Atherosclerosis 232 (2014) 59–64

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Airflow limitation in smokers is associated with arterial stiffness: The Nagahama Study

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ARTICLE INFO

Article history:
Received 16 May 2013
Received in revised form
18 September 2013
Accepted 22 October 2013
Available online 1 November 2013

Keywords:
Airflow limitation
Chronic obstructive pulmonary diseases
Arterial stiffness
Pulse wave velocity
Smoking

ABSTRACT

Background: Pathophysiological mechanisms of associations between airflow limitation (AL) and arterial stiffness remain unclear. One factor that might affect both AL and arterial stiffness is habitual smoking. The aim of this study is to investigate a possible interaction of smoking on the association between AL and arterial stiffness.

Methods: Study subjects consisted of 8790 apparently healthy community residents. Airflow limitation was defined as a ratio of forced expiratory volume in 1 s (FEV_1) to forced vital capacity of less than 70%. Brachial-to-ankle pulse wave velocity (baPWV) was used as an index of arterial stiffness. Smoking habit was investigated using a structured questionnaire.

Results: Subjects with AL had significantly higher baPWV (AL 1381 ± 334, control 1261 ± 227 cm/s, $p < 0.001$). In a separate analysis by smoking habit, advanced arterial stiffness in AL was observed only in smokers (non-smokers: AL 1300 ± 220, control 1260 ± 218; smokers: AL 1436 ± 384, control 1264 ± 243 cm/s). Other clinical features of subjects with AL were older age; increased plasma hsCRP levels; and a high prevalence of male sex, hypertension, and smoking experience. Multiple linear regression analysis adjusted for these covariates identified the smoking × AL interaction as an independent determinant of baPWV ($\beta = 0.066$, $p < 0.001$). Conversely, baPWV was an independent determinant of AL in current and past smokers, but not in never smokers.

Conclusions: AL arising from cigarette smoking, but not AL in non-smokers, was associated with arterial stiffness in a general population independently of established risk factors. Measurement of subclinical arterial change in smokers may be useful in identifying persons at risk for AL.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a major global health burden, reportedly responsible for approximately 25% of deaths from ischemic heart disease [1], and forecast to be the third-leading cause of death in 2020, after ischemic heart disease and cerebrovascular disease [2]. In general populations, airflow limitation, as assessed by forced expiratory volume in 1 s (FEV_1), is associated with the incidence of cardiovascular diseases including stroke [3], myocardial infarction [4], and heart failure [5]. Further, persons with comorbid hypertension or diabetes with airflow limitation have a further risk for adverse outcomes of hospitalization and mortality [6].

The mechanism by which airflow limitation increases cardiovascular diseases (CVD) has not been precisely determined. Although these pathologies share several risk factors, systemic inflammation, represented by elevated plasma levels of C-reactive protein (CRP) [7], might be a key factor in this comorbidity [8]. The co-occurrence of CVD in persons with reduced pulmonary function is more directly explained by a second factor, arteriosclerotic

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http://dx.doi.org/10.1016/j.atherosclerosis.2013.10.020

vascular change [9]. Several studies have reported atherosclerotic vascular changes and arterial stiffening in subjects with COPD [10,11], and atherosclerosis is known to be associated with an increased risk of cerebral disease [12], coronary artery disease, and total mortality [13]. In general populations, two studies have reported a direct association between airflow limitation and subclinical vascular changes [14,15]. The MESA lung study [14] reported greater carotid arterial thickness in subjects with reduced FEV_1, while the ARIC study [15] reported increased carotid arterial thickness and also decreased ankle-brachial index in subjects with lower FEV_1.

Smoking is an established risk factor for reduced pulmonary function [16]. Habitual smoking, even of low-tar cigarettes, also increases risks for CVD and mortality [17,18] through the initiation and progression of atherothrombotic vascular change [19]. It is therefore hypothesized that smokers with airflow limitation show synergistically greater arteriosclerotic vascular change. If smoking habit were involved in the relationship between airflow limitation and changes in vasculature, this would be a clue in elucidating the pathophysiological mechanisms of atherosclerotic progression in persons with airflow limitation.

Given this background, we investigated cross-sectional interrelationships between airflow limitation and habitual smoking on arterial stiffness in a large-scale general population sample.

