Association between Comorbidities and Preserved Ratio Impaired Spirometry: Using the Korean National Health and Nutrition Examination Survey IV–VI

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Keywords

Preserved ratio impaired spirometry · Prevalence · Comorbidities · Obstructive lung disease

Abstract

Background: Preserved ratio impaired spirometry (PRISm) patients have more frequent respiratory symptoms and an increased risk of mortality. However, studies on comorbidities in these patients are lacking. **Objectives:** We investigated the association between PRISm and comorbidities using the Korea National Health and Nutrition Examination Survey (KNHANES). **Method:** This cross-sectional study included participants aged ≥ 50 years from the KNHANES (2007–2015). Participants who did not undergo spirometry or performed inadequately were excluded. We classified participants into 3 groups according to spirometry: PRISm (forced expiratory volume in one second [FEV1] /forced vital capacity [FVC] ≥ 0.7 and FEV1 $< 80\%$), chronic obstructive pulmonary disease (COPD) (FEV1/ FVC < 0.7), and normal. Multivariate logistic regression analyses were used to evaluate the risk of comor-

bidities in the PRISm group compared to that in the normal group. **Result:** The study included 17,515 participants: 12,777 (73.0%), 1,563 (8.9%), and 3,175 (18.1%) in normal, PRISm, and COPD groups, respectively. After adjustment for known risk factors of each disease, hypertension (adjusted odds ratio [95% confidence interval]; 1.31 [1.14–1.50]), diabetes (1.51 [1.29–1.78]), hypercholesterolemia (1.20 [1.04–1.37]), obesity (1.31 [1.15–1.48]), ischemic heart disease (1.58 [1.13–2.22]), chronic renal disease (2.31 [1.09–4.88]), and thyroid disease (1.41 [1.09–1.83]) risks were significantly higher in the PRISm group than in the normal group. The average number of comorbidities was 2.45 in the PRISm group, which was higher than that in the normal (2.1) and COPD (2.03) groups ($p < 0.05$). **Conclusion:** The number of comorbidities was significantly higher in the PRISm group than in others. Hypertension, diabetes, obesity, ischemic heart disease, chronic renal disease, and thyroid disease were associated with PRISm after adjustment for risk factors.

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Introduction

Preserved ratio impaired spirometry (PRISm) is characterized by decreased forced expiratory volume in one second (FEV1 <80% predicted) without airflow limitation (FEV1/forced vital capacity [FVC] $\geq$ 0.7), and is also called “GOLD unclassified” or “Restrictive spirometry.” The risk of chronic obstructive pulmonary disease (COPD) development was increased in PRISm patients, despite no initial observation of airway obstruction [1, 2]. Not only for COPD, several studies showed the association between PRISm and extrapulmonary disease, like obesity, hypertension, diabetes, and metabolic syndrome [3–5]. Restrictive spirometry was associated with diabetes in patients without known pulmonary disease [6] and was also significantly more frequent in patients with chronic renal disease [7]. Risk of developing end-stage renal disease was higher in restrictive spirometry in a long-term follow-up study [8]. In addition to increased risk of comorbidities, increased mortality risk was associated in patients with restrictive disease, after adjustment of risk factors, including age, sex, and body mass index (BMI) [2, 9, 10].

Most studies mentioned above investigated restrictive lung disease. Though PRISm and restrictive spirometry were considered to have similar characteristics, or to be the same disease for patients with overlap, diagnostic criteria of the 2 groups are different in actuality. A few studies about PRISm have been conducted, and none of them investigated various comorbidities. We intended to investigate clinical characteristics and comorbidities of PRISm in a population-based national survey. In addition, we investigated the difference of health-care utilization by comparing the number of admitted patients in the past year.

