

Research Paper

# Retrospective Analysis of the Relationship between Decline in FEV<sub>1</sub> and Abdominal Circumference in Male Smokers: the Takahata Study

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## Abstract

**Background:** Metabolic syndrome (Mets) is reportedly associated with chronic obstructive pulmonary disease (COPD). However, the relationship between abdominal circumference (AC) and decline in FEV<sub>1</sub> has not been elucidated. We aimed to investigate this relationship among male current smokers.

**Methods:** Spirometry was performed on subjects (n = 3,257) ≥ 40 years of age, who participated in a community-based annual health check in Takahata, Japan, from 2004 through 2006 (visit 1). Spirometry was re-evaluated, and AC was assessed in 147 of the male current smokers in 2009 (visit 2). The diagnosis of Mets was based on the criteria used in the Hisayama Study.

**Results:** No significant relationships were observed between AC and spirometric parameters such as % predicted forced vital capacity (FVC), % predicted forced expiratory volume in 1 s (FEV<sub>1</sub>) and FEV<sub>1</sub>/FVC. However, decline in FEV<sub>1</sub> was significantly correlated with AC. Multivariate logistic regression analysis showed that AC was a significant discriminating factor for decline in FEV<sub>1</sub>, independently of age, Brinkman index and change in body mass index from visit 1 to visit 2. At visit 2, there was a greater prevalence of decline in FEV<sub>1</sub> among subjects with Mets (n=17) than among those without Mets. Although there were no differences in % predicted FVC, % predicted FEV<sub>1</sub> or FEV<sub>1</sub>/FVC between subjects with or without Mets, the rate of decline in FEV<sub>1</sub> was significantly greater in subjects with Mets than in those without.

**Conclusions:** This retrospective analysis suggested that measuring AC may be useful for discriminating male smokers who show a decline in FEV<sub>1</sub>.

Key words: decline in FEV<sub>1</sub>, abdominal circumference, smoker, health check.

## Introduction

Long-term cigarette smoking is most important cause of chronic obstructive pulmonary disease (COPD) (1). In patients with COPD, forced expiratory volume in 1 s (FEV<sub>1</sub>) is progressively reduced as the disease develops. In addition, patients with COPD

have various systemic comorbidities, including atherosclerosis, cachexia, diabetes mellitus, and osteoporosis (2-7). These comorbidities are thought to be associated with systemic inflammation due to leakage of mediators from sites of local inflammation in the

lung, and this is an important determinant of the morbidity associated with the disease (8). Recently, metabolic syndrome (Mets) has received attention as a comorbidity of COPD (9-12).

Mets is also thought to be a disease of systemic inflammation that is derived from visceral fat (13). Patients with Mets have higher risks of cardiovascular disease, stroke, and death, compared to subjects without Mets (14). Since Mets and COPD both involve states of systemic inflammation, it is conceivable that these diseases share common inflammatory pathways.

The results of recent cross-sectional investigations from China and France suggested that the central obesity component of Mets was associated with impairment of pulmonary function (10,15). However, it was not clear whether Mets is a risk factor for decline in pulmonary function parameters such as FEV<sub>1</sub>, among healthy smokers. We hypothesized that excess abdominal circumference (AC), one of the major signs of Mets, is associated with a decline in FEV<sub>1</sub> among smokers. To examine this hypothesis, we retrospectively investigated the relationship between AC and the rate of decline in FEV<sub>1</sub>.

## Methods

### Study population

This study formed part of the Molecular Epidemiological Study of the Regional Characteristics of 21<sup>st</sup> Century Centers of Excellence (COE) Program and the Global Centers of Excellence Program in Japan (16). The study was approved by the institutional ethics committee and all participants gave written informed consent.

