

# Association Between Airflow Limitation and Carotid Intima-Media Thickness in the Japanese Population

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**Purpose:** This study aimed to reveal the association between airflow limitation (AL) and carotid intima-media thickness (IMT) according to smoking status in Japan.

**Subjects and Methods:** This cross-sectional study was performed in 2809 subjects, who underwent a comprehensive health examination with pulmonary function tests and carotid ultrasonographic measurement. AL was defined as forced expiratory volume in 1 s/forced vital capacity of <0.7. The subjects were divided into the following four groups: never smokers without AL, never smokers with AL, former/current smokers without AL, and former/current smokers with AL. Mean IMT, the maximum measurable IMT value in the left and right common carotid arteries (IMT-C max), and mean IMT-C max were measured by carotid ultrasonography. The carotid wall thickness as defined as follows:  $IMT \geq 1.1$  mm ( $IMT_{1.1}$ ),  $IMT-C \max \geq 1.2$  mm ( $IMTc_{1.2}$ ), and  $IMT-C \max > 1.5$  mm ( $IMTc_{1.5}$ ), based on each measured region. The association between AL and the carotid wall thickness according to smoking status was assessed by logistic regression analysis.

**Results:** The mean carotid IMT and mean IMT-C max were significantly higher in never smokers with AL and former/current smokers with or without AL than in never smokers without AL. In logistic regression models adjusted for sex, age, body mass index, hypertension, dyslipidemia, hyperglycemia, physical activity, and alcohol consumption, the risk of carotid wall thickness ( $IMT_{1.1}$  [odds ratio {OR}: 1.55; 95% confidence interval {CI}: 1.07–2.24];  $IMTc_{1.2}$  [OR: 1.52; 95% CI: 1.03–2.24];  $IMTc_{1.5}$  [OR: 1.99; 95% CI: 1.15–3.46]) were significantly higher in former/current smokers with AL than in never smokers without AL.

**Conclusion:** The present results suggest that greater IMT and risk of carotid wall thickness were associated with AL and smoking experience.

**Keywords:** chronic obstructive pulmonary disease, cardiovascular disease, comorbidity, atherosclerosis, airflow limitation, carotid intima-media thickness

## Introduction

Chronic obstructive pulmonary disease (COPD) represents an important public health challenge characterized by persistent respiratory symptoms and airflow limitation (AL), which are both preventable and treatable.<sup>1</sup> COPD is the third leading cause of death globally, as reported by the World Health Organization in 2016.<sup>2</sup> The incidence of COPD is likely to increase in the coming years due to an increase in smoking habits and an aging population in several countries.<sup>3</sup>

COPD is regarded as a systemic disease because it can affect other organs beyond the lungs and induce comorbidities.<sup>1,4</sup> In particular, cardiovascular disease

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(CVD) is a common and important comorbidity in COPD,<sup>1,4–7</sup> associated with mortality in patients with COPD.<sup>6,8</sup> Lung function impairment is associated with the prevalence of CVD,<sup>9</sup> and reduced forced expiratory volume in 1 second (FEV<sub>1</sub>) has been reported as an independent risk factor for cardiovascular mortality in the general population.<sup>10,11</sup>

Smoking is the leading environmental risk factor for COPD, which is the most well studied.<sup>1</sup> Smoking is a widely acceptable cause of not only COPD but also CVD. Nevertheless, a multicenter international study has reported that never smokers may also develop AL.<sup>12</sup> Furthermore, a prospective cohort study has indicated that the relationship between airflow limitation and atherosclerosis was similar in both never smokers and ever smokers.<sup>13</sup> Therefore, subclinical atherosclerosis should be diagnosed as early as possible in patients with COPD and population with AL regardless of being smokers or nonsmokers.

Several studies reported that subjects with ischemic heart disease,<sup>14</sup> CVD,<sup>15</sup> and coronary artery disease<sup>16</sup> had a high prevalence of AL compatible with COPD, most of which were undiagnosed and untreated. Similarly, a Japanese multicenter study in outpatients with CVD also demonstrated that the prevalence of AL (FEV<sub>1</sub>/FEV<sub>6</sub> ratio < 0.73) was higher and undiagnosed.<sup>17</sup> Thus, it might be beneficial to find AL in patients with CVD and the population with CVD risk factors.

Several studies have reported that AL was associated with subclinical atherosclerosis that is intima-media thickness (IMT) of carotid artery.<sup>18–24</sup> Carotid artery ultrasonography, is a non-invasive method,<sup>25</sup> which has widely been indicated in subjects with risk factors for atherosclerosis and those in whom the possibility of progression to atherosclerosis cannot be ruled out.<sup>26</sup> An increase in IMT is correlated with atherosclerotic diseases such as cerebral and myocardial infarction and lifestyle-related diseases, which are risks for atherosclerotic diseases.<sup>26</sup> Recent study demonstrated that IMT measurement value is used as a risk of CVD occurrence in Japanese population.<sup>27</sup> A previous case–control study in Japanese males indicated that carotid IMT was significantly higher in former/current smokers with AL than in control smokers and nonsmokers without pulmonary function abnormalities.<sup>18</sup> Nevertheless, the relationship between AL and atherosclerosis in smokers and never smokers is unknown. The currently available data regarding AL and carotid artery IMT in Japanese subjects

stratified by smoking status, especially in never smokers, are limited. The aim of this study was to examine the relationship between AL and carotid artery IMT as CVD risk according to smoking status in the Japanese population.