Materials and Methods

Study Population

The Korea National Health and Nutrition Examination Survey (KNHANES) is a cross-sectional national surveillance system that consists of a health interview, a health examination, and a nutrition survey. The survey has been conducted every 3 years from 1998 to 2005 and has changed to an annual rotation sample survey since 2007. The sampling was done by stratified multistage cluster sampling design. The spirometry was performed in adults aged 19 years and over in 2007–2009, 40 years and over in 2010–2012, and between 40 and 80 years old in 2013–2015.

We used the data from 2007 to 2015 (the KNHANES IV~VI) that contained information about hospital admissions occurring within 1 year prior to the survey. We included participants older

than 50 years old, considering prevalence of comorbidities according to age [11, 12]. Participants who did not undergo spirometry or performed inappropriate spirometry were excluded. This study used data from the KNHANES, which was approved by the Institutional Review Board Committee of the Korea Centers for Disease Control (IRB No.1401-047-547). All participants signed a written informed consent.

Definition

Patients whose FEV1/FVC was >0.7 were classified as PRISm group when FEV1 was $<80\%$ of predicted percent, otherwise they were classified as normal group. If FEV1/FVC was <0.7 , participants were classified as obstructive group. Economic state in the original questionnaire was classified into 4 groups, namely low, mid-low, high-low, and high. Among them, we combined mid-low and high-low into “mid” group. Ever smoker was defined as a person with a smoking history of >5 pack-years. Alcohol consumption was classified into 3 groups. Heavy drinkers were defined as drinking >21 glasses for men and 14 glasses for women. Drinking less than those criteria was defined as moderate.

Comorbidities were defined in 2 ways. First, presence of comorbidity was identified by the questionnaire. Second, prevalence was investigated based on the definition by physical examination and laboratory data. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg. Diabetes was defined as fasting blood sugar ≥ 126 mg/dL or hemoglobin A1c $\geq 6.5\%$. Hypercholesterolemia was defined as total cholesterol ≥ 240 mg/dL, and obesity as BMI ≥ 25 . Anemia was defined as hemoglobin values <13 g/dL in men and <12 g/dL in women. We calculated the number of comorbidities by summing up the total number of affected disease for each participant. For cancers, only 1 point was counted if there were multiple primary cancers in different organs. The cause of hospitalization was identified according to a disease code based on the Korean Standard Classification of Diseases.

Statistical Analysis

We compared baseline characteristics among 3 groups by using χ^2 test for categorical variable and analysis of variance for continuous variable. The prevalence of comorbidities was also analyzed by using χ^2 test, and risk of comorbidity was analyzed by univariate and multivariate logistic regression. Multivariate logistic regression was adjusted for each risk factor as follows: (1) age, sex-adjusted: obesity, chronic renal disease, chronic hepatitis, anemia, thyroid disease, rheumatic disease, and depression; (2) age, sex, and BMI-adjusted: hypertension, diabetes, hypercholesterolemia, liver cirrhosis, osteoarthritis, and osteoporosis; (3) age, sex, BMI, hypertension, diabetes, hypercholesterolemia, smoking, and alcohol-adjusted: stroke and ischemic heart disease. Statistical analyses were conducted by the SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Statistical significance (p value) was <0.05 .

Results

Baseline Characteristics

There were 73,353 who participated in the KNHANES from 2007 to 2015. In total, 17,515 participants were ana-

Fig. 1. Flowchart. KNHANES, Korea National Health and Nutrition Examination Survey; PRISm, preserved ratio impaired spirometry; FEV1, forced expiratory volume in one second; FVC, forced vital capacity.

lyzed after excluding 45,117 participants who were younger than 50 years old, 8,795 participants who did not perform spirometry, and 1,926 participants who performed inadequate spirometry (Fig. 1). Among them, 73.0% (12,777 participants) was in normal spirometry group, 18.1% (3,175 participants) was in the obstructive group, and 8.9% (1,563 participants) was in PRISm group.

