

Clinical relevance of multiple confirmed preserved ratio impaired spirometry cases in adults

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Abstract (248/250 words)

Background

Preserved ratio impaired spirometry (PRISm) is a common spirometry finding, but its heterogeneous manifestations and frequent transitions to airflow limitation (AFL), chronic obstructive pulmonary disease, or normal spirometry hinder establishing an appropriate management strategy. This study examined whether transition to AFL and other comorbidities is more frequent in subjects with definite PRISm (PRISm confirmed on both current and past two spirometry tests) versus incident PRISm (PRISm confirmed only on a current test with past normal spirometry records) than in normal spirometry.

Methods

Archived medical check-up data of subjects aged ≥ 40 years ($n = 10828$) with two past spirometry records, in a Japanese hospital, were cross-sectionally analyzed. Among them, data from those with follow-up spirometry after three years ($n = 6467$) were used to evaluate transition to AFL. PRISm was defined as forced volume in 1 s (FEV_1)/forced vital capacity ≥ 0.7 and % predicted $FEV_1 < 80\%$.

Results

Overall PRISm prevalence was 6.5%. In multivariable models adjusted for age, sex, smoking status, and body mass index, definite PRISm ($n = 290$), but not incident PRISm ($n = 183$), was associated with elevated hemoglobin A1c and C-reactive protein levels, and higher rates of asthma, hypertension, hyperlipidemia, and diabetes than was consistent normal spirometry ($n = 9694$). The transition to AFL after three years was more

frequent in definite PRISm, but not incident PRISm, than in normal spirometry (adjusted hazard ratio [95% confidence interval] = 6.21 [3.42—10.71] and 1.45 [0.23—4.73], respectively).

Conclusions

Multiple confirmed PRISm on past and baseline spirometry is closely associated with metabolic syndrome factors, asthma history, and future AFL development.

Keywords: spirometry, preserved ratio impaired spirometry, airflow limitation, chronic obstructive pulmonary disease

1. Introduction

Chronic lung disease is a major cause of morbidity and mortality. Spirometry is widely used to evaluate lung function [1]. Among various spirometry abnormalities, preserved ratio impaired spirometry (PRISm), defined as a reduction in forced expiratory volume in 1 s (FEV_1) with normal FEV_1 /forced vital capacity (FVC), is considered an important physiological finding. The prevalence of PRISm is 7-22% worldwide [2-6] and 9.9% in the Japanese population [7]. Compared to normal spirometry, PRISm is associated with a higher risk of cardiovascular mortality and all-cause mortality in non-smokers (never smokers) and current or former smokers (ever smokers) in Western countries [2, 8] and Japan [7]. Further exploration of the clinical and physiological nature is needed to establish the management strategy for subjects with PRISm.

Longitudinal studies have identified the clinical heterogeneity and fluctuation of spirometry categories as a feature of PRISm [3, 7, 9-11]. A substantial portion of subjects with PRISm undergo baseline transitions to airflow limitation (AFL) and chronic obstructive pulmonary disease (COPD), but other portions of subjects with PRISm may transition to normal spirometry at follow-up examinations [2, 12, 13]. Three PRISm subtypes exist, including that of: 1) PRISm that transitions to AFL and COPD, 2) PRISm with high cardiovascular comorbidity and mortality, and 3) persistent PRISm [2]. The importance of longitudinal multiple spirometry assessments is thus apparent. However, many longitudinal studies have defined baseline spirometry categories based on a single assessment at enrollment. Whether a combination of past examinations (spirometry record) and current examination (starting point for longitudinal follow-up) allows for better PRISm subtyping remains unclear.

It was hypothesized that PRISm with distinct clinical features from normal

spirometry could be enriched by incorporating past records of PRISm to a current finding of PRISm on spirometry. Therefore, this study used spirometry data of adults who continuously participated in a medical check-up program to test whether transition to AFL and baseline comorbidities, after a three-year follow-up, are more frequent in subjects with multiple PRISm confirmations (on both the past two and baseline spirometry tests), versus subjects with single PRISm confirmations (only on a baseline spirometry), than in normal spirometry.