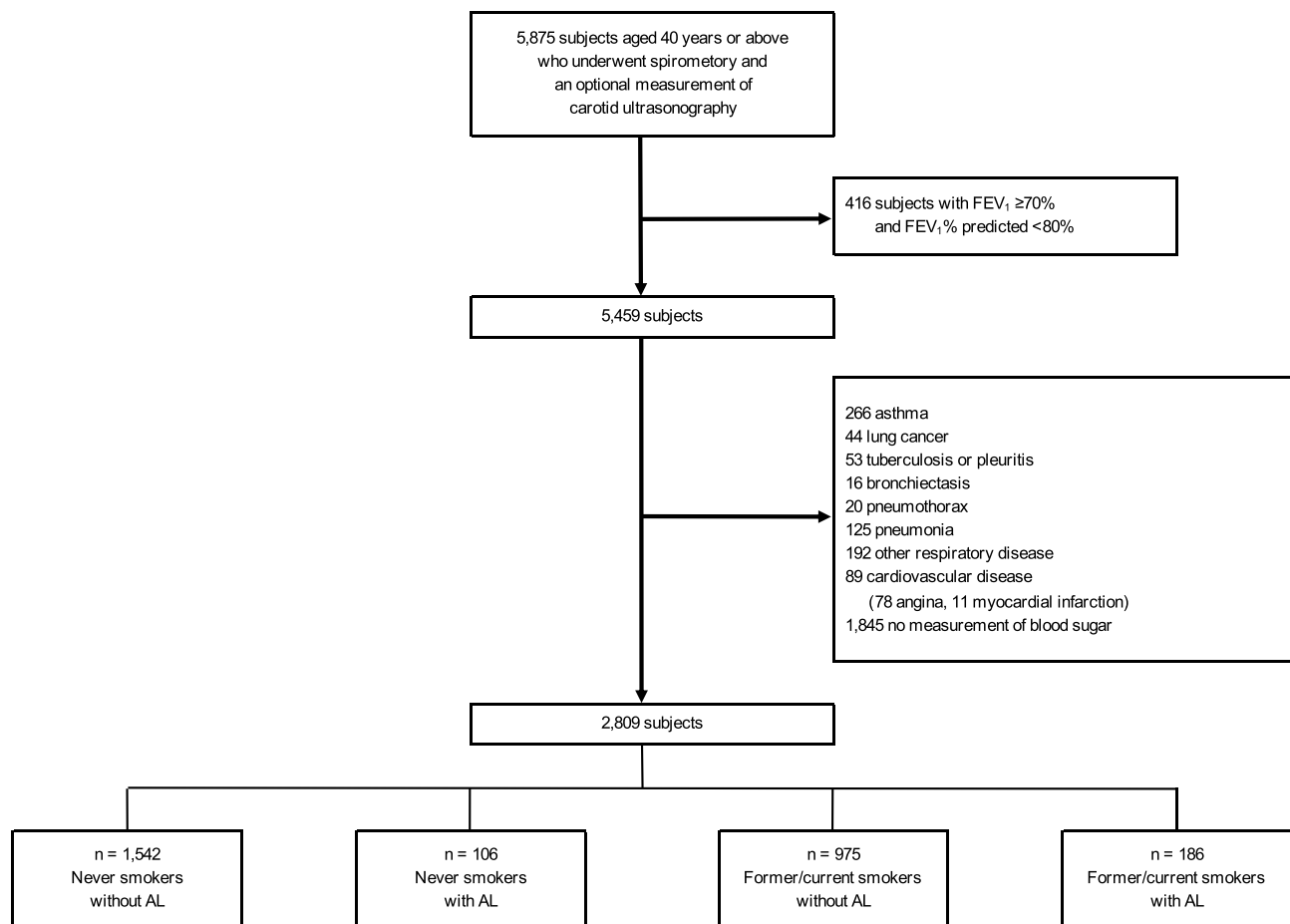
## Subjects and Methods

### Subject Selection

A total of 46,594 people visited the Japanese Red Cross Kumamoto Health Care Center for medical health check-ups between April 2016 and September 2017. Of these, 5875 subjects aged 40 years or above underwent spirometry and measurement of carotid ultrasonography (Figure 1). All subjects underwent a health screening examination that included interview questionnaires, a physical examination, and blood sampling, as previously described.<sup>28–34</sup> Data on medical history, the use of medications, physical activity, alcohol consumption, and smoking status were obtained in the questionnaires by a trained public health nurse.<sup>34</sup> Subjects were classified based on their smoking status as never smokers, former smokers, or current smokers. The never smokers consisted of those who had never smoked a cigarette in their lifetime. The former smokers were defined as those who reported smoking cessation prior to the examination, and did not currently smoke. Current smokers were those who currently smoke at the time of the interview. The number of cigarette pack-years was calculated by dividing the average number of cigarettes smoked per day by 20 and multiplying it by the number of years of smoking. All subjects were evaluated by a physician.

Subjects with forced expiratory volume in 1 s/forced vital capacity (FEV<sub>1</sub>/FVC)  $\geq$ 70% and FEV<sub>1</sub> < 80% predicted value (n = 416) were excluded from the present study. Subjects with self-reported asthma (n = 266), lung cancer (n = 44), tuberculosis or pleuritis (n = 53), bronchiectasis (n = 16), pneumothorax (n = 20), pneumonia (n = 125), and other respiratory diseases (n = 192), those without data for blood sugar (n = 1845) were excluded from our analysis. We also excluded 89 subjects with a history of clinical cardiovascular diseases (78 angina and 11 myocardial infarction). None of the subjects were diagnosed with COPD or had earlier received treatment for the same in the present study.

Data from a total of 2809 subjects (mean age 61.2, standard deviation [SD] 10.3) were included in the final analyses (Figure 1, Table 1). We classified subjects



**Figure 1** Flow chart for selecting subjects according to smoking status and AL.  
**Abbreviations:** AL, airflow limitation; FEV<sub>1</sub>, forced expiratory volume in 1 s.

without smoking experience into two groups as follows: never smokers without AL and never smokers with AL. Similarly, we classified former and current smokers into two groups: former and current smokers without AL and former and current smokers with AL.

All the subjects in the present study gave their informed consent. This study was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Epidemiological Research (partially revised on December 1, 2008, by the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare). The research protocol was approved by the Human Ethics Committee of Kumamoto University (Number 84) and the Japanese Red Cross Kumamoto Health Care Center.