Average age was lowest in the PRISm group at 59.0 years old, followed by the normal group at 59.6 years old, and the obstructive group, highest at 64.7 years old (Table 1). There were significant differences for age and sex among the 3 groups, with the prevalence of PRISm being higher in women (9.3%) than in men (8.4%), and the obstructive group having a higher proportion of men (73.8%). For socioeconomic status, income and education statuses were similar between the PRISm and the normal group. The proportion of “Low economic status” was significantly higher in the obstructive group than the other 2 groups, and education level was lowest in the obstructive group. The average BMI was highest in the PRISm group (24.7), followed by the normal group (24.4), and the obstructive group (23.6).

Average value of FEV1 (2.13 ± 0.01), FEV1 predicted% ($74.0 \pm 0.2\%$), FVC (2.80 ± 0.02), and FVC predicted% ($74.8 \pm 0.2\%$) were lowest in the PRISm group and were significantly lower than the normal group. For the ob-

structive group, only the FVC value was higher than in the normal group while the rest of the values were significantly lower. FEV1/FVC ratio was 0.63 in the obstructive group, 0.76 in the PRISm group, and 0.79 in the normal group.

Proportions of ever smoker and current smoker were highest in the obstructive group (68.9 and 31.9%, respectively). The PRISm group had less ever smokers (42.9%) and current smokers (23.1%) than the obstructive group, but had the highest average pack-year. Alcohol consumption, which was the proportion of participants who drank alcohol, and heavy drinkers, are also highest in the obstructive group.

Prevalence of Comorbidities

The prevalence of comorbidities is shown in Table 2. In the PRISm group, hypertension was most common (51.5%), followed by obesity (45.4%), hypercholesterolemia (31.2%), and diabetes (24.0%). Seventy-five participants (4.9%) had ischemic heart disease and 59 participants (3.3%) had a history of stroke. Compared to the normal group, hypertension, diabetes, hypercholesterolemia, obesity, stroke, ischemic heart disease, chronic renal disease, thyroid disease, and osteoarthritis were more prevalent in the PRISm group. Hypertension, diabetes, stroke, and ischemic heart disease were more common in

Table 1. Baseline characteristics

	Total (N = 17,515)	Normal group (N = 12,777)	PRISm group (N = 1,563)	Obstructive group (N = 3,175)	p value
Age, mean	60.4±0.1	59.6±0.1 ^{*,†}	59.0±0.2 [‡]	64.7±0.2	<0.001
Sex, n (%)					
Male	7,495 (47.5)	4,572 (41.5) ^{*,†}	627 (46.6) [‡]	2,296 (73.8)	<0.001
Female	10,020 (52.5)	8,205 (58.5) ^{*,†}	936 (53.4) [‡]	879 (26.2)	
Income, n (%)					
High	4,799 (27.0)	3,561 (27.5) [†]	443 (27.3)	795 (24.4)	0.009
Mid	8,769 (50.3)	6,396 (50.4) [†]	768 (50.2)	1,605 (50.2)	
Low	3,947 (22.7)	2,820 (22.1) [†]	352 (22.5)	775 (25.4)	
Education, n (%)					
≤Elementary	7,368 (38.6)	5,292 (37.6) [†]	614 (34.5) [‡]	1,462 (45.1)	<0.001
Middle	3,144 (19.5)	2,288 (19.4) [†]	302 (20.2) [‡]	554 (19.4)	
High	4,246 (27.3)	3,106 (27.5) [†]	421 (30.8) [‡]	719 (24.5)	
≥College	2,309 (14.6)	1,752 (15.5) [†]	192 (14.5) [‡]	365 (11.1)	
BMI, mean	24.28±0.03	24.38±0.03 ^{*,†}	24.74±0.10 [‡]	23.6±0.06	<0.001
Waist circumference	84.0±0.1	83.7±0.1 ^{*,†}	85.4±0.3 [‡]	84.7±0.2	<0.001
Spirometry, average					
FEV1, L	2.57±0.01	2.69±0.01 ^{*,†}	2.13±0.01	2.27±0.02	<0.001
FEV1, predicted %	91.6±0.1	96.9±0.1 ^{*,†}	74.0±0.2 [‡]	77.9±0.3	<0.001
FVC, L	3.39±0.01	3.42±0.01 ^{*,†}	2.80±0.02 [‡]	3.58±0.02	<0.001
FVC, predicted %	91.9±0.1	94.5±0.1 ^{*,†}	74.8±0.2 [‡]	90.2±0.3	<0.001
FEV1/FVC	0.761±0.001	0.790±0.001 ^{*,†}	0.764±0.001 [‡]	0.633±0.001	<0.001
Smoking, n (%)					
Nonsmoker	10,564 (57.5)	8,585 (63.7) ^{*,†}	957 (57.1) [‡]	1,022 (31.1)	<0.001
Ex-smoker	3,947 (23.8)	2,448 (21.2) ^{*,†}	301 (19.8) [‡]	1,198 (37.0)	
Current smoker	2,664 (18.7)	1,501 (15.1) ^{*,†}	275 (23.1) [‡]	888 (31.9)	
Pack-year, mean	27.7±1.6	25.7±1.8	37.3±10.9	29.3±1.2	
Alcohol, n (%)					
None	3,014 (21.2)	2,130 (19.7) [†]	289 (21.0)	595 (21.4)	0.001
Moderate	9,529 (69.0)	6,975 (70.1) [†]	819 (67.9)	1,735 (65.3)	
Heavy	1,233 (10.8)	826 (10.2) [†]	113 (11.1)	294 (13.3)	