2. Materials and methods

2.1. Study subjects

This study retrospectively analyzed data of adults aged ≥ 40 years old who had participated in a medical check-up program in Takeda Hospital in Japan, between 2016 and 2017. Subjects whose two past spirometry datasets were unavailable were excluded, since the aim of the study was to examine clinical features of multiple confirmed PRISm — at baseline and at two past spirometry tests. The study was performed in accordance with the Declaration of Helsinki and approved by the Ethics Committees of Kyoto University Hospital (approval No. R2751, approval date November 11, 2020) and Takeda Hospital (approval No. 2019, approval date December 24, 2020). Informed consent was waived due to the retrospective nature of the study.

2.2. Clinical assessments

Subjects completed self-reported questionnaires and underwent spirometry, blood tests, and plain chest X-rays on the same day. The questionnaires assessed past medical history, regular exercise habits (performing exercise ≥ 2 times/week), history of weight

gain > 10 kg from age 20, self-reported hypertension, hyperlipidemia, diabetes, and smoking status (never/former/current) [14]. Because information regarding smoking status was lacking in former smokers, smoking pack-year was not assessed in this study. Hemoglobin A1c (HbA1c) and C-reactive protein (CRP) in the blood were dichotomized, based on cut-off values of 6.5% and 0.1 mg/dL [15], respectively.

2.3. Spirometry

Trained technicians performed spirometry without a bronchodilator, using a Spiroshift SP-770 COPD (Fukuda Denshi, Tokyo, Japan), according to the guidelines set out by the American Thoracic Society/European Respiratory Society [16]. The lambda-mu-sigma (LMS) method for the Japanese population was used to calculate predicted FEV₁ and FVC, and the lower limit of normal (LLN) for FEV₁ and FEV₁/FVC [17]. PRISm was defined as the percentage of predicted FEV₁ < 80% and FEV₁/FVC ≥ 0.7, and AFL was defined as FEV₁/FVC < 0.7 in the main analyses [10, 18]. In sensitivity analyses, PRISm was defined as FEV₁ < LLN and FEV₁/FVC ≥ LLN, and AFL was defined as FEV₁/FVC < LLN.

2.4. Statistical analysis

Statistical analyses were performed using R, version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) [19]. Data were expressed as mean (standard deviation). Based on spirometry at enrollment, subjects were classified into normal, PRISm, and AFL groups. Then, subjects with PRISm were further classified into four groups based on two past spirometry tests, including: 1) PRISm at enrollment + definite PRISm (PRISm at both past tests), 2) PRISm at enrollment + probable PRISm (PRISm at one past test + normal spirometry at another past test), 3) PRISm at enrollment + incident PRISm (normal spirometry at both past tests), and 4) PRISm at enrollment + PRISm with

AFL history (AFL at ≥ 1 past tests). Normal spirometry was defined as a consistent finding of normal spirometry at enrollment and at the two past tests. AFL was defined as a consistent finding of AFL at enrollment and the two past tests. To compare clinical features at enrollment and upon development of AFL after three years, between the normal spirometry group and the other groups, multivariable logistic regression models were constructed. Each model included the spirometry group (using the normal spirometry group as a reference), age, sex, body size (height, or both height and body mass index [BMI]), smoking status, and a history of asthma as independent variables.

3. Results

3-1. Subjects' flow

As shown in Figure 1, of the 17276 subjects aged ≥ 40 years participating in the medical check-up between 2016 and 2017, 10828 subjects with two past spirometry records were included in this study. The median (interquartile range) length of the period between the earliest past spirometry and baseline spirometry assessments was 2.03 (1.99—2.36) years. Based on baseline spirometry, subjects were classified into normal spirometry ($n = 9495$, 87.7%), PRISm ($n = 706$, 6.5%), and AFL ($n = 627$, 5.8%) groups.

Based on the two past spirometry records, 706 subjects with PRISm at baseline assessments were further classified into incident PRISm ($n = 169$, $169/706 = 24\%$), probable PRISm ($n = 188$, $188/706 = 27\%$), definite PRISm ($n = 290$, $290/706 = 41\%$), and PRISm with AFL history ($n = 59$, $59/706 = 8\%$) groups. As normal and disease controls, subjects with consistent normal spirometry (normal spirometry at all tests, including that at baseline and at the two past exams, $n=9058$) and consistent AFL (AFL

at all tests, n = 375) were also used for further analyses.