The study was based on an annual community health check, in which all residents of Takahata town in northern Japan, who were aged 40 years or older, were invited to participate. We have previously reported cross-sectional analyses of spirometry data for subjects who were included in the database from 2004 through 2005 (n = 3,165: 1,380 males; 1,735 females) (16-20). We continued to enroll subjects from Takahata in 2006, and recently the additional 2006 database became available for analysis. From 2004 through 2006 (visit 1), 1,579 males and 1,941 females (a total of 3,520 subjects) were enrolled in the study, and performed initial spirometry. Two-hundred and sixty-three subjects were excluded from the analysis because their spirometry data did not meet the specified criteria. The data for a total of 3,257 subjects (1,502 males, 1,755 females) was entered into the final statistical analysis. Subjects used a self-report questionnaire to document their medical histories, smoking habits,

current use of medications, and clinical symptoms. The lifetime consumption of cigarettes was expressed as the Brinkman index (number of cigarettes per day x years of smoking). One-hundred and forty-seven of the 523 male current smokers (visit 1) performed subsequent follow-up spirometry in 2009 (visit 2). Body mass index (BMI), Brinkman index, mean blood pressure (BP), triglyceride (TG), high-density lipoprotein-cholesterol (HDL-c), fasting blood sugar (FBS), % predicted forced vital capacity [FVC (% predicted)], and % predicted forced expiratory volume in 1 s [FEV<sub>1</sub> (% predicted)] were not significantly different between these 147 male current smokers and the remaining 376 male smoker who did not participate in follow-up spirometry in 2009 (data not shown). However, the mean age of these 147 participants was significantly lower than that of the 376 non-participants assessed in 2004-2006 [mean age (years): 56.40 ± 9.06 vs. 61.09 ± 10.59, P < 0.0001].

### Measurements

AC around the navel was determined at visit 2 using a tape measure. Systolic and diastolic BP were measured using a mercury sphygmomanometer, which was placed on the right arm of seated subjects, who had rested in a sitting position for at least 5 min before the measurement. Measurements were performed twice. Blood samples were taken from the antecubital vein of subjects who had been fasting, and the samples were immediately transferred to chilled tubes.

The diagnosis of Mets was based on the criteria used in the Hisayama Study, a Japanese cohort study in a general population: abdominal obesity with abdominal circumference >90 cm in men; elevated blood pressure with average systolic/diastolic blood pressures ≥130/85 mm Hg; hypertriglyceridemia, defined as a serum TG level ≥150 mg/dL; a low HDL-c level, defined as <40 mg/dL in men; elevated blood glucose with a FBS level ≥110 mg/dL. Metabolic syndrome was defined as the presence of three or more of these factors (21).

Spirometric parameters (FVC and FEV<sub>1</sub>) were measured using standard techniques, with subjects performing FVC maneuvers on a CHESTAC-25 part II EX instrument (Chest Corp., Tokyo, Japan), according to the guidelines of the Japanese Respiratory Society (JRS) (22). Bronchodilator was not administered prior to spirometry. The highest value from at least three FVC maneuvers by each subject was used for the analysis. The results were assessed by two pulmonary physicians, who visually inspected the flow-volume curves and excluded subjects with inadequate data, as defined by the JRS criteria (22). The rate of decline in

spirometric measures [ $\Delta$ FEV<sub>1</sub> (% predicted)/year (%/year) and  $\Delta$ FVC (% predicted)/year (%/year)] were calculated as [(% predicted value at visit 2 - % predicted value at visit 1)/% predicted value at visit 1]  $\times$  100/ time between observations (years).

### Statistical analyses

The student's t-test for parametric data or the Mann-Whitney U test for non-parametric data were used to analyze the differences between two groups of subjects. The chi-square test was used to evaluate differences in proportions. All statistical analyses, including linear regression and logistic regression analyses were performed using JMP version 8 software (SAS Institute Inc., Cary, NC, USA). Data are presented in the Figures and Tables as means (SD) or medians (interquartile range). Significance was inferred for differences with *P* values < 0.05.