PRISm, preserved ratio impaired spirometry; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; BMI, body mass index. * Normal group versus PRISm group $p < 0.05$. [†]Normal group versus obstructive group $p < 0.05$. [‡] PRISm group versus obstructive group $p < 0.05$.

the obstructive group than in the normal group. Average number of comorbidities was 2.45 in the PRISm group, which had significantly more comorbidities than the normal (2.1) or obstructive (2.03) group.

The risk of comorbidity of PRISm and obstructive group was compared with that of normal spirometry group (Table 3). Without adjustment, risk of hypertension, diabetes, stroke, and ischemic heart disease significantly increased in both the PRISm and obstructive group. In addition, obesity, chronic kidney disease, and thyroid disease also showed higher risk in the PRISm group than the normal group. After adjustment for risk factors, there was no significant difference in stroke in the PRISm group compared to the normal group, but it was

still significant in other diseases: hypertension (aOR 1.31 [95% confidence interval (CI) 1.14–1.50]), diabetes (aOR 1.51 [95% CI 1.29–1.78]), hypercholesterolemia (aOR 1.20 [95% CI 1.04–1.37]), obesity (aOR 1.31 [95% CI 1.15–1.48]), ischemic heart disease (aOR 1.58 [95% CI 1.13–2.22]), chronic kidney disease (aOR 2.31 [95% CI 1.09–4.88]), and thyroid disease (aOR 1.41 [95% CI 1.09–1.83]). The subgroup analysis stratified by BMI showed that the risk of hypertension (aOR 1.27 [95% CI 1.06–1.52]), diabetes (aOR 1.59 [95% CI 1.26–2.00]) and chronic kidney disease (aOR 4.48 [95% CI 1.99–10.12]) was increased even in the PRISm group without obesity (BMI <25 kg/m²) (see online suppl. Table 1; see www.karger.com/doi/10.1159/000517599 for all online suppl.