3-2. Comparisons of clinical features at enrollment between the normal spirometry group and the other groups

Table 1 compares demographic and clinical features between the consistent normal spirometry, four PRISm, and consistent AFL groups (total n=10139). Compared to the normal spirometry group, age was higher in the definite and probable PRISm, PRISm with AFL history, and AFL groups. BMI, waist circumference, rates of a history of 10kg of weight gain after the age of 20 years, hypertension, hyperlipidemia, diabetes, CRP and HbA1c levels, and cardiothoracic ratios on X-ray were higher in the definite and probable PRISm groups. A history of asthma was more prevalent in the AFL and PRISm with AFL history groups (followed by the incident, probable, and definite PRISm groups) than in the normal spirometry group. Regular exercise was more frequent in the AFL group (but not in the incident, probable, and definite PRISm groups) than in the normal spirometry group.

Table 2 shows that, in the multivariable logistic regression models, the rates of $\text{BMI} \geq 25\text{kg/m}^2$, diabetes, and $\text{HbA1c} \geq 6.5\%$ were significantly higher in the probable and definite PRISm groups than in the normal spirometry group, whereas no difference was found between the normal spirometry and incident PRISm groups. A history of asthma was more prevalent in the incident, probable, and definite PRISm; PRISm with AFL history; and AFL groups than in the normal spirometry group. The definite PRISm group also exhibited significantly higher rates of hypertension, hyperlipidemia, and $\text{CRP} \geq 0.1 \text{ mg/dl}$.

In additional multivariable models (including never and ever smokers separately), the rates of $\text{BMI} \geq 25\text{kg/m}^2$, asthma history, diabetes, and $\text{CRP} \geq 0.1 \text{ mg/dl}$ were

significantly higher in the definite PRISm group than in the normal spirometry (Supplementary Tables S1 and S2).

These associations were confirmed when defining PRISm and AFL based on the LLN criterion (Supplementary Table S3).

3-3. Transition of spirometry categories from baseline to three years thereafter

Of 10139 subjects used for cross-sectional comparisons (Tables 1 and 2), 6467 underwent follow-up spirometry three years after baseline examinations. As shown in Table 3, age, the frequency of male sex, and smoking status in the definite, probable, and incident PRISm groups did not differ from those in the normal spirometry group. As visualized in Figure 2, 84.1%, 56.4%, and 33.0% subjects within baseline definite, probable, and incident PRISm groups (respectively) exhibited PRISm at the three-year follow-up. Development of AFL was found in 9.7%, 8.2%, 1.9%, and 40.0% subjects within the definite, probable, incident PRISm, and PRISm with AFL history groups, respectively.

Table 4 shows that hazard ratios (HRs) for the development of AFL were significantly higher in the PRISm with AFL history group (followed by the probable and definite PRISm groups) than in the normal group (HR [95% confidence interval (95% CI)] = 35.9 [16.30—76.97], 6.21 [3.42—10.71], 6.34 [2.86—12.58], respectively) in multivariable logistic models adjusted for age, sex, height, BMI, smoking status, and history of asthma. In contrast, the risk of AFL development was not different between the normal spirometry and incident PRISm groups (HR [95% CI] = 1.45 [0.23—4.73]). These trends were confirmed in the sub-analysis of ever smokers (n = 2148), never smokers (n = 4101), and subjects without a history of asthma (n = 5824). Moreover, in sub-analyses of subjects with PRISm (n = 424), HRs for the development of AFL were significantly

higher in the definite PRISm and PRISm with AFL history groups than in the incident PRISm groups (HR [95% CI] = 4.65 [1.27—30.04] and 28.82 [6.99—30.05], respectively).

When defining PRISm and AFL based on the LLN criterion, 79.9%, 66.3%, and 33.3% of subjects within the definite, probable, and incident PRISm groups exhibited PRISm at the three-year follow-up. Moreover, the incidence of the development of AFL was higher in the definite and probable PRISm groups than in the control group (Supplementary Table S4).

4. Discussion

This study showed that multiple confirmed PRISm (probable and definite PRISm) had a closer association with BMI $\geq 25\text{kg/m}^2$ and diabetes than did consistent normal spirometry. In contrast, these factors did not differ between single confirmed (incident) PRISm and normal spirometry. Notably, 84.1% and 9.7% of patients with definite PRISm (at baseline) exhibited PRISm and developed AFL, respectively, three years after baseline assessments. In the multivariable models, the incidence of AFL development was considerably higher in the PRISm with AFL history group and relatively higher in the probable and definite PRISm groups (but not in the incident PRISm group) than in the normal spirometry group. To best of our knowledge, this is the first study to incorporate past spirometry to stratify PRISm subjects and show differences in baseline clinical characteristics and subsequent transition rate of spirometry categories between multiple confirmed PRISm patients and normal spirometry patients in never and ever smokers.