## Pulmonary Function Tests

Pulmonary function was measured using an electronic spirometer (DISCOM-21 FX; CHEST MI, Tokyo, Japan)

according to the American Thoracic Society/European Respiratory Society guidelines,<sup>35</sup> as previously described.<sup>28–34</sup> Bronchodilator reversibility testing was not performed in the present study. According to the Global Initiative for Chronic Obstructive Pulmonary Disease guidelines,<sup>1</sup> AL was defined as pre-bronchodilator FEV<sub>1</sub>/FVC ratio of <70%. Predicted values were calculated using the equations published by the Japanese Respiratory Society:<sup>36</sup> males,  $0.036 \times \text{height (cm)} - 0.028 \times \text{age} - 1.178$ ; females,  $0.022 \times \text{height (cm)} - 0.022 \times \text{age} - 0.005$ . Subjects without AL were defined as having pre-bronchodilator FEV<sub>1</sub>/FVC  $\geq 70\%$  and FEV<sub>1</sub>  $\geq 80\%$  of predicted values.

## Carotid Intima-Media Thickness Measures

Carotid IMT values were measured by ultrasonography (Aplio Mx; Toshiba, Tokyo, Japan) in the common carotid artery on the left and right sides.<sup>25</sup> Well-trained medical

**Table 1** The Characteristics of the Subjects According to Smoking Status and Presence of AL

	Never Smokers AL (-) n=1542	Never Smokers AL (+) n=106	Former/Current Smokers AL (-) n=975	Former/Current Smokers AL (+) n=186	p value
Age, yr	61.0 (10.1)	70.0 (10.3)**	59.6 (9.8)**††	67.4 (8.8)**§§	<0.001
Male, n (%)	438 (28.4)	37 (34.9)	813 (83.4)	172 (92.5)	<0.001
Height, cm	158.6 (8.3)	157.6 (8.3)	166.2 (7.3)**††	166.5 (7.3)**††	<0.001
Weight, kg	57.9 (11.5)	55.9 (10.2)	65.8 (11.0)**††	64.5 (10.0)**††	<0.001
BMI, kg/m <sup>2</sup>	22.9 (3.5)	22.4 (3.0)	23.7 (3.1)**††	23.2 (2.8)	<0.001
BMI classification, n (%)					
Underweight: BMI <18.5	101 (6.6)	7 (6.6)	31 (3.2)	10 (5.4)	
Normal: 18.5 ≤ BMI <25.0	1066 (69.1)	75 (70.8)	639 (65.5)	134 (72.0)	
Over weight: 25 ≤ BMI	375 (24.3)	24 (22.6)	305 (31.3)	42 (22.6)	<0.001
Abdominal circumference, cm	83.9 (9.4)	83.6 (8.9)	86.6 (8.7)**††	86.3 (8.6)*	<0.001
Pulmonary function					
FVC, mL Total	3074.8 (751.1)	2935.8 (835.6)	3779.8 (691.8)**††	3593.8 (727.5)**††§§	<0.001
Male	3952.0 (638.6)	3768.7 (700.5)	3955.7 (597.7)	3666.2 (694.6)**§§	<0.001
Female	2726.9 (447.2)	2489.1 (488.3)**	2897.0 (391.9)**††	2704.3 (515.2)	<0.001
FEV <sub>1</sub> , mL Total	2416.7 (603.4)	1927.8 (558.9)**	2935.6 (554.8)**††	2304.6 (511.5)††§§	<0.001
Male	3101.4 (522.8)	2457.3 (498.4)**	3070.7 (485.8)††	2347.9 (495.6)**§§	<0.001
Female	2145.1 (374.7)	1643.9 (341.3)**	2257.5 (342.3)**††	1772.1 (402.0)**§§	<0.001
FEV <sub>1</sub> /FVC, %	78.7 (5.0)	65.7 (3.0)**	77.8 (4.6)**††	64.1 (5.3)**§§	<0.001
FEV <sub>1</sub> % predicted, %	102.8 (12.9)	89.2 (12.8)**	97.6 (10.9)**††	80.3 (13.8)**††§§	<0.001
SBP, mm Hg	125.7 (16.7)	130.0 (15.8)	126.7 (15.2)	130.1 (15.0)**	0.007
DBP, mm Hg	73.7 (11.0)	73.8 (11.3)	76.6 (10.7)**	76.4 (11.3)*	<0.001
Pack-years	0 (0)	0 (0)	21.1 (17.8)**††	33.6 (24.6)**††§§	<0.001
Physical activity, n (%)					
Inactivity	670 (43.5)	47 (44.3)	381 (39.1)	77 (41.4)	
Regular activity	872 (56.5)	59 (55.7)	594 (60.9)	109 (58.6)	0.173
Alcohol consumption, n (%)					
Non	933 (60.5)	66 (62.2)	221 (22.7)	49 (26.3)	
1–6 days per week	498 (32.3)	34 (32.1)	466 (47.8)	81 (43.6)	
Daily	111 (7.2)	6 (5.7)	288 (29.5)	56 (30.1)	<0.001
Laboratory data					
Fasting glucose, mg/dL	99.7 (13.9)	101.8 (21.1)	105.1 (16.5)**	105.1 (14.8)**	<0.001
Triglycerides, mg/dL (interquartile range)	86.00 (63.75–121.00)	87.00 (62.75–117.25)	105.00 (74.00–154.00)**††	107.50 (79.75–147.25)**††	<0.001
HDL cholesterol, mg/dL	67.5 (16.8)	70.4 (19.3)	62.0 (16.9)**††	60.6 (16.7)**††	<0.001
LDL cholesterol, mg/dL	128.2 (28.3)	123.8 (28.6)	124.7 (28.2)*	115.0 (29.6)**§§	<0.001
White blood cell count/μL	4974.8 (1245.8)	4950.0 (1222.8)	5456.7 (1505.3)**††	5625.3 (1635.8)**††	<0.001
hsCRP, n=2727 <sup>a</sup> hsCRP, mg/ L (interquartile range)	n=1495 <sup>a</sup> 0.06 (0.03–0.11) <sup>a</sup>	n=104 <sup>a</sup> 0.06 (0.04–0.11) <sup>a</sup>	n=942 <sup>a</sup> 0.07 (0.04–0.12) <sup>a</sup>	n=186 0.07 (0.04–0.15)**§§	0.005