Table 2. Prevalence of comorbidities

	Total (N = 17,515)	Normal group (N = 12,777)	PRISm group (N = 1,563)	Obstructive group (N = 3,175)	<i>p</i> value
Hypertension, <i>n</i> (%)	8,299 (46.6)	5,850 (44.9)*, †	815 (51.5)	1,634 (51.1)	<0.001
Diabetes, <i>n</i> (%)	3,140 (18.2)	2,126 (16.7)*, †	361 (24.0)	653 (21.6)	<0.001
Hypercholesterolemia, <i>n</i> (%)	4,773 (27.1)	3,575 (27.7)*, †	488 (31.2)‡	710 (22.4)	<0.001
Obesity, <i>n</i> (%)	6,553 (38.0)	4,943 (39.0)*, †	679 (45.4)‡	931 (29.7)	<0.001
Stroke, <i>n</i> (%)	487 (2.5)	321 (2.2)*, †	59 (3.3)	107 (3.2)	0.004
Ischemic heart disease, <i>n</i> (%)	705 (3.7)	483 (3.4)*, †	75 (4.9)	147 (4.6)	0.003
Chronic renal disease, <i>n</i> (%)	100 (0.5)	63 (0.5)*	15 (1.0)	22 (0.7)	0.048
Chronic hepatitis, <i>n</i> (%)	390 (2.4)	298 (2.4)†	43 (3.3)‡	49 (1.7)	0.018
Liver cirrhosis, <i>n</i> (%)	82 (0.5)	60 (0.5)	6 (0.5)	16 (0.5)	0.992
Anemia, <i>n</i> (%)	1,269 (6.5)	925 (6.6)	116 (6.1)	228 (6.7)	0.756
Thyroid disease, <i>n</i> (%)	836 (4.5)	652 (4.7)*, †	95 (6.1)‡	89 (2.9)	<0.001
Rheumatic arthritis, <i>n</i> (%)	653 (3.4)	503 (3.5)	58 (3.8)	92 (2.6)	0.083
Osteoarthritis, <i>n</i> (%)	4,187 (21.6)	3,218 (22.4)*, †	333 (18.9)	636 (19.2)	<0.001
Osteoporosis, <i>n</i> (%)	984 (12.3)	755 (12.8)†	106 (14.4)‡	123 (9.1)	0.004
Depression, <i>n</i> (%)	2,322 (12.1)	1,783 (12.6)†	234 (13.7)‡	305 (9.1)	<0.001
Cancer, <i>n</i> (%)	597 (2.9)	415 (2.8)	65 (3.4)	117 (2.8)	0.455
Comorbidities, <i>n</i>	2.18±0.01	2.19±0.02*, †	2.45±0.04‡	2.03±0.03	<0.001

PRISm, preserved ratio impaired spirometry. *Normal group versus PRISm group *p* <0.05. †Normal group versus obstructive group *p* <0.05. ‡PRISm group versus obstructive group *p* <0.05.

Table 3. Risk of comorbidities in PRISm and obstructive group compared to normal group