Over 80% of the definite PRISm patients exhibited PRISm three years after

baseline testing, whereas only 33% and 43% of the incident PRISm and PRISm with AFL history patients, respectively, exhibited PRISm three years after baseline testing. In contrast, 40.0% and 9.7% of the PRISm with AFL history and definite PRISm patients (but only 1.9% of the incident PRISm patients) developed AFL. Higher rates of transitions in and out of PRISm over years have been described in longitudinal studies [2, 3, 7, 20]. Our data extend those previous findings by showing that patients with PRISm with AFL history display frequent transition to AFL, and definite PRISm represents not only persistent PRISm on follow-up spirometry, but also a relatively higher rate of transition to AFL than in incident PRISm and normal spirometry. Therefore, a combination of past and current spirometry results may be useful to enrich clinically-relevant PRISm among subjects who are labeled with PRISm in a single spirometry measurement.

The overall prevalence of PRISm was 6.5% — a finding consistent with the Rotterdam study (7.1%) [2], but lower than the prevalence found in a Japanese population-based cohort (9.9%; mean age 63.0) [7] and the prevalence found in community-dwelling older adults in Japan (12%; mean age 72.8) [21]. This difference might be due to differences in study design and age of the enrolled subjects. Nonetheless, the associations of probable and definite PRISm with hypertension, hyperlipidemia, and diabetes, found in this study, are consistent with previous reports in Japan [7, 22] and other countries [2, 8, 10].

The rate of a history of asthma was higher in the incident, probable, and definite PRISm, and PRISm with AFL history groups than in the normal spirometry group. This finding is consistent with a study by Higbee et al. [10], where these researchers used a United Kingdom biobank cohort and showed an association between asthma and PRISm. Furthermore, this study showed that, even when excluding subjects with a history of

asthma, the probable and definite PRISm groups had a higher risk of developing AFL than did the normal spirometry group (with no difference between the incident PRISm and normal spirometry groups). These observations suggest that, in addition to a history of asthma, other factors are also associated with the development of AFL in subjects with multiple confirmed PRISm. Since air-trapping is associated with the development of COPD in subjects with PRISm [23], and centrilobular emphysema on computed tomography is associated with air-trapping in smokers with PRISm [18], a subgroup of smokers with multiple confirmed PRISm may be susceptible to emphysema and the subsequent development of COPD.

BMI was higher and percentage of predicted FVC was lower in the probable and definite PRISm groups than in the normal spirometry group. This finding is consistent with a previous notion that being overweight or obese is associated with restrictive ventilatory impairment [24], and lower FVC is associated with metabolic syndrome [25]. Moreover, in multivariable models, probable and definite PRISm were associated with higher rates of diabetes, $HbA1c \geq 6.5\%$, and future AFL development — even after adjusting for BMI. These results suggest that factors other than being overweight may induce metabolic syndrome and future AFL development in subjects with probable or definite PRISm.

The mechanisms of transitions from and into PRISm remain unclear. Wan et al. showed that spirometry transitions cannot be fully attributable to artifact variability in spirometry measurements [3]. In that study, even when significant transitions were strictly defined based on a combination of spirometry category change and $> 10\%$ changes in FEV_1 and/or FVC, subjects with PRISm frequently transitioned to both AFL and normal spirometry over time. In this context, we speculate that incident PRISm might occur not

only from artifact variability of spirometry, but also from changes in pulmonary and extrapulmonary conditions. Whether smoking and environmental-related airway inflammation and reactivity, fluid shift associated with heart and kidney functions, and changes in fat and skeletal muscle are associated with the frequent transitions between PRISm and normal spirometry needs to be explored further.

This study also showed that even never smokers within the probable and definite PRISm groups were more likely develop AFL than were those within the normal spirometry group. The rate of $\text{CRP} \geq 0.1\text{mg/dL}$ was higher in the incident and definite PRISm groups than in the normal group for both never and ever smokers. Miura et al. showed that, independent of smoking, clinically-remitted childhood asthma is associated with rapid lung function decline [26]. Moreover, Park et al. showed that a higher eosinophil count in never smokers was associated with a higher risk of developing AFL, despite the study excluding those with a history of asthma [27]. Collectively, we speculate that enhanced systemic inflammation and thus airway inflammation might be involved in the development of AFL in a portion of never smokers with PRISm.