(Continued)

**Table 1** (Continued).

	<b>Never Smokers AL (-) n=1542</b>	<b>Never Smokers AL (+) n=106</b>	<b>Former/Current Smokers AL (-) n=975</b>	<b>Former/Current Smokers AL (+) n=186</b>	<b>p value</b>
Clinical information, n (%)					
Hypertension	806 (52.3)	69 (65.1)	559 (57.3)	130 (69.9)	<0.001
Hyperglycemia	238 (15.4)	17 (16.0)	257 (26.4)	51 (27.4)	<0.001
Dyslipidemia	917 (59.5)	74 (69.8)	577 (59.2)	105 (56.5)	0.143

**Notes:** Data are expressed as means (standard deviation), median (interquartile range), or as number (n) (percentage). AL was defined as FEV<sub>1</sub>/FVC <0.7. Pack-years = (average number of cigarettes smoked per day × number of year of smoking)/20. <sup>a</sup>hsCRP data were only recorded for 2727 of the 2809 total subjects, 1495 of 1542 never smokers without AL, 104 of the 106 never smokers with AL, and 942 of 975 former/current smokers without AL. Hypertension was defined as SBP of ≥130 mm Hg, DBP of ≥85 mm Hg, and/or current use of antihypertensive medication. Hyperglycemia was defined as a fasting blood glucose level of ≥110 mg/dL and/or the current use of blood glucose lowering medication. Dyslipidemia was defined as triglycerides ≥ 150 mg/dL, LDL-C ≥ 140 mg/dL, HDL-C < 40 mg/dL, and/or current use of medication. \*p <0.05, \*\*p <0.01 compared with never smokers without AL. †p <0.05, ††p <0.01 compared with never smokers with AL. §p <0.05, §§p <0.01 compared with former and current smokers without AL.

**Abbreviations:** AL, airflow limitation; AL (-), without AL; AL (+), with AL; BMI, body mass index; FVC, forced vital capacity; FEV<sub>1</sub>, forced expiratory volume in 1 s; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; hsCRP, high-sensitivity C-reactive protein.

technologists performed all the examinations. Mean IMT was defined as the average of IMT values in both the right and left sides of the common carotid arteries. IMT-C max was defined as the maximum measurable IMT value in the left and right common carotid arteries. Mean IMT-C max was computed as the average of both the right and left IMT-C max values. In the present study, we defined the carotid wall thickness as follows: IMT ≥ 1.1 mm (IMT<sub>1.1</sub>), IMT-C max ≥ 1.2 mm (IMTc<sub>1.2</sub>), and IMT-C max > 1.5 mm (IMTc<sub>1.5</sub>), based on each measured region. The criteria of IMT<sub>1.1</sub> and IMT<sub>1.5</sub> are used to evaluate carotid artery plaque according to the guidelines.<sup>25</sup> The criterion of IMTc<sub>1.2</sub> was suggested to be the risk of CVD in the Japanese general population.<sup>27</sup> Therefore, we defined these three criteria as the carotid wall thickness of subclinical atherosclerosis in this study.

## Physical Examination and Blood Measurements

Body mass index (BMI) was calculated by dividing the body weight (kg) by the square of the height (m<sup>2</sup>). BMI was classified as follows: underweight (<18.5), normal weight (18.5 ≤ BMI < 25.0), and overweight (≥25.0).<sup>37</sup> Subjects abdominal circumference was measured at the end of a normal expiration in a standing position. Physical activity was divided into two categories: “regular physical activity” was defined as engaging in sports or other forms of exercise at least once weekly regularly, and “physical inactivity” was defined as engaging in irregular physical activity or no form of physical activity.<sup>34</sup> Subjects were classified based on alcohol consumption as “nondrinkers,” “consuming alcohol for 1–6 days per week,” and “daily drinkers.”<sup>34</sup> After

overnight fasting, fasting glucose, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), white blood cell (WBC) count, and high-sensitivity C-reactive protein (hsCRP) were measured in serum samples. Before blood samples were obtained, subjects were placed at rest.

## Clinical Information

Trained nurses measured systolic blood pressure (SBP) and diastolic blood pressure (DBP) using an automatic digital sphygmomanometer (HEM-904; OMRON, Kyoto, Japan), which was placed on the upper arm at the height of the heart with the subject in a seated position.<sup>34</sup> Subjects were rest for at least 5 minutes before the initial BP reading was obtained. The SBP and DBP were taken to be the average of two measurements. Hypertension was defined as SBP of ≥130 mm Hg, DBP of ≥85 mm Hg, and/or current use of antihypertensive medication.

Hyperglycemia was defined as a fasting blood glucose level of ≥110 mg/dL and/or the current use of blood glucose lowering medication. Dyslipidemia was defined as triglycerides ≥ 150 mg/dL, LDL-C ≥ 140 mg/dL, HDL-C < 40 mg/dL, and/or current use of medication.<sup>28</sup>

## Statistical Analyses

Data are expressed as number of cases with percentages, mean (SD), or median with interquartile range. Bar graphs presented mean values, and error bars indicated SD. Normality of data was assessed using the Shapiro–Wilk test. Analysis of variance (ANOVA), Kruskal–Wallis test, and  $\chi^2$  test were used to assess the differences in characteristics among never smokers without AL, never smokers

with AL, former and current smokers without AL, and former and current smokers with AL. Post-hoc analysis comparing differences in characteristics between groups was done using Scheffe's test. The effects of AL and smoking, as well as the interaction of these factors in IMT and IMT-C max were verified by two-way ANOVA and Scheffe's post-hoc test.

