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ORIGINAL RESEARCH

Prevalence and Characteristics of Individuals with Preserved Ratio Impaired Spirometry (PRISm) and/or Impaired Lung Function in Japan: The OCEAN Study

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Purpose: Many individuals with obstructive airway disease (OAD), including chronic obstructive pulmonary disease (COPD) and asthma, remain undiagnosed, despite the potential for reducing disease burden through early detection and treatment. OCEAN aimed to determine the prevalence of, and characteristics associated with, impaired lung function in a Japanese population, with the goal of improving strategies for early OAD detection.

Methods: OCEAN was an observational, cross-sectional study in sequentially recruited Japanese individuals ≥40 years of age undergoing routine health examinations. Participants completed screening questionnaires and spirometry testing. Airflow limitation was defined as forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) <0.7 by pre-bronchodilator spirometry. Preserved ratio impaired spirometry (PRISm) was defined as FEV_1/FVC ≥0.7 and FEV_1 <80% predicted. The primary endpoint was prevalence of spirometry-based airflow limitation and PRISm. The characteristics of study participants were reported as secondary endpoints.

Results: Overall, 2518 individuals were included; 79% were <60 years of age (mean 52.0 years). Airflow limitation and PRISm were observed in 52 (2.1%) and 420 (16.7%) participants, respectively. FEV_1 in the PRISm group was between that in the no airflow limitation/PRISm and airflow limitation groups, FVC was similar in the PRISm and airflow limitation groups. The PRISm group had higher mean body mass index and a higher proportion of comorbid metabolic disease compared with the airflow limitation group. The prevalence of airflow limitation and PRISm was highest among current smokers (3.9% and 21.3%, respectively) versus former or never smokers.

Conclusion: A significant proportion of Japanese individuals <60 years of age attending their annual health examination had impaired lung function (airflow limitation and PRISm); prevalence was highest among current smokers. These findings support screening of current or former smokers ≥40 years of age using patient-reported questionnaires to inform the need for spirometry to confirm an OAD diagnosis.

Keywords: CAPTURE, CAAT, PRISm, COPD-Q, Japan, airflow limitation

Plain Language Summary

Why was this study done?

- Obstructive airway disease (OAD) including chronic obstructive pulmonary disease (COPD) and asthma is associated with high medical and economic burden for patients and healthcare systems. Early diagnosis and management of OAD could reduce the impact on patient health and well-being, lower healthcare use and costs, and potentially slow disease progression.

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- The goals of the OCEAN study were to find the proportions of people with undiagnosed OAD or who may be at risk of OAD in a Japanese population and to investigate their characteristics.

What did the researchers do/find?

- Researchers measured participants' lung function and identified patients with airflow limitation, who may have undiagnosed OAD, or preserved ratio impaired spirometry (PRISm), who are at risk of developing OAD. Participants also completed COPD screening questionnaires.
- Of the 2518 participants in the study, 52 (2.1%) had airflow limitation and 420 (16.7%) had PRISm.
- Current smokers were more likely to have airflow limitation and PRISm compared with former or never smokers. Additionally, participants in the PRISm group had a higher body mass index and more metabolic disease versus those with airflow limitation.

What do these results mean?

- The OCEAN study demonstrated that a significant proportion of Japanese people <60 years of age have impaired lung function (OAD and PRISm).
- These findings support screening of current or former smokers who are ≥40 years of age, using patient-completed questionnaires, followed by lung function testing when indicated by questionnaire responses. This approach could lead to early diagnosis and more effective OAD management.

Introduction

Chronic respiratory diseases are a leading cause of morbidity and mortality worldwide.[1] An estimated 545 million individuals were living with a chronic respiratory disease in 2017, representing approximately 7.4% of the world's population.[1] They were the third leading cause of death worldwide in 2017, accounting for an estimated 7.0% of all deaths in 2017 and with a mortality rate of 51.2 per 100,000 population.[1,2] Obstructive airway diseases (OAD) are a subset of chronic respiratory diseases that share common features and includes asthma and chronic obstructive pulmonary disease (COPD).[3] COPD and asthma are the most and second most prevalent obstructive airway diseases, respectively, with an estimated global prevalence of 3.9% (5.9% in high-income areas) for COPD and 3.6% for asthma in 2017.[1]