Age and the rate of regular exercise were higher in the AFL group. This finding is consistent with previous Japanese cohort data, showing that the rate of regular exercise is more frequent in older than in younger persons [28, 29]. Because exercise potentially reduces risks for being overweight and developing metabolic syndrome [30], higher rates of regular exercise might have affected BMI and metabolic syndrome factors in the AFL group.

A recent study [31] showed that, compared to the normal spirometry group, rates of hypertension, diabetes, hypercholesterolemia, and obesity were higher in the PRISm group, whereas rates of obesity and hypercholesterolemia tended to be lower in the airflow

obstruction group. Therefore, the observed lower rates of being overweight, hyperlipidemia, and $\text{HbA1c} \geq 6.5\%$ in the PRISm with AFL history group than in the normal spirometry group suggests that PRISm with AFL history group may include both subjects with features of definite PRISm and subjects with features of consistent AFL.

The distinct differences in clinical features associated with metabolic syndrome and future transition rate of spirometry categories, between the multiple confirmed versus single confirmed PRISm subjects, could provide clinical implications. Physicians should check patients' two past spirometry results when they first diagnose PRISm. For subjects with multiple confirmed PRISm, screening for metabolic syndrome and careful monitoring of spirometry should be performed. In contrast, for subjects with single confirmed PRISm (PRISm on current spirometry and normal spirometry on the two past tests), the probability of transitioning from PRISm to normal spirometry would be higher, and the risk of metabolic syndrome and development of AFL would be comparable to that of normal spirometry.

Some limitations regarding this study need to be mentioned. First, spirometry was performed without the use of bronchodilators because post-bronchodilator spirometry was not performed in a medical check-up setting. This action might have affected the prevalence of PRISm that we obtained. Second, details of smoking history, such as information regarding pack-years, is not available. However, the associations of definite PRISm with metabolic syndrome factors and the development of AFL were confirmed even in never smokers, suggesting the clinical relevance of multiple confirmed PRISm. Third, this study enrolled subjects in the medical check-up program who may care for their health more so than the general population. Thus, the generalizability of the present findings should be carefully considered.

5. Conclusion

In conclusion, this study showed that rates of obesity, hypertension, hyperlipidemia, and diabetes, higher CRP and HbA1c levels, and the development of AFL were higher in subjects with multiple confirmed PRISm than in those with consistent normal spirometry, whereas no difference was found between those with single confirmed PRISm and normal spirometry. Moreover, the transition to AFL was considerably high in the PRISm with AFL history group when compared to the other PRISm types and normal spirometry groups. Therefore, a combinational approach, using past and current spirometry results, should be used to define the clinical relevance of PRISm, which hopefully helps establish management methods for subjects with PRISm and thus improves their outcomes.

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Conflict of interest

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Preserved Ratio Impaired Spirometry: Using the Korean National Health and Nutrition Examination Survey IV-VI. *Respiration* 2022;101:25-33.