## Results

### Characteristics of the subjects

The characteristics of the male smoking subjects who participated in this study and performed spirometry at both visit 1 and visit 2 are summarized in Table 1. Mean BMI did not differ between visit 1 and visit 2. Mean FVC (% predicted) at visit 2 was significantly higher than that at visit 1, although FEV<sub>1</sub> (% predicted) at visit 2 did not differ from that at visit 1. FEV<sub>1</sub>/FVC was significantly lower at visit 2 than at visit 1, and the prevalence of airflow limitation was significantly greater at visit 2 than at visit 1 (Table 1). There was a strong correlation between BMI and AC at visit 2 ( $r = 0.89$ ,  $P < 0.0001$ ).

**Table 1.** Characteristics of the study subjects at visit 1 and visit 2.

	Visit 1	Visit 2
Age, years	56.4 (9.1)	60.9 (9.1)***
BMI, kg/m <sup>2</sup>	22.8 (2.8)	22.9 (2.9)
AC, cm	Not measured	83.5 (8.7)
Brinkman index, cigarette· years	751.7 (413.8)	847.9 (449.5)***
FVC, % predicted	94.4 (13.5)	98.5 (14.4)**
FEV <sub>1</sub> , % predicted	92.4 (15.8)	91.9 (17.1)
FVEV <sub>1</sub> /FVC, %	77.3 (8.4)	73.0 (9.3)***
FEV <sub>1</sub> /FVC<0.7, n (%)	23 (15.6)	48 (32.7)**

A total of 147 subjects were included in the study. AC data were not available for nine subjects. Brinkman index data were not available for 19 subjects due to the lack of precise information about cigarette smoking habit. Values are means (SD) or number (%) of subjects. Difference in Brinkman index between visit 1 and visit 2 was evaluated by the Mann-Whitney U test. Difference in the proportion of FEV<sub>1</sub>/FVC<0.7 was evaluated by the chi-square test. Differences in other variables were evaluated by Student's t-test. \*\*  $P < 0.001$ , \*\*\*  $P < 0.0001$  compared with data for visit 1. BMI, body mass index; AC, abdominal circumference; FVC, forced vital capacity; FEV<sub>1</sub>, forced expiratory volume in 1 s.

### Relationship between abdominal circumference and spirometric measures

The relationship between AC and spirometric measures, and that between BMI and spirometric measures was investigated. No significant correlations between AC and unadjusted spirometric measures, and between BMI and unadjusted spirometric measures were detected (data not shown). In addition, there were no significant correlations between AC and adjusted spirometric measures for Brinkman index and status of Mets (Table 2A), and nor was BMI correlated with adjusted spirometric measures (Table 2B). The relationships between AC and changes in spirometric values were also evaluated. As shown in Figure 1, AC was inversely correlated with changes in FEV<sub>1</sub> (% predicted) ( $r = -0.19$ ,  $P = 0.024$ ; Figure 1B), but not with changes in FVC (% predicted) (Figure 1A). However, there were no correlations between BMI and the changes in FVC (% predicted) or FEV<sub>1</sub> (% predicted) (Figures 1C & 1D). In addition, the relationship between changes in spirometric values and change in BMI ( $\Delta$ BMI = BMI<sub>visit2</sub> - BMI<sub>visit1</sub>) were investigated, since weight gain may reduce spirometric values (23). Both  $\Delta$ FVC (% predicted)/year and  $\Delta$ FEV<sub>1</sub> (% predicted)/year did not correlate with  $\Delta$ BMI [ $\Delta$ FVC (% predicted)/year:  $r = -0.06$ ,  $P = 0.44$ ;  $\Delta$ FEV<sub>1</sub> (% predicted)/year:  $r = -0.11$ ,  $P = 0.16$ ]. We set the cut-off value for decline in FEV<sub>1</sub> (% predicted) as a reduction from baseline of  $\geq 1.6\%$ , because this was the lowest quintile of  $\Delta$ FEV<sub>1</sub> (% predicted)/year. Multiple logistic regression analysis revealed that AC significantly discriminated subjects who showed a decline in FEV<sub>1</sub>, independently of age, cigarette consumption (Brinkman index), and  $\Delta$ BMI (Table 3).