Despite the high global prevalence and associated mortality, many individuals with COPD, including those in Japan, remain undiagnosed.[4–8] Population-based studies suggest that worldwide, about 70% of individuals with COPD are underdiagnosed.[4] Additionally, the Global Initiative for Asthma 2021 report notes that asthma is frequently undiagnosed, especially in the elderly.[9] In the Nippon COPD Epidemiology study, which assessed airflow parameters in a Japanese population ≥40 years of age, 10.9% of individuals were identified as having airflow limitation, of whom only 9.4% had been previously diagnosed with COPD, emphysema or chronic bronchitis by their physician.[8] Undiagnosed COPD has been shown to significantly contribute to healthcare burden and associated costs,[10,11] emphasizing the need for early identification of individuals with COPD through screening measures that can be easily implemented during routine care. Early diagnosis and subsequent management, including smoking cessation, could significantly limit and control COPD progression.

Underdiagnosis of COPD may arise from a lack of awareness of the disease, lack of educational programs on signs and symptoms of COPD, misdiagnosis, and/or low use of pulmonary function tests in primary care.[4,12] Spirometry testing is a well-recognized and valuable tool for early identification of individuals with airflow limitation who are at increased risk of COPD.[13–17] Preserved Ratio Impaired Spirometry (PRISm) is an airflow limitation status that identifies a group of individuals with impaired lung function who do not meet the spirometry-assessed definition of COPD.[18–21] Individuals with PRISm resemble those with COPD in terms of reduction in forced expiratory volume in 1 second (FEV_1), but not in terms of FEV_1/forced vital capacity (FVC) ratio. PRISm is defined as percent predicted FEV_1 <80% with an FEV_1/FVC ≥0.7.[19]

Although PRISm is not included in the current definition of COPD, it does resemble COPD in terms of reduced lung function. It is similarly associated with the occurrence of respiratory symptoms and systemic inflammation, and with increased cardiovascular morbidity and mortality.[18–20] PRISm has therefore been proposed to be included in an expanded definition of COPD and may be used to identify individuals at risk of rapid progression to COPD during routine health checks.[22]

The prevalence of airflow limitation or PRISm and the characteristics of individuals with early lung function impairment in the general Japanese population are unclear, particularly among individuals younger than 60 years of age. Understanding the characteristics of individuals with

PRISm is likely to inform strategies for early diagnosis, enabling effective treatment that would slow or halt OAD progression and leading to improved clinical outcomes. With this in mind, the aim of the OCEAN (Okinawa COPD casE finding AssessmeNt) study was to determine the prevalence of, and characteristics associated with, impaired lung function including airflow limitation and PRISm in a Japanese population 40 years of age or older using screening questionnaires and spirometry, with the goal of improving early identification of individuals with, or at risk of, OAD.

Materials and Methods

Study Design

OCEAN was an observational, cross-sectional study (GSK Study HO-18-19229/209243). The protocol, applicable amendments, and other relevant documents were reviewed and approved by the Nahanishi Clinic Ethics Committee. The study complied with all applicable laws regarding participant privacy, and all participants provided written informed consent. The full methodology and primary analyses from this study have been reported previously.[23]

Participants undergoing routine health examinations were sequentially recruited without any prespecified selection or sampling and completed screening questionnaires and routine spirometry testing during the study enrollment period (September 2018 – July 2019). These self-administered questionnaires were completed at the study site and included the COPD Assessment in Primary Care to Identify Undiagnosed Disease and Exacerbation Risk (CAPTURE),[24] Chronic Airways Assessment Test (CAAT),[25] and COPD screening questionnaire (COPD-Q).[26] The CAAT questionnaire is a modified (with permission) version of the COPD Assessment Test (CAT)[2,27] with an introductory sentence referring to "chronic airways disease" in place of "COPD" to support its use in evaluating individuals who are not diagnosed with COPD. These questionnaire modifications were conducted by the CAT Governance Board. Full details of these questionnaires in the context of the OCEAN study have been reported previously.[23]

Spirometry testing (SP-370 COPD Hyper Plus, Fukuda Sangyo) was undertaken by a skilled, full-time spirometry technician. Airflow limitation was defined as FEV_1/FVC <70% by pre-bronchodilator spirometry. The severity of airflow limitation in COPD was further evaluated using a four-grade scale adapted from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy document[17] as follows: Grade 1, mild (% predicted FEV_1 ≥80%); Grade 2, moderate (% predicted FEV_1 ≥50–<80%); Grade 3, severe (% predicted FEV_1 ≥30–<50%); and Grade 4, very severe (% predicted FEV_1 <30%). PRISm was defined as FEV_1/FVC ≥70% and FEV_1 <80% predicted.