Table 1. Characteristics of spirometry categories at baseline

	Normal spirometry	Incident PRISm	Probable PRISm	Definite PRISm	PRISm AFL history	AFL
n	9058	169	188	290	59	375
Age, years	54.8 (9.5)	56.3 (9.7)	57.8 (10.4)*	59.1 (9.7)*	60.4 (10.3)*	62.4 (10.0)*
Male	53.5%	48.5%	53.7%	53.8%	69.5%	82.7%†
Height, cm	164.4 (8.7)	163.4 (8.9)	163.7 (9.0)*	162.6 (8.9)	164.9 (8.8)	167.5 (7.4)*
BMI, kg/m ²	22.9 (3.4)	23.1 (3.6)	23.8 (4.6)*	23.4 (4.3)*	22.6 (3.5)	22.5 (2.7)
BMI≥25 kg/m ²	22.6%	24.3%	33.5%†	32.1%†	20.3%	15.7%†
Waist circumference, cm	81.5 (9.1)	82.3 (10.2)	84.8 (12.0)*	83.9 (11.2)*	82.5 (9.9)	82.7 (7.9)
+10kg weight after age 20	35.1%	45.6%†	50.5%†	43.8%†	42.4%	34.7%
Smoking status						
never	65.4%	62.1%	63.8%	62.4%	47.5%†	33.9%†
former	21.7%	19.5%	22.9%	20.0%	25.4%	36.5%
current	12.9%	18.3%	13.3%	17.6%	27.1%	29.6%
FEV ₁ /FVC	0.81 (0.05)	0.77 (0.04)*	0.78 (0.05)*	0.78 (0.05)*	0.73 (0.02)*	0.62 (0.07)*
FEV ₁ , % predicted	100.9 (10.9)	77.0 (3.3)*	75.7 (4.1)*	71.8 (6.7)*	71.1 (7.7)*	76.0 (16.1)*
FVC, % predicted	99.6 (10.9)	79.6 (5.5)*	77.7 (6.0)*	73.2 (8.6)*	77.4 (8.9)*	94.7 (15.6)*
SBP, mmHg	121.5 (16.4)	123.5 (17.8)	125.9 (16.6)*	127.3 (18.5)*	124.3 (16.0)	126.5 (16.4)*
DBP, mmHg	77.5(12.1)	78.5 (12.4)	79.2 (11.6)	79.3 (12.6)	79.1 (12.7)	79.7 (11.3)*
Heart rate, /min	63.9 (9.3)	65.1 (10.1)	65.1 (9.3)	65.8 (10.3)*	65.7 (10.7)	65.1 (10.8)
A history of asthma	6.0%	11.2%†	9.6%	12.1%†	16.9%†	22.9%†
A history of heart disease	2.4%	4.7%	3.2%)	4.5%	5.1%	6.1%
A history of stroke	1.3%	1.8%	2.7%	3.1%	5.1%	2.4%
Hypertension	18.1%	21.9%	29.8%†	33.1%†	27.1%	35.2%
Hyperlipidemia	15.7%	18.3%	22.3%	27.9%†	16.9%	21.9%†
Diabetes	4.1%	8.3%	12.2%†	13.8%†	10.2%	6.4%
CRP ≥ 0.1mg/dL	20.2%	33.8%†	32.9%†	37.0%†	30.8%	30.6%†
HbA1c ≥ 6.5%	5.6%	9.3%	15.1%†	13.5%†	3.6%	9.4%†
Cardiothoracic ratio on X-ray	44.7 (4.6)	47.5 (4.9)*	48.2 (4.7)*	48.7 (5.3)*	47.4 (5.2)*	44.5 (4.6)
Exercise (> 30min, ≥ 2/week)	32.9%	32.0%	30.9%	31.0%	33.9%	40.3%†

Data were expressed as mean (standard deviation) or %.

* indicates $p < 0.05$ compared to the normal spirometry group, based on Dunnett's Test.

† indicates $p < 0.05$ compared to the normal spirometry group, based on multiple Fisher's exact tests with Holm correction.

Normal indicates consistent normal spirometry at baseline and at the past two spirometry tests.

PRISm = preserved ratio impaired spirometry. Incident PRISm = PRISm confirmed only

on a baseline spirometry assessment with two past normal spirometry records. Probable PRISm = PRISm confirmed at baseline assessment and one past spirometry with one past normal spirometry record. Definite PRISm = PRISm consistently confirmed on both baseline and two past spirometry tests. PRISm AFL = PRISm confirmed at baseline spirometry with at least one past AFL record.

PRISm, preserved ratio impaired spirometry; AFL, airflow limitation; BMI, body mass index; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; SBP, systolic blood pressure; DBP, diastolic blood pressure; CRP, C-reactive protein; HbA1c = hemoglobin A1c.

Table 2. Multivariable logistic models exploring associations of baseline spirometry groups with clinical findings

	Normal spirometry	Incident PRISm	Probable PRISm	Definite PRISm	PRISm AFL history	AFL
BMI ≥ 25 kg/m ² †	1.0 (Ref)	1.15 [0.79—1.63]	1.77* [1.29—2.40]	1.64* [1.26—2.11]	0.79 [0.40—1.45]	0.54* [0.40—0.72]
A history of asthma	1.0 (Ref)	2.08* [1.24—3.30]	1.77* [1.04—2.83]	2.48* [1.69—3.54]	4.29* [2.02—8.27]	7.42* [5.59—9.77]
A history of heart disease	1.0 (Ref)	1.75 [0.77—3.47]	0.89 [0.34—1.92]	1.28 [0.68—2.23]	1.27 [0.30—3.64]	1.19 [0.73—1.87]
Hypertension	1.0 (Ref)	1.08 [0.70—1.62]	1.27 [0.87—1.83]	1.55* [1.15—2.07]	1.09 [0.58—2.05]	1.35* [1.05—1.74]
Hyperlipidemia	1.0 (Ref)	1.00 [0.64—1.52]	1.05 [0.71—1.52]	1.43* [1.07—1.91]	0.70 [0.32—1.40]	0.85 [0.64—1.11]
Diabetes	1.0 (Ref)	1.78 [0.95—3.09]	2.20* [1.33—3.50]	2.52* [1.71—3.64]	1.60 [0.59—3.64]	0.77 [0.48—1.17]
CRP ≥ 0.1 mg/dL	1.0 (Ref)	1.95* [1.34—2.80]	1.56 [1.09—2.21]	2.01* [1.52—2.65]	1.65 [0.87—3.03]	1.68* [1.30—2.16]
HbA1c $\geq 6.5\%$	1.0 (Ref)	1.44 [0.78—2.49]	1.97* [1.21—3.08]	1.67* [1.12—2.43]	0.36 [0.58—1.22]	0.95 [0.63—1.39]