Multivariate logistic regression models were used to examine the association between AL and carotid wall thickness according to smoking status. Statistical significance was defined as  $p < 0.05$ . All statistical analyses were performed with the IBM SPSS Statistics 22.0 software (IBM Corporation, Armonk, NY, USA).

## Results

### Study Population Characteristics

The present study subjects had a mean age of 61.2 years with 52.0% were males, 41.3% were former or current smokers, and 10.4% had AL.

Table 1 shows the characteristics of the subjects according to smoking status and presence of AL. A total of 2809 subjects were included in the final analysis. The mean age of never smokers with AL and former/current smokers with AL was significantly higher than that in never smokers without AL. Former/current smoker groups included many males compared to never smokers. The subjects in former/current smoker groups were taller with higher weight than those in the never smoker group. Former and current smokers without AL had significantly higher BMI than those in the never smoker group. In particular, the number of subjects who were overweight ( $BMI \geq 25$ ) were higher (31.3%,  $n = 305$ ) than the other groups. Abdominal circumference was significantly larger in the former and current smoker groups than in never smokers without AL. Former and current smoker groups had significantly higher FVC, mean DBP, fasting glucose level, triglyceride level, WBC count, and prevalence of hyperglycemia than those in the never smoker

group. Similarly, the number of alcohol drinkers in former and current smoker groups was larger than those in the never smoker group. HDL-C and LDL-C levels were significantly lower in the former and current smoker groups than in never smokers without AL. Median hsCRP level was significantly higher in former and current smokers with AL than in the other groups. Mean SBP was higher in the former and current smokers with AL than in never smokers without AL, and the highest prevalence of hypertension was 69.9% in former and current smokers with AL. There was no significant difference in physical activity and prevalence of dyslipidemia among the groups.

### Association Between AL and Mean Carotid IMT Values According to Smoking Status

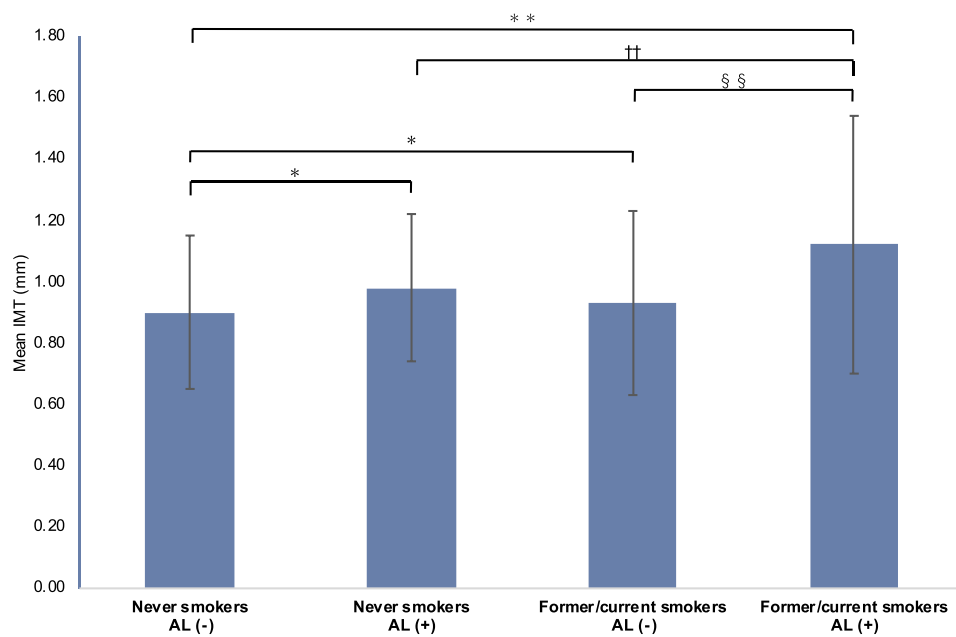
Table 2 shows the effects of AL and smoking on IMT and IMT-C max assessed by two-way ANOVA. There was a significant additive interaction between AL and smoking in IMT ( $F = 7.33$ ,  $p = 0.007$ ) and IMT-C max values ( $F = 6.37$ ,  $p = 0.012$ ). Therefore, we compared mean IMT and IMT-C max values in the four groups stratified by AL and smoking status (Figures 2 and 3).

Mean IMT was significantly higher in never smokers with AL (0.98 mm) ( $p = 0.026$ ), former/current smokers without AL (0.93 mm) ( $p = 0.024$ ), and former/current smokers with AL (1.12 mm) ( $p < 0.001$ ) than those in never smokers without AL (0.90 mm) (Figure 2). Additionally, the mean IMT in former/current smokers with AL (1.12 mm) was significantly higher than that in both never smokers with AL (0.98 mm) ( $p = 0.002$ ) and former/current smokers without AL (0.93 mm) ( $p < 0.001$ ) (Figure 2). Similarly, mean IMT-C max in never smokers with AL (0.98 mm) ( $p = 0.014$ ), former/current smokers without AL (0.92 mm) ( $p = 0.037$ ), and former/current smokers with AL (1.10 mm) ( $p < 0.001$ ) were significantly

**Table 2** The Effects of AL and Smoking on IMT and IMT-C Max

	AL		F	Smoking		F	AL Plus Smoking		F	p value
	Yes (n=292)	No (n=2517)		Yes (n=1161)	No (n=1648)		Yes (n=186)	No (n=1542)		
IMT	1.07 (0.37)	0.91 (0.27)	55.67**	0.96 (0.33)	0.90 (0.25)	21.78**	1.12 (0.42)	0.90 (0.25)	7.33**	0.007
IMT-C max	1.06 (0.37)	0.90 (0.27)	57.99**	0.95 (0.33)	0.89 (0.25)	19.20**	1.10 (0.43)	0.88 (0.25)	6.37*	0.012