Study Population

Male and female participants ≥40 years of age who attended the Lifestyle-Related Disease Medical Center study site in Naha, Okinawa for their routine annual health examination were enrolled. Individuals who were judged as inappropriate to participate by the investigator, based on the presence of pre-existing conditions that could exclude a participant from spirometry testing (including eye surgery, chest/abdominal surgery, stroke, or heart attack in the last 3 months), were excluded.

Study Endpoints

Primary analyses from the CAPTURE and COPD-Q questionnaires have been reported previously.[23] The present analysis reports the prevalence of spirometry-based airflow limitation and PRISm among all study participants (primary endpoint). The characteristics of participants with airflow limitation, with PRISm, and without airflow limitation or PRISm, and the characteristics of never smokers, past smokers, and current smokers are reported as secondary endpoints.

Statistical Analyses

This was a descriptive study, and therefore no specific statistical tests were specified a priori. Full details of sample size calculations have been reported previously.[23] The following were conducted as post-hoc analyses: the association between history of childhood asthma and PRISm was evaluated using the Chi-square test. Statistical differences between patients with airflow limitation, with PRISm, and without airflow limitation or PRISm for BMI values were evaluated by ANOVA Tukey's test. Statistical differences between groups for hypertension, diabetes and hyperlipidemia were evaluated by Fisher's exact test and Tukey style multiple comparison test.

Results

Study Population

A total of 2550 individuals consented to participate in the study and evaluable data were available for 2518 participants. Full details of the study population have been reported previously.[23] In brief, the enrolled population comprised company employees and their dependents, self-employed individuals and their dependents, and retired people. The mean (standard deviation [SD]) age of the evaluable population was 52.0 (8.8) years, with 79.3% of the population <60 years of age. Approximately 55.1% (1387/2518) of participants were male, mean body mass index (BMI) was 24.3 kg/m^2, and 24.8% were current smokers. Overall, demographics and characteristics were generally similar in participants with airflow limitation, with PRISm, and those with neither airflow limitation nor PRISm (Table 1).

Most participants (>99%) completed the CAPTURE, COPD-Q, CAAT, and Patient-Reported Outcomes Measurement Information System (PROMIS) questionnaires, while fewer completed study-specific (95.6%) and health examination (76.6%) questionnaires.

Prevalence of Impaired Lung Function

Of the 2518 participants with evaluable data, 52 (2.1%) had airflow limitation (FEV_1/FVC <0.7) and 420 (16.7%) participants were classified as having PRISm (FEV_1/FVC ≥0.7 and FEV_1 <80% predicted; Table 1). Of 2518 participants, 162 had a history of childhood asthma defined as the participant experiencing their first attack of asthma at ≤18 years of age. There was a significant association between history of childhood asthma and PRISm; 44 of the 162 participants with a history of childhood asthma had PRISm compared with 376 participants out of 2356 with no history of childhood asthma who had PRISm ($p < 0.01$).

Characteristics of Participants According to Lung Function

Participants with airflow limitation were older than those in the PRISm and no airflow limitation/PRISm groups (mean [SD] age: 54.7 [10.9], 52.5 [8.6] and 51.8 [8.8] years, respectively), with most <60 years of age (63.5%; Table 1). Overall, and across all lung function subgroups, the majority of participants were 40–49 years of age (range, 45–48 years).

The proportion of participants who reported being a current smoker was higher among those with airflow limitation compared with those with PRISm or no airflow limitation/PRISm (46.2% vs 31.7% and 22.8%) (Table 1). Of the participants who were current or past smokers, 65.4%, 47.9%, and 34.7% in the airflow limitation, PRISm, and no airflow limitation/PRISm groups, respectively, had a smoking history of ≥10 pack-years. Among participants with PRISm 40–49 years of age, 48.7% had never smoked, 16.9% were past smokers, and 34.4% were current smokers (Table 2).