**Table 2.** Relationship of abdominal circumference and body mass index with spirometric measures at visit 2.

	Coefficient	<i>P</i> value
<b>A. Abdominal circumference</b>		
FVC, % predicted	0.124	0.48
FEV <sub>1</sub> , % predicted	0.017	0.93
FEV <sub>1</sub> /FVC	-0.050	0.66
<b>B. BMI</b>		
FVC, % predicted	0.584	0.26
FEV <sub>1</sub> , % predicted	0.609	0.31
FEV <sub>1</sub> /FVC	0.261	0.44

Correlations between spirometric measurements and (A) abdominal circumference or (B) BMI were shown. Results were adjusted for Brinkman index and status of metabolic syndrome using multivariate linear regression assay. BMI, body mass index; FVC, forced vital capacity; FEV<sub>1</sub>, forced expiratory volume in 1 s.

**Table 3.** Multivariate logistic regression analysis for discrimination of subjects showing a decline in FEV<sub>1</sub>.

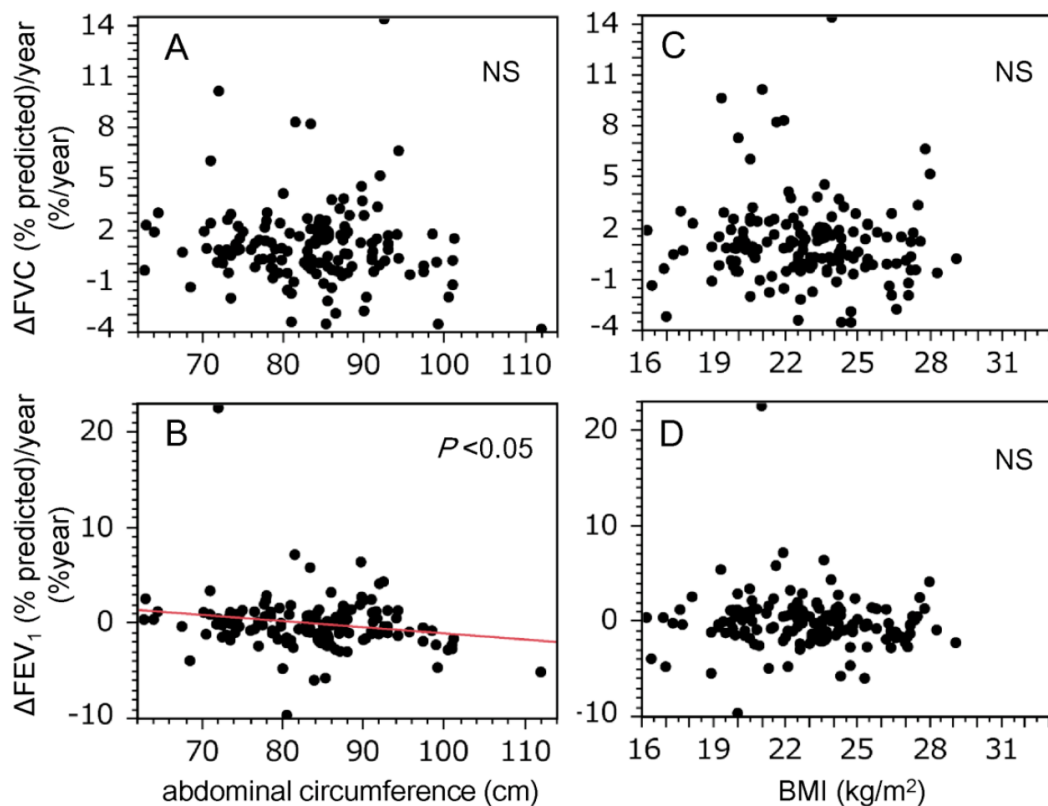
	OR	95% CI	P value
Age (per 1-year increase)	1.043	(0.976-1.120)	0.217
Brinkman Index (per 1-cigarette· year increase)	1.000	(0.999-1.001)	0.479
AC (per 1-cm increase)	1.095	(1.027-1.178)	0.005
ΔBMI (per 1-kg/m <sup>2</sup> increase)	1.002	(0.656-1.564)	0.992