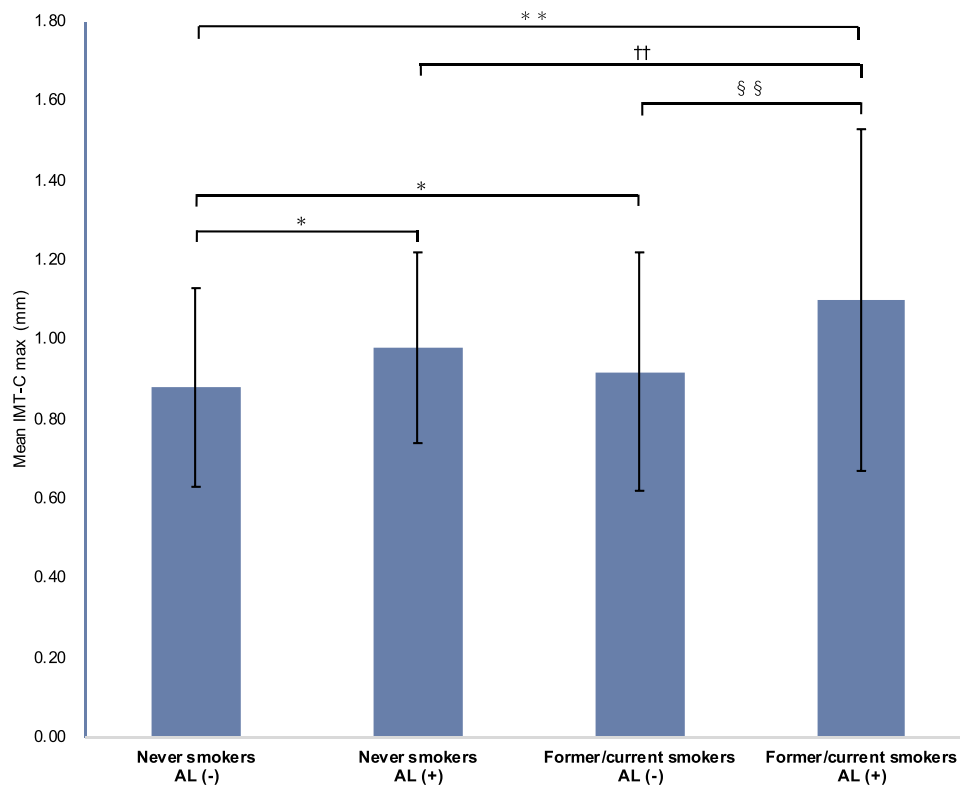
**Notes:** Data are expressed as means (standard deviation). AL was defined as  $FEV_1/FVC < 0.7$ . Smoking was defined as former or current smoking. \* $p < 0.05$ , \*\* $p < 0.01$ .  
**Abbreviations:** AL, airflow limitation; IMT, intima-media thickness; IMT-C max, the maximum measurable IMT value in the left and right common carotid arteries.



**Figure 2** Association between AL and mean IMT values according to smoking status.

**Notes:** Data are expressed as means (standard deviation). AL was defined as  $FEV_1/FVC < 0.7$ . Mean IMT was defined as the average of IMT values in both the right and left sides of the common carotid arteries. \* $p < 0.05$ , \*\* $p < 0.01$  compared with never smokers without AL. †† $p < 0.01$  compared with never smokers with AL. §§ $p < 0.01$  compared with former/current smokers without AL. Error bars indicate standard deviation.

**Abbreviations:** AL, airflow limitation; AL (-), without AL; AL (+), with AL; IMT, intima-media thickness.



**Figure 3** Association between AL and mean IMT-C max values according to smoking status.

**Notes:** Data are expressed as means (standard deviation). AL was defined as  $FEV_1/FVC < 0.7$ . IMT-C max was defined as the maximum measurable IMT value in the left and right common carotid arteries. Mean IMT-C max was defined as the average of both the right and left IMT-C max values. \* $p < 0.05$ , \*\* $p < 0.01$  compared with never smokers without AL. †† $p < 0.01$  compared with never smokers with AL. §§ $p < 0.01$  compared with former/current smokers without AL. Error bars indicate standard deviation.

**Abbreviations:** AL, airflow limitation; AL (-), without AL; AL (+), with AL; IMT, intima-media thickness.

**Table 3** Association Between AL and Carotid Wall Thickness According to Smoking Status

	Never Smokers			Former/Current Smokers			
	AL (-)	AL (+)	p value	AL (-)	p value	AL (+)	p value
	n = 1542	n = 106		n = 975		n = 186	
<b>IMT<sub>1,1</sub></b>							
Crude	1.00 (Reference)	2.11 (1.42–3.13)**	<0.001	1.25 (1.05–1.48)*	0.012	3.29 (2.41–4.50)**	<0.001
Model 1	1.00 (Reference)	1.03 (0.67–1.61)	0.883	0.99 (0.79–1.23)	0.898	1.50 (1.05–2.15)*	0.028
Model 2	1.00 (Reference)	1.01 (0.65–1.58)	0.965	0.97 (0.78–1.21)	0.793	1.53 (1.06–2.20)*	0.024
Model 3	1.00 (Reference)	1.00 (0.64–1.56)	0.998	1.01 (0.80–1.27)	0.939	1.55 (1.07–2.24)*	0.020
<b>IMT<sub>C1,2</sub></b>							
Crude	1.00 (Reference)	2.10 (1.35–3.27)**	0.001	1.59 (1.30–1.94)**	<0.001	3.44 (2.48–4.75)**	<0.001
Model 1	1.00 (Reference)	1.03 (0.64–1.68)	0.896	1.21 (0.94–1.57)	0.135	1.54 (1.06–2.25)*	0.024
Model 2	1.00 (Reference)	1.01 (0.62–1.64)	0.978	1.21 (0.94–1.57)	0.146	1.54 (1.05–2.26)*	0.028
Model 3	1.00 (Reference)	1.00 (0.61–1.63)	0.999	1.20 (0.92–1.57)	0.169	1.52 (1.03–2.24)*	0.034
<b>IMT<sub>C1,5</sub></b>							
Crude	1.00 (Reference)	0.91 (0.32–2.54)	0.850	1.79 (1.26–2.53)**	0.001	4.44 (2.79–7.06)**	<0.001
Model 1	1.00 (Reference)	0.47 (0.17–1.35)	0.161	1.35 (0.89–2.04)	0.163	2.05 (1.21–3.48)**	0.008
Model 2	1.00 (Reference)	0.46 (0.16–1.32)	0.148	1.36 (0.89–2.09)	0.154	2.05 (1.19–3.52)*	0.010
Model 3	1.00 (Reference)	0.48 (0.17–1.38)	0.175	1.30 (0.84–2.02)	0.232	1.99 (1.15–3.46)*	0.014