Data were expressed as hazard ratio [95% confidence interval].

* indicates $p < 0.05$ compared to the normal spirometry group.

† Model for BMI included the spirometry group, age, height, sex, smoking status, and a history of asthma as independent variables. The normal spirometry group was treated as the reference (Ref). Other models included the spirometry group, age, height, BMI, sex, smoking status, and a history of asthma as independent variables.

Normal = consistent normal spirometry at baseline assessment and at the past two spirometry tests.

PRISm = preserved ratio impaired spirometry. Incident PRISm = PRISm confirmed only at baseline spirometry with the two past normal spirometry records. Probable PRISm = PRISm confirmed at baseline and on one past spirometry with one past normal spirometry

record. Definite PRISm = PRISm consistently confirmed on both baseline and two past spirometry tests. PRISm AFL = PRISm confirmed at baseline spirometry with at least one past AFL record.

PRISm, preserved ratio impaired spirometry; AFL, airflow limitation; BMI, body mass index; CRP = C-reactive protein. HbA1c = hemoglobin A1c.

Table 3. Baseline characteristics and spirometry categories at the three-year follow-up

	Normal spirometry	Incident PRISm	Probable PRISm	Definite PRISm	PRISm AFL history	AFL
n	5825	103	110	176	35	218
Age, years	54.0 (9.1)	54.6 (8.9)	55.7 (9.3)	58.2 (9.1)*	59.3 (10.1)*	60.9 (9.7)*
Male	54.5%	49.5%	55.5%	54.5%	68.6%	82.6%†
Height, cm	164.7 (8.6)	163.4 (9.1)	164.3 (9.0)	163.4 (8.8)	164.0 (7.3)	167.8 (7.1)*
BMI $\geq$ 25kg/m ²	22.8%	24.3%	36.4%†	33.5%†	25.7%	15.6%†
Smoking status						
never	65.9%	66.0%	62.7%	61.4%	51.4%	34.9%†
former	21.3%	19.4%	23.6%	19.3%	20.0%	39.0%
current	12.8%	14.6%	13.6%	19.3%	28.6%	26.1%
A history of asthma	6.3%	9.7%	11.8%	16.5%†	17.1%	24.8%†
FEV ₁ /FVC	0.81 (0.05)	0.78 (0.04)*	0.78 (0.05)*	0.78 (0.05)*	0.73 (0.02)*	0.63 (0.06)*
FEV ₁ , % pred	101.1 (11.0)	77.3 (2.8)*	75.9 (4.3)*	72.0 (5.9)*	71.1 (8.2)*	77.3 (15.1)*
FVC, % pred	99.8 (11.0)	79.9 (4.7)*	77.8 (6.3)*	73.9 (8.0)*	77.7 (9.5)*	95.8(15.2)*
Subsequent spirometry category (three years later)						
Normal	97.3%	65.0%	35.5%	6.2%	17.1%	3.2%
PRISm	1.3%	33.0%	56.4%	84.1%	42.9%	3.2%
AFL	1.4%	1.9%	8.2%†	9.7%†	40.0%†	93.6%†

Data were expressed as mean (standard deviation) or %.

* indicates $p < 0.05$ compared to the normal spirometry group, based on Dunnett's Test.

† indicates $p < 0.05$ compared to the normal spirometry group, based on multiple Fisher's exact tests with Holm correction.

Normal = consistent normal spirometry at baseline assessment and at the two past spirometry tests.