2. Materials and methods

2.1. Study subjects

The study subjects consisted of 8790 participants of the Nagahama Prospective Genome Cohort for Comprehensive Human Bioscience (The Nagahama Study). The Nagahama Study cohort was recruited from the general population living in Nagahama City, a largely rural city of 125,000 inhabitants in Shiga Prefecture, located in the center of Japan. Among 9804 total study participants recruited from 2008 to 2010, the study enrolled persons who were free from any symptomatic cardiovascular diseases, whose fasting plasma and urine samples were available, and who were not receiving treatment for COPD or asthma. Cigarette smoking habit and the medical history of each person was investigated using a structured questionnaire. Past smoking was defined as smoking at any time prior to baseline measurement. Smoking intensity (pack-year) for every age decade was obtained by the questionnaire and life-time exposure to cigarette smoke was expressed by the Brinkman index. All study procedures were approved by the ethics committee of Kyoto University Graduate School of Medicine. Signed informed consent was obtained from all participants.

2.2. Pulmonary function

Pulmonary function was measured by a forced vital capacity (FVC) maneuver on a computed spirometer with automated quality checks (SP-350 COPD, Fukuda Denshi Co., Ltd., Tokyo, Japan). Airflow limitation was defined as a ratio of forced expiratory volume in 1 s (FEV_1) to FVC of less than 70%. The severity of airflow limitation was graded by the ratio of FEV_1 to FEV_1 predicted value as <50%, severe; 50%–80%, moderate; and ≥80%, mild. FEV_1 predicted value was calculated using the following formulas according to a guideline from the Japan Respiratory Society: males, $0.036 \times \text{height} - 0.028 \times \text{age} - 1.178$; females, $0.022 \times \text{height} - 0.022 \times \text{age} - 0.005$. Pulmonary function was measured by trained and certified medical technologists according to a standardized protocol.

2.3. Evaluation of arterial stiffness

baPWV was used as an index of arterial stiffness. To measure baPWV, cuffs were applied to both brachia and ankles, and all blood pressures were measured simultaneously by a cuff-oscillometric method (Vasera-1500, Fukuda Denshi). The pulse volume waveforms were also recorded simultaneously using a plethysmographic sensor connected to the cuffs. baPWV was calculated from the time interval between the wave fronts of the brachial and ankle waveforms, and the path length from the brachia to ankle ($0.597 \times \text{height} + 14.4014$) [20]. Co-linearity of baPWV with a cfPWV, a standard measure of arterial stiffness, has been reported elsewhere [21], though some portions of baPWV may be determined by peripheral arterial stiffness [22].

2.4. Evaluation of risk factors

Plasma markers were measured using peripheral blood obtained after fasting. The homeostasis model assessment index for insulin resistance (HOMA-IR; [insulin (μU/ml) × glucose (mg/dl)]/405) was used as an index of insulin resistance. Kidney function was evaluated by estimated glomerular filtration rate (eGFR) calculated from serum creatinine levels using the following formula: $194 \times \text{creatinine}^{-1.094} \times \text{age}^{-0.287} \times 0.739$ (if female). Chronic kidney disease (CKD) was defined as eGFR <60 ml/min/1.73 m^2, or urinary albumin ≥30 mg/day. Hypertension was defined as any or all of systolic BP ≥ 140 mmHg, diastolic BP ≥ 90 mmHg, or use of antihypertensive drugs. Type 2 diabetes was defined as a fasting blood glucose level ≥126 mg/dl or use of antihyperglycemic drugs.

2.5. Statistical analysis

Values are mean ± standard deviation. Group differences in numeric and categorical variables were assessed by analysis of variance (ANOVA) or a chi-squared test. Post-hoc analysis comparing group differences was done using Tukey's test. Factors independently associated with baPWV were analyzed by multiple linear regression analysis. Multiple logistic regression analysis was used to calculate odds ratio for airflow limitation, and high baPWV in this regression model was defined as baPWV faster than 1395 cm/s (4th quartile). p values less than 0.05 were considered to indicate statistical significance.