Chronic mucus hypersecretion (CMH), defined as cough with production of phlegm for ≥3 months in 2 successive years, and asthma were most prevalent in participants with airflow limitation, consistent with the increased proportion of current smokers in this subgroup. CMH was reported in 3.9%, 2.4%, and 1.6% of participants in the airflow limitation, PRISm, and no airflow limitation/PRISm groups, respectively (Table 1). Asthma was the most common medical history reported in all subgroups and occurred in substantially more participants in the airflow limitation group than in the PRISm and no airflow limitation/PRISm groups (44.2%, 17.4%, and 10.5%, respectively; Table 1). The incidence of comorbid metabolic disease, including hypertension, diabetes, and hyperlipidemia, was higher in participants from the PRISm group compared with the other subgroups (Figure 1). Mean body weight and BMI were also higher in the PRISm group than in the airflow limitation and no airflow limitation/PRISm groups (Table 1 and Figure 1).

Spirometry

Mean (SD) FEV_1 was highest in the no airflow limitation/PRISm group (2.72 [0.65] L), intermediate in the PRISm group (2.24 [0.50] L), and lowest in the airflow limitation group (1.88 [0.53]; Table 1). In contrast, FVC in the PRISm and airflow limitation groups was similar (mean [SD] FVC: 2.78 [0.65] L and 2.89 [0.80] L, respectively) and lower than in the no airflow limitation/PRISm group (3.24 [0.78] L; Table 1). FEV_1/FVC was only slightly lower in the PRISm group compared with the no airflow limitation/PRISm group (mean [SD]: 0.81 [0.06] vs 0.84 [0.05]) but was markedly lower in the airflow limitation group (0.65 [0.05]; Table 1). Mean (SD) percent predicted FEV_1 was 94.8% (9.5) in participants with no airflow limitation/PRISm compared with 73.1% (6.2) in those with PRISm and 66.9% (14.0) in those with airflow limitation (Table 1).

Table 1 Characteristics of Participants with Airflow Limitation, PRISm, or No Airflow Limitation/PRISm

	AL* (n=52)	PRISm† (n=420)	No AL/PRISm (n=2046)
Age, mean (SD), years	54.7 (10.9)	52.5 (8.6)	51.8 (8.8)
Age categories, n (%)			
40–49 years	24 (46.2)	189 (45.0)	981 (48.0)
50–59 years	9 (17.3)	147 (35.0)	647 (31.6)
60–69 years	13 (25.0)	69 (16.4)	341 (16.7)
≥70 years	6 (11.5)	15 (3.6)	77 (3.8)
Sex, n (%)			
Male	30 (57.7)	296 (70.5)	1061 (51.9)
Female	22 (42.3)	124 (29.5)	985 (48.1)
Height, mean (SD), cm	162.1 (9.3)	163.8 (8.3)	162.1 (9.0)
Weight, mean (SD), kg	63.2 (12.8)	68.8 (15.7)	63.4 (13.0)
Smoking history, n (%)			
Not reported	0	0	1 (0.1)
Never	15 (28.9)	178 (42.4)	944 (46.1)
Past	13 (25.0)	109 (26.0)	634 (31.0)
Current	24 (46.2)	133 (31.7)	467 (22.8)
Pack years, n (%)			
0 (never smoked)	15 (28.9)	178 (42.4)	944 (46.1)
<10	3 (5.8)	41 (9.8)	391 (19.1)
≥10	34 (65.4)	201 (47.9)	710 (34.7)
CMH‡, n (%)	2 (3.9)	10 (2.4)	33 (1.6)
Medical history, n (%)			
Asthma	23 (44.2)	73 (17.4)	214 (10.5)
Stroke	2 (3.9)	13 (3.1)	21 (1.0)
Heart disease	3 (5.8)	18 (4.3)	50 (2.4)
Chronic renal failure	0	1 (0.2)	8 (0.4)
Anemia	6 (11.5)	34 (8.1)	296 (14.5)
Lung function, mean (SD)			
FEV_1 (L)	1.88 (0.53)	2.24 (0.50)	2.72 (0.65)
FVC (L)	2.89 (0.80)	2.78 (0.65)	3.24 (0.78)
FEV_1/FVC	0.65 (0.05)	0.81 (0.06)	0.84 (0.05)
FEV_1% predicted	66.9 (14.0)	73.1 (6.2)	94.8 (9.5)

Notes: *AL was defined as FEV_1/FVC <0.7; †PRISm was defined as FEV_1/FVC ≥0.7 and FEV_1 <80% predicted; ‡CMH was defined as chronic cough with production of phlegm for at least 3 months in 2 successive years.

Abbreviations: AL, airflow limitation; CMH, chronic mucus hypersecretion; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; PRISm, Preserved Ratio Impaired Spirometry; SD, standard deviation.