	Unadjusted OR (95% CI)		Adjusted OR (95% CI)*	
	PRISm group (N = 1,563)	Obstructive (N = 3,175)	PRISm group (N = 1,563)	Obstructive group (N = 3,175)
Hypertension	1.30 (1.15–1.48)	1.28 (1.17–1.41)	1.31 (1.14–1.50)	0.96 (0.86–1.07)
Diabetes	1.58 (1.35–1.84)	1.37 (1.22–1.55)	1.51 (1.29–1.78)	1.05 (0.92–1.19)
Hypercholesterolemia	1.18 (1.03–1.35)	0.75 (0.67–0.85)	1.20 (1.04–1.37)	0.90 (0.80–1.02)
Obesity	1.30 (1.15–1.48)	0.66 (0.60–0.73)	1.31 (1.15–1.48)	0.64 (0.58–0.71)
Stroke	1.50 (1.05–2.16)	1.47 (1.12–1.93)	1.46 (0.97–2.19)	0.91 (0.64–1.28)
Ischemic heart disease	1.50 (1.11–2.03)	1.38 (1.09–1.74)	1.58 (1.13–2.22)	1.02 (0.78–1.34)
Chronic renal disease	2.27 (1.07–4.83)	1.55 (0.86–2.78)	2.31 (1.09–4.88)	1.64 (0.89–3.01)
Chronic hepatitis	1.38 (0.94–2.02)	0.68 (0.47–0.98)	1.32 (0.90–1.94)	0.62 (0.42–0.91)
Liver cirrhosis	0.99 (0.38–2.59)	0.96 (0.51–1.80)	0.91 (0.35–2.35)	0.73 (0.37–1.44)
Anemia	0.92 (0.73–1.16)	1.02 (0.85–1.22)	0.99 (0.78–1.25)	0.95 (0.78–1.14)
Thyroid disease	1.31 (1.01–1.70)	0.59 (0.45–0.78)	1.41 (1.09–1.83)	1.06 (0.79–1.40)
Rheumatic arthritis	1.07 (0.78–1.46)	0.74 (0.56–0.98)	1.15 (0.84–1.57)	0.91 (0.68–1.23)
Osteoarthritis	0.81 (0.69–0.94)	0.82 (0.73–0.92)	0.87 (0.73–1.02)	0.98 (0.85–1.13)
Osteoporosis	1.15 (0.88–1.49)	0.68 (0.54–0.87)	1.21 (0.91–1.62)	0.91 (0.66–1.24)
Depression	1.10 (0.92–1.32)	0.69 (0.59–0.81)	1.17 (0.97–1.41)	0.99 (0.83–1.17)
Cancer	1.23 (0.88–1.71)	1.01 (0.78–1.31)	1.30 (0.93–1.81)	0.96 (0.74–1.26)

PRISm, preserved ratio impaired spirometry; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; OR, odds ratio; CI, confidence interval.

Table 4. The number of hospital admissions and length of hospital stay in the previous one year

	Total (N = 17,515)	Normal group (N = 12,777)	PRISm group (N = 1,563)	Obstructive group (N = 3,175)	p value
Total admission					
Patients, n (%)	1,944 (11.3)	1,338 (10.7) [†]	196 (11.9)	410 (13.4)	0.002
Respiratory					
Patients, n (%)	120 (0.6)	65 (0.5)*, [†]	16 (1.0)	39 (1.2)	<0.001
Hospital days	10.4±1.4	9.7±2.2	13.6±3.7	10.2±1.3	0.648
Cardiology					
Patients, n (%)	184 (1.0)	113 (0.8)*, [†]	25 (1.3)	46 (1.3)	0.013
Hospital days	7.6±0.9	5.9±0.7	10.7±4.9	10.3±1.9	0.064
Gastrointestinal					
Patients, n (%)	187 (1.1)	125 (1.0)	20 (1.1)	42 (1.3)	0.247
Hospital days	12.9±4.5	15.5±6.5	6.9±2.1	7.7±1.2	0.448
Infection					
Patients, n (%)	57 (0.3)	44 (0.3)	3 (0.2)	10 (0.3)	0.324
Hospital days	23.1±10.7	10.0±1.5	38.3±16.3	63.3±42.1	0.100
Cancer					
Patients, n (%)	152 (0.8)	102 (0.8)	11 (0.4) [‡]	39 (1.1)	0.029
Hospital days	14.9±2.5	13.7±1.6	9.9±2.4	19.7±9.3	0.315
Endocrinology					
Patients, n (%)	34 (0.2)	24 (0.2)	3 (0.2)	7 (0.2)	0.839
Hospital days	18.3±5.1	17.4±5.1	15.2±5.6	22.4±16.4	0.901
Neurology					
Patients, n (%)	27 (0.2)	19 (0.2)	3 (0.1)	5 (0.1)	0.671
Hospital days	10.4±2.7	6.9±1.0	8.2±1.9	32.0±14.5	0.145
Neuropsychiatry					
Patients, n (%)	9 (0.04)	7 (0.04)	0	2 (0.05)	–
Hospital days	17.0±6.6	19.5±8.1	–	7.9±1.1	0.153
Genitourinary					
Patients, n (%)	75 (0.4)	62 (0.5)	3 (0.2)	10 (0.4)	0.236
Hospital days	8.2±1.9	8.0±2.2	7.4±4.5	9.6±2.0	0.832
Musculoskeletal					
Patients, n (%)	384 (2.1)	275 (2.1)	35 (1.9)	74 (2.0)	0.785
Hospital days	18.0±1.4	16.5±1.0	29.5±13.5	19.2±2.4	0.374