3. Results

Mean baPWV was 1265 ± 232 cm/s baPWV was significantly higher in males (male, 1321 ± 252; females, 1238 ± 217 cm/s, $p < 0.001$), and positively associated with age ($r = 0.648$, $p < 0.001$) and systolic BP ($r = 0.626$, $p < 0.001$). eGFR was inversely associated with baPWV ($r = -0.318$, $p < 0.001$), and subjects with CKD showed markedly higher baPWV (CKD, 1392 ± 268; normal renal function, 1245 ± 215, $p < 0.001$). In contrast, HOMA-IR and high-sensitive C reactive protein (hsCRP) showed only weak associations with baPWV (HOMA-IR, $r = 0.167$, $p < 0.001$; hsCRP, $r = 0.255$, $p < 0.001$).

Table 1 shows associations between airflow limitation and atherosclerotic risk factors. Subjects with airflow limitation (FEV_1/FVC <0.7) were significantly older and had a higher prevalence of male sex, hypertension, and smoking experience. Because the frequency of airflow limitation was significantly higher in current (8.0%) and past (4.7%) smokers than in never smokers (2.1%) ($p < 0.001$), we pooled current ($n = 1218$) and past smokers ($n = 1782$) to increase statistical power. Plasma inflammatory marker (hsCRP) and total cholesterol were also significantly associated with pulmonary function. In contrast, no clear relationships were seen for diabetic parameters or renal function.

Table 1
Clinical characteristics of subjects by FEV_1 and FVC.

	$FEV_1/FVC < 0.7$			$FEV_1/FVC \geq 0.7$	*p*	
	FEV_1 to FEV_1 predicted ratio				Crude	Adjusted[b]
	<50%	<80%	≥80%			
	(11)	(122)	(171)	(8486)		
Age (years)	67 ± 7	59 ± 14	61 ± 11	53 ± 13		
Sex (male %)	81.8	63.9	62.6	31.6		
BMI (kg/m^2)	22.1 ± 3.2	21.7 ± 3.1	22.0 ± 2.5	22.3 ± 3.3	0.153	
Smoking (current or past smoking %)	81.8	59.8	57.9	33.2	<0.001	<0.001
Brinkman index	743 ± 493	457 ± 529	410 ± 501	147 ± 301	<0.001	<0.001
Systolic BP (mmHg)	136 ± 29	127 ± 19	128 ± 18	123 ± 18	<0.001	0.742
Diastolic BP (mmHg)	83 ± 22	76 ± 11	78 ± 11	76 ± 11	0.030	0.241
Hypertension (%)	72.7	47.5	42.7	30.0	<0.001	0.111
Glucose (mg/dl)	98 ± 15	89 ± 11	91 ± 11	90 ± 12	0.058	0.024
Type 2 diabetes (%)	27.3	4.1	4.1	3.3	<0.001	0.126
HbA1C (%)	5.79 ± 0.50	5.52 ± 0.46	5.48 ± 0.50	5.46 ± 0.50	0.084	0.191
HOMA-IR	1.32 ± 0.95	1.00 ± 0.74	0.98 ± 0.81	1.13 ± 0.98	0.002[a]	0.071
Total cholesterol (mg/dl)	221 ± 37	196 ± 32	205 ± 35	207 ± 35	0.001	0.002
HDL cholesterol (mg/dl)	60 ± 11	62 ± 17	63 ± 17	66 ± 17	0.012	0.474
Triglyceride (mg/dl)	110 ± 60	94 ± 47	98 ± 49	96 ± 66	0.844	0.132
High-sensitive CRP (μg/mL)	1.34 ± 1.30	1.37 ± 5.06	1.38 ± 5.21	0.89 ± 3.57	0.001[a]	0.058
eGFR (ml/min/1.73 m^2)	72.4 ± 21.9	77.3 ± 15.9	75.4 ± 15.5	79.5 ± 15.7	0.001	0.429
Urinary albumin (mg/day)	15.5 ± 12.3	28.4 ± 60.2	25.3 ± 58.3	22.8 ± 112.9	0.935	0.944
CKD (%)	45.5	28.6	25.4	18.5	0.001	0.536

Values are mean ± standard deviation. Statistical significance was assessed by analysis of variance or a chi-squared test.
[a] Statistical analysis was performed for log-transformed values.
[b] Adjusted for age, sex, and BMI.