Characteristics of Participants According to Smoking Status

The prevalence of airflow limitation and PRISm was highest in participants who were current smokers (3.9% and 21.3%, respectively) compared with those who were past (1.7% and 14.4%) and never (1.3% and 15.7%) smokers (Table 3). More current smokers also had GOLD airflow limitation Stage 2 or 3 compared with past and never smokers (3.7% vs 1.6% vs 1.0%). The prevalence of participants with a history of heart disease was higher in past smokers (4.2%) than in never smokers (2.6%) or current smokers (1.6%). Mean (SD) total CAAT scores

Table 2 Prevalence of PRISm Among Participants 40–49 Years of Age by Smoking History

	History of Smoking				
	Not Reported	**Never**	**Past**	**Current**	**All**
Age 40–49 years, n (%)	1 (0.1)	531 (44.5)	317 (26.5)	345 (28.9)	1194 (100)
Age 40–49 years with PRISm*, n (%)	0	92 (48.7)	32 (16.9)	65 (34.4)	189 (100)
Age 40–49 years, percentage of PRISm* by smoking history	0	17.3	10.1	18.8	15.8

Note: *PRISm was defined as $FEV_1/FVC \geq 0.7$ and FEV_1 <80% predicted.
Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; PRISm, Preserved Ratio Impaired Spirometry.

were 5.7 (4.8) in current smokers compared with 4.5 (4.3) and 4.3 (4.4) in past and never smokers, respectively. Similarly, mean (SD) COPD-Q scores were lower in never smokers compared with current or past smokers (1.2 [1.0] vs 2.7 [1.3] and 2.6 [1.3]). In contrast, mean CAPTURE and PROMIS total scores were similar across smoking categories. Self-reported COPD diagnosis was uncommon across all groups with only 2 participants with COPD included in the study (1 never smoker and 1 past smoker).

Discussion

The aim of the OCEAN study was to increase our understanding of the prevalence of lung function impairment and associated characteristics in a Japanese population 40 years of age or older, with the goal of improving strategies for early diagnosis and management of COPD. This study demonstrated that a significant proportion of participants undergoing an annual health check-up had impaired lung function; 52 (2.1%) participants had airflow limitation and 420 (16.7%) participants had PRISm. Airflow limitation and PRISm were observed among individuals younger than 60 years of age, with 63.5% of participants with airflow limitation and 80.0% of those with PRISm <60 years of age and a prevalence of PRISm of 15.8% in participants 40–49 years of age.

Individuals with PRISm have reduced lung function but do not meet the spirometry definition of COPD.[18,19] PRISm status resembles COPD in terms of reduction in FEV_1, but not in terms of FEV_1/FVC ratio;[19] and as with COPD, PRISm is associated with increased respiratory symptoms, systemic inflammation, and significant risk of mortality, notably due to cardiovascular disease.[18–21] PRISm and