Out of a total of 147 subjects, abdominal circumference data were not available for nine subjects. Brinkman index data were not available for 19 subjects due to the lack of precise information about cigarette smoking habit.  $\Delta\text{BMI} = \text{BMI}_{\text{visit2}} - \text{BMI}_{\text{visit1}}$ ; AC, abdominal circumference; BMI, body mass index; FEV<sub>1</sub>, forced expiratory volume in 1 s.

### Metabolic syndrome and decline in FEV<sub>1</sub>

A diagnosis of Mets could not be made for 10 of the 147 subjects due to the lack of necessary infor-

mation (AC for 9; FBS level for 1). The differences in subject characteristics according to whether or not they had Mets are shown in Table 4. Subjects with Mets were younger, and had a greater BMI, ΔBMI, AC, systolic BP, diastolic BP, and higher TG levels (Table 4). HDL-c levels were significantly lower in subjects with Mets than in those without Mets; however FBS levels and Brinkman index did not differ between subjects with or without Mets (Table 4). A decline in FEV<sub>1</sub> (% predicted) was more prevalent among subjects with Mets compared to those without Mets (Table 5). In addition, the median decline in FEV<sub>1</sub> (% predicted) was significantly greater in subjects with Mets than it was in those without Mets (Table 6). Spirometric measures at visit 2 did not differ significantly between subjects with or without Mets (Table 6). Even after adjustment of FEV<sub>1</sub>/FVC for age, there was no difference in FEV<sub>1</sub>/FVC between the two groups ( $P = 0.91$ ).



**Figure 1.** Abdominal circumference was inversely correlated with decline in FEV<sub>1</sub> in this study population. Graphs show the relationships between decline in spirometric parameters [A and C, ΔFVC (% predicted)/year; B and D, ΔFEV<sub>1</sub> (% predicted)/year] and markers of body size (A and B, abdominal circumference; C and D, BMI). Correlations between spirometric measurements and markers of body size were evaluated using Pearson's product moment correlation coefficient. A statistically significant relationship was only observed for ΔFEV<sub>1</sub> (% predicted)/year and abdominal circumference (B,  $r = -0.19$ ,  $P = 0.024$ ). BMI, body mass index; FVC, forced vital capacity; FEV<sub>1</sub>, forced expiratory volume in 1 s.



**Table 4.** Differences in subject characteristics according to presence or absence of metabolic syndrome (Mets).

	Mets- (n = 120)	Mets+ (n = 17)
Age, years	60.2 (8.0)	56.5 (8.2)*
Brinkman index, cigarette×year	827.9 (408.9)	955.8 (733.5)
BMI, kg/m <sup>2</sup>	22.4 (2.5)	26.9 (2.0)***
ΔBMI, kg/m <sup>2</sup>	-0.01 (0.10)	0.89 (0.27)**
AC, cm	81.6 (7.4)	95.9 (5.7)***
Systolic BP, mm Hg	132.6 (19.1)	144.9 (16.8)*
Diastolic BP, mm Hg	79.9 (11.7)	88.1 (9.9)**
TG, mg/dL	134.0 (121.5)	197.2 (72.8)*
HDL-c, mg/dL	54.7 (13.6)	43.5 (11.3)*
FBS, mg/dL	96.3 (22.6)	100.8 (16.7)

Out of 147 subjects, AC and FBS data were not available for 10 subjects. ΔBMI = BMI<sub>visit2</sub> - BMI<sub>visit1</sub>. Values are means (SD). Differences in variables between subjects with Met and those without Mets were evaluated by Student's t-test. \*  $P < 0.05$ , \*\*  $P < 0.001$ , \*\*\*  $P < 0.0001$  compared with Mets-. BMI, body mass index; AC, abdominal circumference; BP, blood pressure; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; FBS, fasting blood sugar.