Subjects with airflow limitation had significantly higher baPWV (FEV_1/FVC <0.7: 1381 ± 334, control: 1261 ± 227 cm/s, $p < 0.001$). The same relationship was found on analysis sub-divided by the severity of airflow limitation (severe to moderate (FEV_1 predicted <80%), 1395 ± 354; mild (≥80%), 1370 ± 318; control, 1261 ± 227 cm/s, $p < 0.001$). However, this association was only seen in subjects having smoking experience (Fig. 1). Post-hoc analysis indicated that baPWV in subjects having both airflow limitation and smoking experience was significantly higher than that in any other subgroups. Although several clinical parameters, namely total cholesterol, triglyceride, hsCRP, and eGFR, considerably differed among subgroups (Table 2), multiple linear regression analysis adjusted for known risk factors and these covariates identified the smoking × airflow limitation interaction term as an independent determinant of baPWV, in addition to the direct effects of both smoking and airflow limitation (Table 3). The interaction term remained significant in an analysis which included subjects with FEV_1 predicted to be ≥80% within the control group (p for interaction = 0.009).

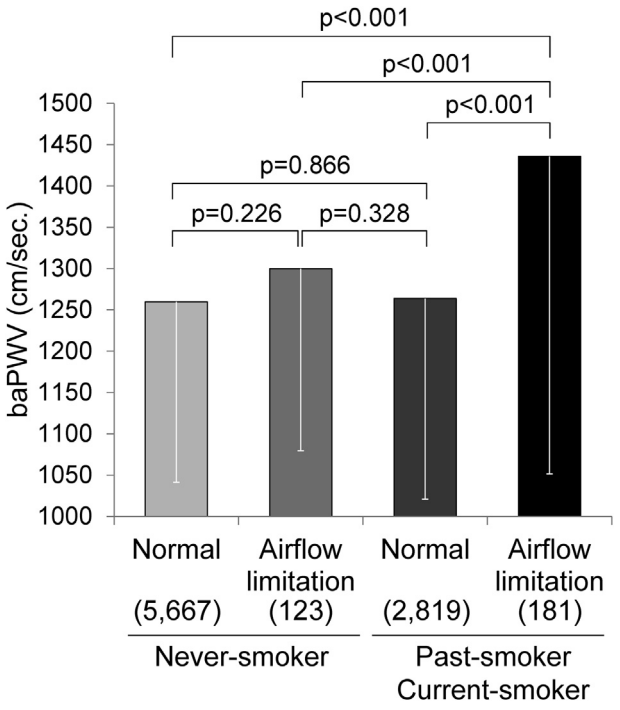

Fig. 1. Synergistic association between airflow limitation and smoking experience on arterial stiffness Values are mean ± standard deviation. Airflow limitation was defined as an FEV1/FVC ratio <70%. Statistical significance was assessed by analysis of variance. Tukey's test was used in post-hoc analysis comparing group differences.

Table 4 shows the association between baPWV and airflow limitation. Current and past smokers with higher baPWV showed a larger odds ratio than other smokers after adjustment for established risk factors. Higher baPWV in nonsmokers was not identified as a significant factor in airflow limitation.

4. Discussion

In this study, we showed that airflow limitation arising from cigarette smoking, but not that in non-smokers, was associated with greater arterial stiffness. To our knowledge, this is the first study to clearly identify a synergistic association between airflow limitation and smoking experience on arterial stiffness in a large-scale general population sample.

Smokers with airflow limitation were older and mostly male. Several clinical parameters of these subjects were also significantly different from other sub-groups. However, in regression analysis adjusted for possible covariates, smoking habit and airflow limitation, as well as the interaction term smoking × airflow limitation, were identified as independent determinant of baPWV. Our present findings, namely synergistically higher baPWV in smokers with airflow limitation, might not therefore be just an epiphenomenon due to differences in clinical background.

The same relationship was suggested by the ARIC study, with a total of 14,480 subjects from a general population [15]. In that

Table 2
Clinical characteristics of subjects by airflow limitation and smoking status.

