; CCA-IMT, common carotid artery intima-media thickness;

Model 1: Adjusted for age, education, occupation, smoking, drinking, occupational dust exposure, self-rated health and physical activity.

Model 2: Additionally adjusted for body mass index, high-sensitivity C-reactive protein, LDL-cholesterol, triglycerides, systolic blood pressure and diabetes.

Thickened CCA-IMT: CCA-IMT \geq 1.0mm

P for sex interaction: (1) thickened CCA-IMT: 0.17; (2) carotid plaque: 0.34

*P<0.05; **P<0.01

Appendix Table 4. Odds ratios (ORs) for the presence of carotid atherosclerosis by tertiles of FVC observed to predicted ratio and by sex

	FVC observed to predicted ratio (%)			P for trend
	Tertile 1	Tertile 2	Tertile 3	
Men				
Range, %	<88.1	88.1-101.1	>101.1	
Number	273	274	274	
Presence of thickened CCA-IMT, n (%)	63 (23.1)	53 (19.3)	35 (12.8)	
Crude OR (95% CI)	2.05 (1.30-3.22)**	1.64 (1.03-2.61)*	1.00	0.008
Model 1, OR (95% CI)	1.60 (0.99-2.59)	1.75 (1.08-2.84)*	1.00	0.06
Model 2, OR (95% CI)	1.52 (0.93-2.49)	1.66 (1.02-2.72)*	1.00	0.11
Presence of carotid plaque, n(%)	107 (39.2)	99 (36.1)	74 (27.0)	
Crude OR (95% CI)	1.74 (1.21-2.50)**	1.53 (1.06-2.20)*	1.00	0.008
Model 1, OR (95% CI)	1.29 (0.87-1.92)	1.65 (1.12-2.44)*	1.00	0.042
Model 2, OR (95% CI)	1.31 (0.88-1.96)	1.64 (1.11-2.44)*	1.00	0.049
Women				
Range, %	<93.1	93.1-103.7	>103.7	
Number	268	268	268	
Presence of thickened CCA-IMT, n (%)	29 (10.8)	14(5.2)	5 (1.9)	
Crude OR (95% CI)	6.38 (2.43-16.75)**	2.90 (1.03-8.17)*	1.00	<0.001
Model 1, OR (95% CI)	4.35 (1.59-11.96)**	2.77(0.96-8.00)	1.00	0.02
Model 2, OR (95% CI)	3.41 (1.22-9.55)*	2.45 (0.83-7.17)	1.00	0.06
Presence of carotid plaque, n (%)	45 (16.8)	31 (11.6)	26 (9.7)	
Crude OR (95% CI)	1.88 (1.12-3.15)*	1.22 (0.70-2.11)	1.00	0.04
Model 1, OR (95% CI)	1.30 (0.74-2.31)	1.21 (0.67-2.16)	1.00	0.66
Model 2, OR (95% CI)	1.09 (0.60-1.98)	1.09 (0.60-1.98)	1.00	0.95

FVC, forced vital capacity; CCA-IMT, common carotid artery intima-media thickness;

Model 1: Adjusted for age, education, occupation, smoking, drinking, occupational dust exposure, self-rated health and physical activity.

Model 2: Additionally adjusted for body mass index, high-sensitivity C-reactive protein, LDL-cholesterol, triglycerides, systolic blood pressure and diabetes.

Thickened CCA-IMT: CCA-IMT \geq 1.0mm

P for sex interaction: (1) thickened CCA-IMT: 0.32; (2) carotid plaque: 0.57

*P<0.05; **P<0.01