**Table 5.** Prevalence of decline in FEV<sub>1</sub> (% predicted) according to the presence or absence of metabolic syndrome (Mets).

FEV <sub>1</sub>	Mets - (n = 120)	Mets + (n = 17)
Decline, n (%)	18 (15)	6 (35.3)
No decline, n (%)	102 (85)	11 (64.7)

$P = 0.039$ , chi-square test. FEV<sub>1</sub>, forced expiratory volume in 1 s.

**Table 6.** Decline in FEV<sub>1</sub> and spirometric measures at visit 2 according to the presence or absence of metabolic syndrome (Mets).

	Mets - (n = 120)	Mets + (n = 17)	P value
ΔFEV <sub>1</sub> (% predicted)/year, %/year	0.04 (-1.02, 1.14)	-1.11 (-2.21, 0.07)	0.04
FVC, % predicted	100.1 (13.3)	94.1 (15.5)	0.09
FEV <sub>1</sub> , % predicted	93.6 (16.3)	88.0 (12.2)	0.17
FEV <sub>1</sub> /FVC, %	73.3 (9.5)	74.3 (6.2)	0.68

Values are median (interquartile range) or mean (SD). Difference in ΔFEV<sub>1</sub> (% predicted)/year between subjects with Mets and those without Mets was evaluated by the Mann-Whitney U test. Differences in other variables were evaluated by Student's t-test. FVC, forced vital capacity; FEV<sub>1</sub>, forced expiratory volume in 1 s.

## Discussion

In this longitudinal study, spirometric values were measured twice in male smokers, who participated in an annual health check. At visit 2, AC was evaluated in these subjects, and a significant correlation between rate of decline in FEV<sub>1</sub> and AC was retrospectively demonstrated. Furthermore, multivariate logistic regression analysis revealed that a decline in FEV<sub>1</sub> was associated with AC, independently of age, cigarette consumption (Brinkman index) and ΔBMI. In addition, a decline in FEV<sub>1</sub> was more prevalent among subjects with Mets, and the rate of decline in FEV<sub>1</sub> in these subjects was significantly greater than that in subjects without Mets.

Mets is a common disease that is characterized by abdominal obesity, high blood pressure, hypertriglyceridemia, low HDL-c levels, and high fasting glucose levels (24). Data from the Third National

Health and Nutrition Examination Survey indicates that this syndrome is present in almost a quarter of US residents aged 20 years or older (25). Although Mets is less prevalent in Asian compared with Western populations, a survey of the incidence of acute myocardial infarction suggested that the prevalence of Mets is also increasing in Japan, resulting in an increased incidence of myocardial infarction among men (26). Mets is associated with an increased risk of diabetes mellitus and cardiovascular disease, leading to increased cardiovascular and all-cause mortality (14). Recent studies have demonstrated that systemic inflammation, derived from visceral fat, is an important mechanism in the pathogenesis of Mets (13). Because both Mets and COPD are associated with the same comorbidities, including atherosclerosis and diabetes, and involve a state of chronic systemic inflammation, the pathogenesis of the two diseases is thought to share a common inflammatory pathway. A recent

study showed that the prevalence of Mets is greater in subjects with COPD compared to those without COPD (11,27).