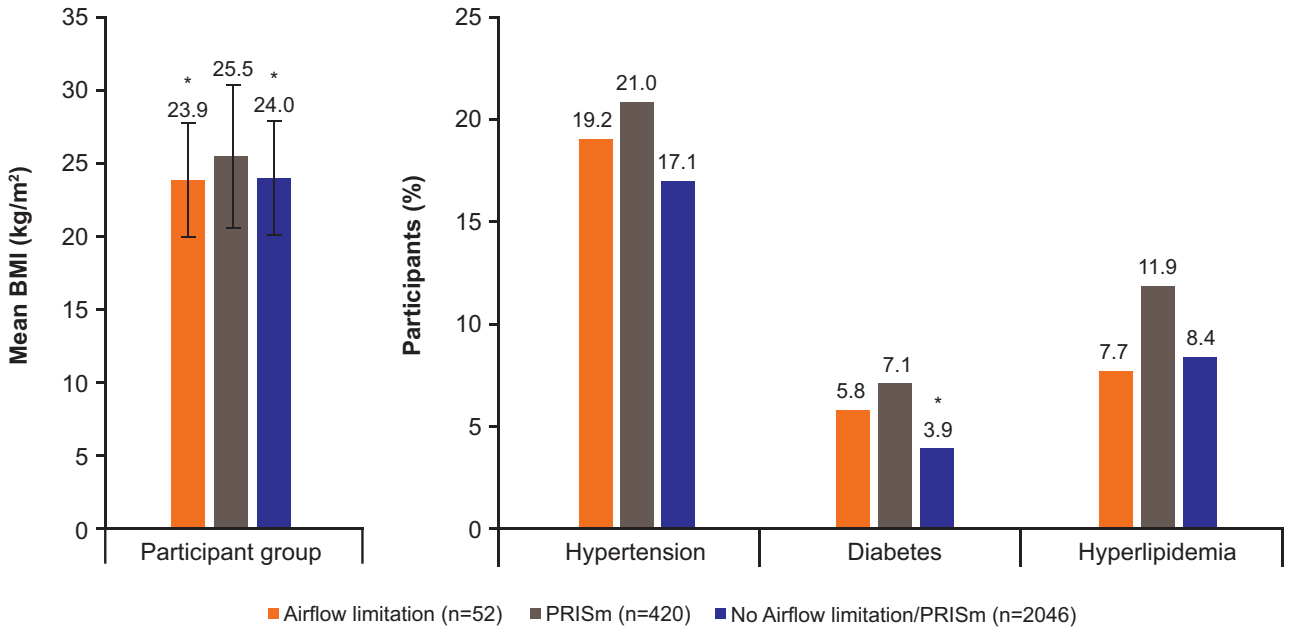

Figure 1 Metabolic comorbidities in participant subgroups.
Notes: *p<0.05 for comparison against PRISm group. Airflow limitation was defined as FEV_1/FVC <0.7; PRISm was defined as $FEV_1/FVC \geq 0.7$ and FEV_1 <80% predicted.
Abbreviations: BMI, body mass index; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; PRISm, Preserved Ratio Impaired Spirometry.

Table 3 Characteristics of Participants According to Smoking History*

	History of Smoking		
	Never (N=1137)	**Past (N=756)**	**Current (N=624)**
Age, mean (SD), years	52.5 (9.4)	52.8 (8.9)	49.9 (7.2)
Age categories, n (%)			
40–49 years	531 (46.7)	317 (41.9)	345 (55.3)
50–59 years	338 (29.7)	253 (33.5)	212 (34.0)
60–69 years	207 (18.2)	152 (20.1)	64 (10.3)
≥70 years	61 (5.4)	34 (4.5)	3 (0.5)
Sex, n (%)			
Male	402 (35.4)	509 (67.3)	476 (76.3)
Female	735 (64.6)	247 (32.7)	148 (23.7)
Height, mean (SD), cm	159.3 (8.8)	164.0 (8.0)	166.1 (8.1)
Weight, mean (SD), kg	61.6 (14.2)	66.2 (12.2)	67.2 (13.4)
BMI, mean (SD), kg/m^2	24.1 (4.4)	24.5 (3.7)	24.3 (4.1)
Pack years, mean (SD)	–	13.9 (14.3)	23.0 (14.2)
Pack years, n (%)			
≥10	–	403 (53.3)	542 (87.0)
<10	–	353 (46.7)	81 (13.0)
CAAT total score, mean (SD)	4.3 (4.4)	4.5 (4.3)	5.7 (4.8)
CAPTURE total score, mean (SD)	0.8 (1.1)	0.8 (1.1)	0.8 (1.1)
COPD-Q total score, mean (SD)	1.2 (1.0)	2.6 (1.3)	2.7 (1.3)
PROMIS total score, mean (SD)	19.8 (0.9)	19.9 (0.7)	19.8 (0.6)
AL[†], n (%)	15 (1.3)	13 (1.7)	24 (3.9)
PRISm[‡], n (%)	178 (15.7)	109 (14.4)	133 (21.3)
No AL/PRISm, n (%)	944 (83.0)	634 (83.9)	467 (74.8)
History of:			
COPD, n (%)	1 (0.1)	1 (0.1)	0
CB, n (%)	30 (2.6)	23 (3.0)	16 (2.6)
PE, n (%)	3 (0.3)	2 (0.3)	5 (0.8)
Asthma, n (%)	140 (12.3)	90 (11.9)	80 (12.8)
Other respiratory disease, n (%)	26 (2.3)	26 (3.4)	18 (2.9)
Stroke, n (%)	13 (1.1)	9 (1.2)	14 (2.2)
Heart disease, n (%)	29 (2.6)	32 (4.2)	10 (1.6)
CKD, n (%)	4 (0.4)	3 (0.4)	2 (0.3)
Anemia, n (%)	185 (16.3)	91 (12.0)	60 (9.6)
Airflow limitation at:			
GOLD Stage 2	10 (0.9)	9 (1.2)	22 (3.5)
GOLD Stage 3	1 (0.1)	3 (0.4)	1 (0.2)

(*Continued*)

Table 3 (Continued).