PRISm, preserved ratio impaired spirometry; FEV1, forced expiratory volume in one second; FVC, forced vital capacity. * Normal group versus PRISm group $p < 0.05$. [†] Normal group versus obstructive group $p < 0.05$. [‡] PRISm group versus obstructive group $p < 0.05$.

material). In the obstructive group, only hypercholesterolemia (aOR 0.88 [95% CI 0.80–0.98]), obesity (aOR 0.64 [95% CI 0.58–0.71]), and chronic liver disease (aOR 0.62 [95% CI 0.42–0.91]) were significantly lower than in the normal group after adjusting risk factors.

Hospitalization

1,944 participants (11.3%) had been admitted to the hospital within 1 year prior to the survey (Table 4). Among the 3 groups, there were significant differences in the proportion of patients who had been admitted for respiratory disease, cardiologic disease, and malignancy, respectively ($p < 0.001$). The proportion of patients

admitted for respiratory disease was highest in the obstructive group (1.2%), followed by the PRISm group (1.0%), and the normal group (0.5%). Admission for cardiologic disease was similar in both the PRISm and obstructive group (1.3%) and was significantly lower in the normal group (0.8%). However, cancer-related admission was lowest in the PRISm group (0.4%), followed by the normal group (0.8%), and the obstructive group (1.1%). Otherwise, there was no significant difference among the 3 groups. Average hospital stay length also showed no difference among the 3 groups for all causative diseases including respiratory, cardiology, and cancer.

Discussion

In this study, the prevalence of comorbidities in PRISm was investigated and compared with that in the normal lung function group using the KNHANES. In total, 17,515 participants, who were older than 50 years and had appropriately performed spirometry, were analyzed; the PRISm group comprised 1,563 participants (8.9%), which was similar to those in the previous studies showing a prevalence of 6–13% [2, 13–15], with a higher prevalence in women [2, 16, 17]. Although the proportion of ever smokers and current smokers was higher in the PRISm group in this study, further investigation is needed to determine the association between smoking and PRISm. In the COPD gene cohort, PRISm had a higher proportion of current smokers with higher average pack-years [4]. Only a few studies have included never smokers, and 1 recent study reported that smoking was inversely associated with PRISm [18].

We investigated the prevalence of comorbidities among the 3 groups and found that PRISm was significantly associated with hypertension, diabetes, hypercholesterolemia, obesity, ischemic heart disease, chronic renal disease, and thyroid disease, even after adjusting for each comorbidity risk factors. Although BMI is a common risk factor for these diseases and was highest in the PRISm group, the association was still significant after adjustment, and subgroup analysis showed an increased risk for hypertension, diabetes, and CKD in the nonobese participants ($\text{BMI} < 25 \text{ kg/m}^2$).

The pathophysiologic mechanisms remain unclear, but previous research has shown a relationship between reduced FEV1 and arterial stiffness [19]. High blood pressure was also associated with lower FEV1 and FVC values, and this was significant in the very high blood pressure group ($\geq 180/110 \text{ mm Hg}$) [20]. In addition, the risk of other metabolic diseases increased in patients with PRISm. Obesity is a well-known risk factor for restrictive lung disease and PRISm, as excessive body fat can restrict mechanical function and reduce lung volume [21]. However, as mentioned previously, the association between comorbidities and PRISm cannot be explained by obesity alone, as there are other factors that have been suggested to lead to comorbidities and lung function impairment, such as oxidative stress, hypoxia, and chronic inflammation [22]. Oxidative stress caused by diabetes can cause lung parenchymal damage, which leads to fibrosis and structural changes [23]. Diabetic patients showed an increase in the alveolar epithelium or endothelial capillary thickness, with decreased degradation of glycated con-