The mechanism underlying the rapid decline in pulmonary function in male smokers with a high AC has not been fully elucidated. One possible mechanism that might explain this phenomenon is endothelial dysfunction in subjects with Mets (28). Accumulating evidence suggests that endothelial dysfunction is one of the important features in the development of COPD (29). In particular, pulmonary endothelial cell apoptosis is thought to play an important role in the loss of pulmonary vasculature (30,31). Systemic inflammation may play a significant role in endothelial dysfunction in COPD patients (32). Mets is characterized by systemic low-grade inflammation, and endothelial dysfunction resulting from this systemic inflammation leads to functional impairment of organ systems (33,34). In addition, long term exposure to cigarette smoke induces systemic inflammation (35). Therefore, in active smokers with Mets, systemic inflammation may be enhanced because it is derived from two sources, namely visceral fat and exposure of the lungs to cigarette smoke. This may result in enhanced endothelial dysfunction and a rapid decline in pulmonary function.

Abdominal obesity may change the compliance of the diaphragm and chest wall. Chen and colleagues reported that a 1-cm increase in AC was associated with a 13-mL reduction in FVC and a 11-mL reduction in FEV<sub>1</sub> (23). In the present study, there was no difference in mean BMI between visit 1 and visit 2, although AC was not measured at visit 1. In addition, multivariate logistic regression analysis demonstrated that AC was a significant factor for discrimination of decline in FEV<sub>1</sub>, independently of  $\Delta$ BMI (Table 3). It is unlikely that the decline in FEV<sub>1</sub> observed in the present study is explained by weight gain during follow-up.

In the present study, the longitudinal decrease in FEV<sub>1</sub> was significantly greater in subjects with Mets, and the prevalence of a decline in FEV<sub>1</sub> was significantly greater in subjects with Mets than in those without Mets. However, FEV<sub>1</sub>/FVC did not differ significantly between subjects with or without Mets. Even after adjustment of FEV<sub>1</sub>/FVC for age, there was no difference in FEV<sub>1</sub>/FVC between the two groups. This finding was in keeping with those from previous studies, which demonstrated that FEV<sub>1</sub>/FVC was not reduced in subjects with Mets compared to those without Mets (36,37).

This study had several limitations. First, there may have been sampling bias. Takahata town has a resident population of 15,222 adults aged 40 years or

older. For visit 1, data for a total of 3,257 enrolled subjects was entered into the final statistical analysis. Among the 1,502 male subjects, there were 523 active smokers. However, follow-up spirometry in 2009 was only performed for 147 subjects who had continued to smoke; the remaining subjects were lost to follow-up or quit smoking before visit 2. The number of subjects who were followed-up was not large, but the only significant difference between participants and non-participants in 2009 was age (see Method section). Thus, we thought the participants in 2009 were not largely different from non-participants. Differences between participants and non-participants in type of employment, socio-economic status or life style may have influenced the results. However, this information was not available in the present study. Second, pulmonary function testing at visit 2 in 2009 was only performed for male current smokers, not for male non-smokers, ex-smokers or females. This was only because we could not find a sufficient number of testers in 2009. Therefore we needed to focus on the data for the subjects who were assessed in the present study. Because of this limitation, the results from the present study may not be applicable to females or ex-smokers. Third, AC measurements were performed at visit 2, not visit 1. Therefore, the association between decline in FEV<sub>1</sub> and AC was retrospectively demonstrated in this study. It should be noted that it could not be concluded that AC is predictive for decline in FEV<sub>1</sub> among male smokers. However, despite these limitations we think this study is clinically significant as an initial investigation, and future prospective studies have the potential to confirm AC as a new and simple biomarker for discriminating subjects with a decline in FEV<sub>1</sub> among active smokers.

In conclusion, AC was significantly associated with the rate of decline in FEV<sub>1</sub> among male smokers in this study population. A decline in FEV<sub>1</sub> was more prevalent among subjects with Mets, and the rate of decline in FEV<sub>1</sub> was significantly greater in subjects with Mets compared to those without Mets. This retrospective analysis suggested that measurement of AC may be a simple and useful method of discriminating subjects with a decline in FEV<sub>1</sub> among male smokers.

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### Ethics approval

This study was approved by the institutional ethics committee and all participants gave written informed consent.

### Conflicts of interest

The authors have no conflicts of interest to disclose.

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