**Notes:** Model 1: adjusted for sex, age, and BMI. Model 2: adjusted for covariates in Model 1 plus hypertension, hyperglycemia, and dyslipidemia. Model 3: adjusted for covariates in Model 2 plus physical activity and alcohol consumption. AL was defined as FEV<sub>1</sub>/FVC <0.7. IMT<sub>1,1</sub> was defined as measurable IMT value in the left, right, or both common carotid arteries ≥1.1mm. IMT<sub>C1,2</sub> was defined as the maximum measurable IMT value in the left, right, or both common carotid arteries ≥1.2mm. IMT<sub>C1,5</sub> was defined as the maximum measurable IMT value in the left, right, or both common carotid arteries >1.5mm. \*p <0.05, \*\*p <0.01.

**Abbreviations:** AL, airflow limitation; AL (-), without AL; AL (+), with AL; IMT, intima-media thickness.

higher than those in never smokers without AL (0.88 mm) (Figure 3). In addition, the mean IMT-C max in former/current smokers with AL (1.10 mm) was also significantly higher than that in both never smokers with AL (0.98 mm) (p = 0.004) and former/current smokers without AL (0.92 mm) (p < 0.001) (Figure 3).

## Association Between AL and Carotid Wall Thickness According to Smoking Status

Table 3 shows the association between AL and carotid wall thickness as IMT<sub>1,1</sub>, IMT<sub>C1,2</sub>, and IMT<sub>C1,5</sub>. The OR of IMT<sub>1,1</sub>, IMT<sub>C1,2</sub>, and IMT<sub>C1,5</sub> were significantly higher in former/current smokers with AL (OR: 1.55; 95% CI: 1.07–2.24, OR: 1.52; 95% CI: 1.03–2.24, OR: 1.99; 95% CI: 1.15–3.46, respectively) than in never smokers without AL after adjusting for sex, age, BMI, hypertension, dyslipidemia, hyperglycemia, physical activity, and alcohol consumption (all p < 0.05). However, the OR of IMT<sub>1,1</sub>, IMT<sub>C1,2</sub>, and IMT<sub>C1,5</sub> in never smokers with AL (OR: 1.00; 95% CI: 0.64–1.56, OR: 1.00; 95% CI: 0.61–1.63, OR: 0.48; 95% CI: 0.17–1.38, respectively) and former/current smokers without AL (OR: 1.01; 95% CI:

0.80–1.27, OR: 1.20; 95% CI: 0.92–1.57, OR: 1.30; 95% CI: 0.84–2.02, respectively) were not significantly different from those in never smokers without AL.

## Discussion

We demonstrated that mean IMT and mean IMT-C max were higher in never smokers with AL and former/current smokers with or without AL than in never smokers without AL. In the logistic regression models, adjusted for sex, age, BMI, hypertension, dyslipidemia, hyperglycemia, physical activity, and alcohol consumption, a combination AL and smoking experience was associated with carotid wall thickness in the present study.

Several studies have demonstrated an association between FEV<sub>1</sub> and carotid atherosclerosis in the general population. A previous study of middle-aged males showed that mean IMT was significantly higher in former/current smokers with AL than in former/current smokers and never smokers without AL.<sup>18</sup> The MESA Lung Study and the ARIC study demonstrated that decreased FEV<sub>1</sub> was associated with increased carotid IMT in the former and current smokers.<sup>19,20</sup> Our findings were similar to the above results. In the present study, we examined clinical covariates including physical activity and alcohol



consumption as CVD risk factors. Moreover, we included never smokers with AL, and excluded subjects with a history or clinical evidence of clinical CVD (myocardial infarction or angina). Thus, we examined more subjects and comprehensive range of clinical CVD risk factors.

Although more females were included in the never smoker group, we found that mean IMT and mean IMT-C max values were higher in never smokers with AL than in those without AL in the present study. However, the three ORs of carotid wall thickness were not significantly different among the never smoker's group in logistic regression models after adjusting for clinical covariates. In the never smoker group, only the mean age was higher in those with AL compared to those without AL, except for pulmonary function status, and there was no significant difference in both hsCRP and WBC at baseline. A recent Japanese study investigated the association between cigarette smoking and subclinical atherosclerosis in a general population and showed that the mean IMT value was not significantly different in never smokers and former/current smokers.<sup>38</sup> However, their pulmonary function was not examined. Therefore, not only smoking exposure but also presence of AL might be associated with greater carotid IMT among the general population.

Epidemiological studies showed that elevated CRP levels were related to an increased risk of cardiac injury in those with moderate airflow obstruction,<sup>39</sup> and is associated with increased CVD in those with detectable atherosclerosis based on carotid ultrasound.<sup>40</sup> Although AL severity was not examined, elevated hsCRP levels were observed in smokers with AL in the present study, which might indicate the risk of cardiac injury or CVD.