nective tissue [24], and a higher incidence of pulmonary fibrosis [25]. Hypoxemia also induces renal damage and inflammation, and chronic renal disease shares common risk factors with PRISm, such as diabetes and hypertension. In a study that investigated the incidence of end-stage renal disease, the cumulative incidence was highest in restrictive pattern spirometry (9.8%), and obstructive pattern spirometry showed the same cumulative incidence as that in the low normal pattern group (3.7%) [8]. In addition, the risk of microalbuminuria was also related to restrictive pattern spirometry, but not to the obstructive pattern [26].

The proportion of patients with thyroid disease was higher in the PRISm group. Hyperthyroidism and, more evidently, hypothyroidism can reduce respiratory drive or muscle function [27], resulting in restrictive spirometry. Additionally, hypothyroidism was found to be more frequent in patients with idiopathic pulmonary fibrosis, which involves restrictive pulmonary impairment [28]. However, since the specific type of disease was not investigated in this survey, further investigation is needed to assess whether hyper- or hypothyroidism is associated with PRISm.

Furthermore, we found that admissions for respiratory or cardiological diseases were significantly higher in the PRISm group. In a previous study, PRISm patients visited the hospital more frequently for both outpatient and inpatient care, including emergency room cases [29]. These results may be related to the previously reported poor prognosis of PRISm. Although the frequency of cancer admissions showed a significant difference, its purpose was often for diagnosis or staging rather than treatment. Therefore, it was difficult to determine whether these differences were clinically significant.

The prevalence of hypertension, diabetes, stroke, and ischemic heart disease was significantly higher in the COPD group, but the risk of these comorbidities did not increase after adjusting for the risk factors for each disease. Only the OR for obesity was significantly lower in the COPD group than that in the normal group. A large cross-sectional study conducted in France showed a similar result, in which the restrictive group was significantly associated with metabolic syndromes and its components, namely, dyslipidemia, impaired fasting glucose, hypertension, and abdominal obesity [30]. However, obstructive lung disease showed no significant association, except for abdominal obesity [30].

This is the first study to investigate the relationship between overall comorbidities and PRISm with adjustment for risk factors for each comorbidity. In addition,

contrary to most previous studies that only included ever smokers, we included never smokers, allowing the results of this study to be generalized more easily. Despite these findings, this study had several limitations. First, we conducted a cross-sectional study; thus, we could not evaluate causal relationships and were only able to analyze the association between PRISm and comorbidities. Second, previous medical history was investigated through a questionnaire in the survey, in which recall bias could have occurred. We defined the prevalence of comorbidities using physical examination and laboratory data based on the diagnostic criteria of each disease to minimize this bias. Third, there were no parameters to assess the severity of respiratory symptoms.

Conclusion

In this study, participants with PRISm had a higher prevalence of hypertension, diabetes, obesity, stroke, ischemic heart disease, chronic renal disease, thyroid disease, and osteoarthritis than that in the normal spirometry group. After adjusting for each risk factor, hypertension, diabetes, obesity, ischemic heart disease, chronic renal disease, and thyroid disease were significantly associated with PRISm. Therefore, possible comorbidities should be considered in patients with PRISm, and regular follow-up is required. In addition, we recommend further research to enhance our findings.

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Statement of Ethics

The KNHANES, which was used in this study, was approved by the Institutional Review Board Committee of the Korea Centers for Disease Control (IRB No.1401-047-547). All participants signed a written informed consent.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

J.K. contributed statistical analysis, data interpretation, drafting of manuscript, and final approval of the manuscript. C.-H.L. contributed study design and final approval of the manuscript. H.Y.L. contributed critical revision and final approval of the manuscript. H.K. contributed study design, statistical analysis, and final approval of the manuscript.

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