	Never smoker		Current/past smoker		*p*	
	Normal	Airflow limitation	Normal	Airflow limitation	Crude	Adjusted[b]
	(5667)	(123)	(2819)	(181)		
FVC (L)	3.00 ± 0.71	3.18 ± 0.90	3.72 ± 0.81	3.77 ± 0.96		
FEV_1 (L)	2.51 ± 0.59	2.11 ± 0.64	3.04 ± 0.66	2.44 ± 0.67		
FEV_1/FVC	83.7 ± 5.4	65.9 ± 4.0	82.0 ± 5.6	64.4 ± 6.6		
FEV_1 to FEV_1 predicted ratio (%)	107 ± 15	87 ± 19	99 ± 14	81 ± 17		
Age (years)	54 ± 13	58 ± 13	52 ± 14	62 ± 11	<0.001	
Sex (male %)	12.3	26.0	70.2	89.5	<0.001	
BMI (kg/m^2)	22.0 ± 3.2	21.2 ± 2.6	22.8 ± 3.3	22.3 ± 2.7	<0.001	
Brinkman index	0	0	445 ± 376	747 ± 468	<0.001	
Systolic BP (mmHg)	122 ± 17	124 ± 17	125 ± 17	131 ± 19	<0.001	0.288
Diastolic BP (mmHg)	75 ± 11	76 ± 11	78 ± 11	79 ± 12	<0.001	0.021
Hypertension (%)	28.3	35.8	33.5	52.5	<0.001	0.465
Glucose (mg/dl)	89 ± 11	88 ± 9	91 ± 14	92 ± 12	<0.001	0.003
Type 2 diabetes (%)	2.3	0.8	5.2	7.7	<0.001	0.157
HbA1C (%)	5.45 ± 0.47	5.42 ± 0.33	5.46 ± 0.57	5.56 ± 0.57	0.025	0.304
HOMA-IR	1.07 ± 0.86	0.95 ± 0.65	1.23 ± 1.18	1.04 ± 0.87	<0.001[a]	0.006[a]
Total cholesterol (mg/dl)	210 ± 34	208 ± 37	201 ± 35	197 ± 32	<0.001	<0.001
HDL cholesterol (mg/dl)	68 ± 17	68 ± 17	61 ± 17	59 ± 16	<0.001	0.067
Triglyceride (mg/dl)	89 ± 55	88 ± 47	111 ± 81	103 ± 48	<0.001	<0.001
High-sensitive CRP (μg/mL)	0.77 ± 2.83	1.10 ± 3.74	1.13 ± 4.71	1.56 ± 5.78	<0.001[a]	<0.001[a]
eGFR (ml/min/1.73 m^2)	79.4 ± 15.4	76.1 ± 16.0	79.8 ± 16.3	76.0 ± 15.9	0.001	<0.001
Urinary albumin (mg/day)	19.5 ± 98.8	18.8 ± 38.4	29.4 ± 136.4	31.1 ± 67.7	0.002	0.642
CKD (%)	17.0	18.3	21.6	33.5	<0.001	0.566

Values are mean ± standard deviation.
[a] Statistical analysis was performed for log-transformed values.
[b] Adjusted for age, sex, and BMI.

study, an association between decreased FEV_1 and carotid arterial intima-media thickness observed in simple correlation analysis was lost after adjustment for CVD risk factors in non-smokers only. The MESA lung study with 3965 subjects from a general population [14] also suggested that the association between airflow limitation and carotid arterial thickening was rather prominent in smokers. In addition to these general population samples, a case–control study comparing middle-aged subjects with airflow limitation and age-matched controls [10] reported a greater carotid hypertrophy and carotid plaque score in smokers with airflow limitation, but not in smokers who had normal pulmonary function. Further, a longitudinal study reported synergistically higher CVD mortality in persons with both airflow limitation and smoking experience; in other words, the regression line between FEV_1 and CVD mortality was steeper in current and past smokers than in non-smokers [23,24]. These cross-sectional observations in general population samples and a case–control panel, as well as prognostic significance observed in a longitudinal data, strongly support our finding that the presence of arterial stiffening related to airflow limitation was a specific manifestation of persons with smoking experience.

The basis of this smoker-limited association is not fully understood. Given the present findings, certain risk factors or pathophysiological pathways common to smoking and airflow limitation may play a key role in the advanced arteriosclerotic vascular change. One potential factor is hypoxia caused by the disruption of pulmonary alveoli by smoking or ventilation-perfusion mismatch that results in mild exertional hypoxia. Since hypoxia evokes several atherogenic pathophysiological pathways, namely endothelial dysfunction, sympathetic nervous activity, and elastolytic activity [25], it appears plausible that hypoxia-induced pathophysiological factors and the direct harmful effect of smoking on arteries may synergistically exaggerate the vascular change. Although we did not measure arterial oxygen tension levels in this population sample, this consideration warrants further investigation.

Another potential factor is decreased production of vascular endothelial growth factor (VEGF). Several studies have reported

Table 3
Multiple linear regression analysis for baPWV.