Many studies have investigated the association between pulmonary abnormalities and atherosclerosis in patients with COPD or the general population; nevertheless, the causal mechanisms linking AL, atherosclerosis, and CVD are not fully understood. Low-grade, chronic systemic inflammation is considered one of the key mechanisms underlying systemic manifestations beyond the lungs, including CVD.<sup>41,42</sup> A previous report showed that, compared with healthy controls, individuals with chronic AL had significantly increased levels of CRP, fibrinogen, leucocytes, and tumor necrosis factor- $\alpha$ , indicating that even among non-current smokers, there was evidence of low-grade systemic inflammation in those with AL.<sup>43</sup> Of these inflammation markers, fibrinogen and hsCRP are recognized as markers of systemic inflammation in COPD. Previous studies have shown that these markers are useful predictors of cardiovascular events in the

general population.<sup>44</sup> Moreover, a study of individuals with COPD demonstrated that increased levels of a combination of CRP, fibrinogen, and leukocyte count were associated with increased risk of ischemic heart disease, myocardial infarction, heart failure, type II diabetes, lung cancer, and pneumonia, and that risk estimates were largely independent of smoking.<sup>45</sup> We did not evaluate other inflammatory markers including fibrinogen; thus, further research is needed to reveal AL involvement and inflammation in atherosclerosis. On the other hand, a recent report indicated that endothelial cell dysfunction and AL were mutually independent predictors of atherosclerosis.<sup>46</sup> AL could be an important predictor of atherosclerosis markers in the general population.

This study has several limitations. First, we included all subjects meeting inclusion criteria, aged 40 years or above; thus, it might increase the risk of confounding by age in subjects with AL. In addition, because we assessed males and females together, therefore, many females were included in the never smoker group. Therefore, sex differences might be a confounding factor for IMT values, which we were unable to determine in our findings. Nevertheless, we precluded these involvements by adjusting in logistic regression analysis.

Second, post-bronchodilator spirometry measurements were not performed because of the absence of high suspicion of clinical disease; thus, some subjects with AL may have a post-bronchodilator  $FEV_1/FVC \geq 70\%$  in the present study. However, we excluded respiratory diseases other than COPD, including asthma, at the subject selection. Therefore, it is likely that the subjects with AL had COPD.

Third, because we examined cross-sectional associations in the present study, we cannot address the temporal relationship between AL and IMT. Therefore, prospective studies are needed to confirm these findings. The detailed mechanisms underlying AL and greater IMT are unclear, except for active smoking, for example, secondhand smoke might be the cause of AL in the never smoker group. However, we did not have available data for these in the present study.

Despite these limitations, presence of AL and smoking experience may be effective in screening for subclinical atherosclerosis in subjects undiagnosed with COPD. In our results, screening for subclinical atherosclerosis using IMT as an indicator might be useful to prevent future CVD in smokers with AL.

In the present study, we observed subjects with AL, who might have been diagnosed with COPD in 10% of all subjects. Moreover, although a small number of ALs was

observed in never smokers, their mean IMT and mean IMT-C max were higher in those with AL than in those without AL. However, the ORs for carotid wall thickness were not significantly different between the never smoker groups. Therefore, greater IMT in never smokers with AL might not require immediate clinical intervention. Similarly, the ORs for carotid wall thickness were not significantly different in former/current smokers without AL than in never smokers without AL after adjusting for CVD risk factors. In contrast, the ORs for carotid wall thickness were significantly higher in former/current smokers with AL than in never smokers without AL in logistic regression models adjusted for CVD risk factors. Additionally, mean IMT and IMT-C max values were greater in former/current smokers with AL than in never smokers with or without AL and former/current smokers without AL. Hence, a combination of AL and smoking seemed to be a risk factor for carotid wall thickness.

Nevertheless, mean IMT and mean IMT-C max were greater in former/current smokers with AL than in former/current smokers without AL, and in never smokers with AL than in never smokers without AL. Considering that there was a significant interaction between AL and smoking status in IMT values, more studies are needed to further confirm the effect of AL on IMT in never smokers.

Even so, from the perspective of preventing CVD or arteriosclerosis and atherosclerotic lesions, it is important to identify the presence of these risks regardless of smoking status before clinical symptoms appear. According to a report that CVD comorbidities appeared to be independent of AL severity in COPD,<sup>47,48</sup> early AL diagnosis might be useful to prevent subclinical AL progression and to identify cardiovascular risk factors at an earlier stage in subjects with undiagnosed COPD. Because COPD risk factors are not only active smoking but also secondhand smoke and environmental factors such as exposure to indoor and outdoor air pollution, occupational dust, and fumes,<sup>1</sup> the early diagnosis of AL in the general population regardless of smoking status may lead to determining the CVD risk factors.

To our knowledge, this is the first study to examine the association between AL and carotid IMT among never smokers in the Japanese population. Efforts aimed at the earlier detection of AL regardless of smoking experience in the general population and identification of greater carotid IMT in smokers may lead to the reduction of the burden of COPD on the society.

## Conclusion

In summary, we showed that mean IMT in former/current smokers with AL was higher than that in never smokers with or without AL and former/current smokers without AL. Additionally, the risk of carotid wall thickness was higher in former and current smokers with AL than in never smokers without AL. Therefore, it might be beneficial to find risk factors for CVD earlier in smokers with AL for preventing future CVD occurrence. In addition, AL may be an early indicator of subclinical arteriosclerosis in smokers and never smokers in preventing atherosclerotic diseases. Our findings suggest that AL and smoking experience are markers to recognize subclinical atherosclerosis in the Japanese general population.

## Abbreviations

AL, airflow limitation; ANOVA, analysis of variance; BMI, body mass index; CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; FEV<sub>1</sub>, forced expiratory volume in 1 second; FEV<sub>6</sub>, forced expiratory volume in 6 second; FVC, forced vital capacity; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; IMT, intima-media thickness; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; SBP, systolic blood pressure; SD, standard deviation; WBC, white blood cell.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Disclosure

The authors have no conflicts of interest in this article.

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