	History of Smoking		
	Never (N=1137)	**Past (N=756)**	**Current (N=624)**
Current treatment for:			
COPD/CB/PE, n (%)	3 (0.3)	1 (0.1)	2 (0.3)
Bronchodilators, n (%)	2 (0.2)	0	0
Hypertension, n (%)	205 (18.0)	161 (21.3)	82 (13.1)
Diabetes, n (%)	48 (4.2)	30 (4.0)	34 (5.5)
Hyperlipidemia, n (%)	109 (9.6)	74 (9.8)	43 (6.9)

Notes: *One female participant did not report smoking history and was therefore not included in this analysis; †AL was defined as FEV_1/FVC <0.7; ‡PRISm was defined as FEV_1/FVC ≥0.7 and FEV_1 <80% predicted.

Abbreviations: AL, airflow limitation; BMI, body mass index; CAAT, Chronic Airways Assessment Test; CAPTURE, Chronic Airways Assessment Test; CB, chronic bronchitis; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COPD-Q, COPD screening questionnaire; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; PE, pulmonary embolism; No-AL/PRISm, without AL or PRISm; PRISm, Preserved Ratio Impaired Spirometry; PROMIS, Patient-Reported Outcomes Measurement Information System; SD, standard deviation.

measurements such as maximal mid-exploratory flow (MMEF) may help identify individuals at risk of developing COPD.[18,28,29] Patients who may have clinical symptoms of COPD but do not have spirometry-defined COPD according to their FEV_1/FVC ratio, may benefit from measurements such as PRISm or MMEF/FVC ratio to help with diagnosis.[18,28,29] One study demonstrated a correlation between the MMEF/FVC ratio and stages of COPD and found significantly lower MMEF/FVC values in patients at risk of developing COPD compared to those in a control group.[28] In order to validate PRISm as a suitable risk factor for progression of airflow limitation to COPD, a longitudinal study conducted in the OCEAN patient population would be beneficial.

Prevalence estimates for PRISm have varied from ~7–12%.[18,21] A European population-based study cohort of 5487 adults ≥45 years of age (which included never smokers) estimated the prevalence of PRISm at 7.1%,[18] which is somewhat lower than the prevalence of approximately 12.5% reported in the COPDGene study.[21] COPDGene examined longitudinal patterns of change in lung function, radiographic characteristics, and mortality in 15,754 participants with PRISm. Although prevalence rates of PRISm were slightly higher in the latter study, this study included only current or further smokers, with study participants having a smoking history (mean) of 44.2 pack years.[20] The mean age in the OCEAN study (52.0 years) was lower than in the COPDGene study (59.6 years) or European population-based study (69.1 years), which may have contributed to the higher proportion of participants with PRISm in this study.[18,20]

Outcomes such as lung function trajectories and mortality are more closely aligned between individuals with PRISm and COPD than between those with PRISm and healthy individuals with normal spirometry.[19] Wijnant et al reported a mortality rate of 18.7% in individuals with PRISm, which was only slightly lower than the 20.8% in the COPD group. Individuals with normal airflow (control group) had a mortality rate of 10.3%.[18] PRISm may therefore represent an important milestone in the development of COPD in a particular subgroup of individuals. Population-based studies have shown that a substantial proportion of individuals with PRISm subsequently develop COPD.[18,21,30,31] In the COPDGene study, 25% of individuals with PRISm at enrollment progressed to GOLD 1–4 status at 5-year follow-up.[21] Thus, PRISm can be considered a marker for identifying individuals at risk of developing COPD during routine health checks.[22]

Previous studies have reported that a higher BMI correlates with a higher prevalence of PRISm.[18–21,31] In the current study, participants with PRISm had a higher BMI than those with either no airflow limitation/PRISm or airflow limitation. As PRISm is assumed to be a pre-COPD stage, and no correlation was observed between higher BMI and having airflow limitation, this finding suggests that there are multiple phenotypes among the PRISm population. This corroborates the results of the Rotterdam cohort study, in which PRISm was indicated to exist in three different subsets: one subset that progresses to COPD, one with high cardiovascular burden and early mortality, and one that experiences persistent PRISm with age-related lung function decline.[18] The association between BMI and PRISm has been attributed to

obesity, which can cause a restrictive spirometry pattern and reduction in FVC while preserving the FEV_1/FVC ratio.[19] The presence of comorbid metabolic disease, including hypertension, diabetes, and hyperlipidemia, was also higher in participants from the PRISm group compared with the other subgroups, raising the question as to whether a subset of individuals with PRISm (who may have never smoked) have restrictive lung disease that is worse in those with higher BMI and comorbidities. This higher proportion of comorbid diabetes was also consistent with the Rotterdam cohort study[18] and underscores the importance of identifying and monitoring these at-risk individuals with PRISm and encouraging a healthy weight and lifestyle, in order to manage disease progression.