	β	*p*
Age (years)	0.422	<0.001
Sex (male)	0.003	0.772
BMI (kg/m^2)	−0.055	<0.001
Systolic BP (mmHg)	0.399	<0.001
Antihypertensive medication	0.114	<0.001
Total cholesterol (mg/dl)	0.006	0.402
Triglyceride (mg/dl)	0.035	<0.001
High-sensitive CRP (log-normalized)	0.071	<0.001
eGFR (ml/min/1.73 m^2)	0.025	0.002
Smoking	0.068	<0.001
Airflow limitation	0.020	0.006
Smoking × Airflow limitation interaction	0.066	<0.001

Smoking habit was introduced into the regression equation as a dichotomous value (current or past smoking = 1; never smoking = 0). Airflow limitation was defined as an FEV_1/FVC ratio <70%.

Table 4
Multiple logistic regression analysis for airflow limitation.

	Airflow limitation (FEV_1/FVC < 0.7)	
	Odds (95% C.I.)	*p*
Age (years)	1.04 (1.03–1.06)	<0.001
Sex (male)	2.69 (1.92–3.76)	<0.001
BMI (kg/m^2)	0.86 (0.82–0.90)	<0.001
Hypertension	1.28 (0.97–1.68)	0.080
hsCRP (log-normalized)	1.07 (0.96–1.18)	0.211
Never smoker, normal baPWV	reference	
Never smoker, high baPWV	0.71 (0.46–1.08)	0.107
Current or past smoker, normal baPWV	1.46 (1.02–2.10)	0.038
Current or past smoker, high baPWV	1.76 (1.16–2.67)	0.008

High baPWV was defined as faster than 1395 cm/s (4th quartile).

that VEGF and VFGF receptor levels in lung tissue and sputum obtained from patients with emphysema are lower than those in normal controls [25,26]. Further, rats treated with VEGF receptor blocker developed alveolar cell apoptosis and emphysema [27]. A second plausible explanation for the synergistic association is decreased VEGF levels and the consequent decreased expression of antiapoptotic proteins [28] for vascular endothelial and alveolar epithelial cells, given that cigarette smoking reduces VEGF production from airway epithelial cells [29]. Although previous studies suggested that systemic inflammation as a causative factor, our regression analysis precluded the involvement of inflammation.

We showed that higher baPWV was associated with an increased risk of airflow limitation only in subjects with a smoking habit. Identifying smokers with reduced but asymptomatic pulmonary function is an important factor in improving smoking cessation rates [30,31] and preventing future COPD [32]. However, early airflow limitation is usually asymptomatic; the NHANES survey showed that only 60% of patients with moderately reduced FEV_1 (50%–85% of predicted) complained of symptoms [33]. Given the wide use of automated measurement of baPWV in clinical and epidemiological settings, particularly in East Asian countries, subclinical arterial stiffness assessed by baPWV in smokers may be a useful clue in identifying persons requiring pulmonary function testing. In never smokers, older age and a history of asthma have been suggested as major risk factors for airflow limitation [34].

Several limitations of this study warrant mention. First, the number of subjects with airflow limitation was small due to the observational setting in a general population. We were therefore unable to evaluate the differences in arterial stiffness between current and past smokers. Second, we did not obtain the time after last smoking in smokers. Clinical measurements were performed during routine medical check-ups in a non-smoking area, and considerable time was therefore needed to start the measurement of arterial stiffness and pulmonary function. The effect of last smoking might have had no substantial impact on the measurements, and any smoking just before the clinical measurements would be independent of pulmonary function and non-differential. Third, we did not measure the physical activity of subjects, although physical activity has been reported to attenuate the adverse effects of smoking on the vasculature [35].

In summary, we showed that airflow limitation in asymptomatic smokers was synergistically associated with increased arterial stiffness in a general population sample. Closer attention to asymptomatic smokers with increased arterial stiffness will facilitate the identification of persons at risk of chronic obstructive pulmonary disease.

Acknowledgments

This study was supported by a University Grant from the Ministry of Education, Culture, Sports, Science & Technology in Japan, and a research grant from the Takeda Science Foundation. We are extremely grateful to Dr Yoshihiko Kotoura for his help in clinical measurements, and the Nagahama City Office and non-profit organization Zeroji Club for their help in performing the Nagahama Study.

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