PRISm = preserved ratio impaired spirometry. Incident PRISm = PRISm confirmed only at baseline spirometry with two past normal spirometry records. Probable PRISm = PRISm confirmed at baseline and at one past spirometry with one past normal spirometry record. Definite PRISm = PRISm consistently confirmed at both baseline and at two past

spirometry tests. PRISm AFL = PRISm confirmed at baseline spirometry with at least one past AFL record.

PRISm, preserved ratio impaired spirometry; AFL = airflow limitation; BMI, body mass index; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; Normal, normal spirometry.

Table 4. Multivariable logistic models for hazard ratios of transition to airflow limitation at three-year follow-up spirometry

	Normal spirometry	Incident PRISm	Probable PRISm	Definite PRISm	PRISm AFL history
All subjects (n = 6249)	1.0 (Ref)	1.45 [0.23—4.73]	6.34* [2.86—12.58]	6.21* [3.42—10.71]	35.9* [16.30— 76.97]
Ever smokers (n = 2148)	1.0 (Ref)	1.66 [0.09—8.26]	5.11* [1.44—14.06]	5.74* [2.20—13.24]	23.62* [7.48—71.49]
Never smokers (n = 4101)	1.0 (Ref)	1.31 [0.07—6.22]	7.42* [2.47—18.07]	6.56* [2.95—13.36]	5.13* [1.71— 145.88]
Subjects without a history of asthma (n = 5824)	1.0 (Ref)	1.60 [0.26—5.25]	6.01* [2.57—12.34]	6.63* [3.53—11.74]	38.57* [16.67— 87.67]
Subjects without normal spirometry (n = 424)	-	1.0 (Ref)	4.37 [1.07—29.43]	4.65* [1.27—30.04]	28.82* [6.99—30.05]

Data were expressed as hazard ratio [95% confidence interval].

* indicates $p < 0.05$ compared to the normal spirometry group.

Models of all subjects and ever smokers were adjusted for age, height, body mass index, sex, smoking status, and a history of asthma. Smoking status was not included in the model of never smokers, and a history of asthma was not included in the model of subjects without a history of asthma.

Normal = consistent normal spirometry at baseline assessment and at the two past spirometry tests.

PRISm = preserved ratio impaired spirometry. Incident PRISm = PRISm confirmed only

at baseline spirometry with two past normal spirometry records. Probable PRISm = PRISm confirmed at baseline and at one past spirometry with one past normal spirometry record. Definite PRISm = PRISm consistently confirmed at both baseline and at two past spirometry tests. PRISm AFL = PRISm confirmed at baseline spirometry with at least one past AFL record.

PRISm, preserved ratio impaired spirometry; AFL, airflow limitation.

Figure 1. Subjects' spirometry categorization based on baseline and past assessments

PRISm = preserved ratio impaired spirometry. Incident PRISm = PRISm confirmed only at baseline spirometry with two past normal spirometry records. Probable PRISm = PRISm confirmed at baseline and at one past spirometry with one past normal spirometry record. Definite PRISm = PRISm consistently confirmed at both baseline and two past spirometry tests. PRISm AFL = PRISm confirmed at baseline spirometry with at least one past airflow limitation (AFL) record.

Figure 2. Associations of baseline and two past spirometry results with subsequent spirometry categories, three years later

PRISm = preserved ratio impaired spirometry. Incident PRISm = PRISm confirmed only at baseline spirometry with two past normal spirometry records. Probable PRISm = PRISm confirmed at baseline and at one past spirometry with one past normal spirometry record. Definite PRISm = PRISm consistently confirmed at both baseline and two past spirometry tests. PRISm AFL = PRISm confirmed at baseline spirometry with at least one past airflow limitation (AFL) record. The median (interquartile range) length of the period between the earliest past spirometry and baseline spirometry assessments was 2.03 (1.99—2.36) years.

17276 adults aged ≥ 40 underwent spirometry between 2016-2017

8950 excluded (lack of 2 past spirometry tests)

10828 enrolled and
classified based on
spirometry at enrollment

PRISm
(N=706; 6.5%)

Incident PRISm (N=169)

Probable PRISm (N=188)

Definite PRISm (N=290)

PRISm with AFL history (N=59)

AFL
(N=627; 5.8%)

(Consistent) AFL (N=375)

PRISm/Normal on 2 past
tests (N=252)

Normal
(N=9495; 87.7%)

(Consistent) Normal (N=9058)

PRISm/AFL on 2 past
tests (N=437)