Our study also showed a significant association between the history of childhood asthma and PRISm. This finding is in agreement with previous studies that have suggested that childhood asthma may be a risk factor for fixed airflow limitation and COPD in early adulthood.[32,33] However, it should be noted that this study was not powered to analyze results by history of childhood asthma and thus this finding should be interpreted with caution.

Smoking has also been shown to be associated with an increased risk of developing COPD or PRISm.[20,34] In the current study, we found that current smokers had the highest prevalence of airflow limitation and PRISm, and it is known that continued smoking and the onset of frequent exacerbations are predictors of declining quality of life in smokers with PRISm.[35] These findings support the screening of individuals 40 years of age or older who are current or former smokers to facilitate early diagnosis of COPD and identify those at risk of developing COPD or at increased risk of COPD-related mortality.[36] Specifically, such individuals should undergo spirometry testing for COPD diagnosis and should be offered smoking cessation, dietary, and exercise interventions.

In our study 42.4% of participants with PRISm had never smoked. While smoking is the major risk factor for OAD, the prevalence of PRISm in participants with no smoking history is likely due to other factors that are known to influence disease development. Genetic factors as well as exposure to second-hand smoke and other non-tobacco environmental exposures may influence airflow limitation, while lung growth and development and age are known risk factors for COPD development.[17]

A strength of our study was the use of spirometry testing by experienced technicians within the setting of a health examination. Adopting this approach can provide standardized and high-quality spirometry data and yield reliable estimates of the prevalence of respiratory disease. Spirometry testing in this study was performed pre-bronchodilator, and participants found to have airflow limitation also included individuals with asthma or other respiratory diseases as well as COPD. It is important when interpreting the findings of our study to acknowledge that the age and gender distribution of participants may differ from that of the general population because of the setting of health examination; a limitation of our study is that it was based on participants attending a single study site in Naha City, Okinawa and, though this is the largest facility for health check-ups in the city, the study population may not be representative of the general population in the Okinawa prefecture.[28,29]

Conclusions

A significant proportion of individuals younger than 60 years attending their annual health examination in general practice in Okinawa were found to have impaired lung function (airflow limitation and PRISm). Current smokers had the highest prevalence of airflow limitation and PRISm, and because PRISm does not fall within the diagnostic criteria for COPD, detection of these individuals who are at risk of COPD may be missed during routine health checks. Furthermore, spirometry testing is currently optional during annual health examinations in Japan. Our findings provide support for screening individuals 40 years of age or older who are current or former smokers, via the use of questionnaires to inform the need for spirometry. This approach could facilitate early diagnosis of OAD and identify those at risk of developing OAD. Healthy lifestyle interventions, such as smoking cessation programs and healthy eating programs, in those meeting spirometric criteria for COPD or PRISm are also warranted.

Abbreviations

AL, airflow limitation; BMI, body mass index; CAAT, Chronic Airways Assessment Test; CAPTURE, Chronic Airways Assessment Test; CAT, COPD Assessment Test; CB, chronic bronchitis; CKD, chronic kidney disease; CMH, chronic mucus hypersecretion; COPD, chronic obstructive pulmonary disease; COPD-Q, COPD screening questionnaire; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; MMEF, maximal mid-exploratory flow; OAD, obstructive airway disease; PE, pulmonary embolism; PRISm, Preserved

Ratio Impaired Spirometry; PROMIS, Patient-Reported Outcomes Measurement Information System; SD, standard deviation.

Data Sharing Statement

Anonymized individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

Ethics Approval and Informed Consent

This study was conducted in accordance with the Declaration of Helsinki. The protocol, applicable amendments, and other relevant documents were reviewed and approved by the Nahanishi Clinic Ethics Committee (Number NNCEC2018004). The study complied with all applicable laws regarding subject privacy, and all participants provided written informed consent before data collection began.

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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.

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