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ORIGINAL RESEARCH

Comorbidities in obstructive lung disease in Korea: data from the fourth and fifth Korean National Health and Nutrition Examination Survey

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Background: Comorbidities can occur frequently in patients with chronic obstructive pulmonary disease (COPD) and can influence mortality and morbidity independently. It is increasingly recognized that many patients with COPD have comorbidities that have a major impact on their quality of life and survival. Therefore, we investigated the prevalence of comorbidities in Korean COPD populations.

Methods: We used data obtained in the 6 years of the fourth and fifth Korean National Health and Nutrition Examination Survey (KNHANES) IV and V. Among 50,405 subjects, 16,151 subjects aged ≥40 years who performed spirometry adequately were included in this study. Airway obstruction was defined as forced expiratory volume in 1 second/forced vital capacity <0.7, and the Global Initiative For Chronic Obstructive Lung Disease stage was used to evaluate the severity of airway obstruction. Statistical analyses were performed using SAS 9.2.

Results: Among the 16,151 subjects (43.2% male, 56.8% female; mean age: 57.1 years for men and 57.2 years for women), 13.1% had obstructive lung function; 11.3%, restrictive lung function; and 75.6%, normal lung function. Among individuals with obstructive lung function, 45.3%, 49.4%, and 5.3% had mild, moderate, and severe and very severe airflow limitation. The prevalence of hypertension, diabetes mellitus (DM), underweight, and hypertriglyceridemia was higher in the obstructive lung function group than in the normal lung function group (49.6% vs 35.2%; 16.8% vs 10.5%; 3.3% vs 1.3%; 19.7% vs 17.0%). According to the severity of airway obstruction, hypertension and underweight were more common as severity increased, although the prevalence of DM and hypertriglyceridemia was lower in subjects with severe airway obstruction. The prevalence of hypercholesterolemia, overweight, and osteoarthritis was lower in the obstructive lung function group, especially in the severe airway obstruction groups.

Conclusions: Overall, our analysis is similar to research that was conducted earlier. Our study showed that hypertension and underweight are common comorbidities in COPD patients, and are higher as the severity of airflow obstruction increased in both men and women. DM, hypertriglyceridemia, and low high-density lipoprotein cholesterol are more common in subjects with airway obstruction, although their incidence is lower in the severe group.

Keywords: chronic obstructive pulmonary disease, comorbidity, hypertension, underweight

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Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitation that is usually progressive.[1] COPD is a major cause of morbidity and mortality around the world.[2] The frequencies of other causes of death are expected to decrease in the future, whereas COPD is expected to have a significant impact on morbidity, mortality, and health costs worldwide.[3] Patients with COPD frequently show cardiovascular disease, skeletal muscle dysfunction, metabolic syndrome,

osteoporosis, depression, and lung cancer. These can influence mortality and morbidity independently, so they should be actively looked for and treated appropriately if present.[1,4] However, these comorbidities are reported to occur mainly in the West, and there are few studies of COPD comorbidities among Asian patient populations. Therefore, we investigated the prevalence of COPD comorbidities using the data from the fourth and the fifth Korean National Health and Nutrition Examination Survey (KNHANES).

Material and methods
Study design
We retrospectively analyzed the database of the fourth and fifth (2007–2012) KNHANES, a nationally representative stratified random sample of 50,405 subjects who were selected from the Korean population. The KNHANES database included the results of various health-related questionnaires (eg, smoking history, income status, various diseases) by trained interviewers; physical examination (eg, blood pressure, body weight, height); laboratory studies (eg, complete blood cell, routine chemistry, lipid profile); image studies (eg, bone mineral density, joint X-ray); and pulmonary function test (PFT). Of these, 16,151 were aged $\geq$40 years and underwent acceptable

PFT. Finally, these latter subjects were used to analyze the prevalence of COPD and the comorbidities (Figure 1). But we inevitably included subjects with airway obstruction caused by other diseases, such as asthma, pulmonary tuberculosis, and bronchiectasis, because it was not possible to exclude these diseases using inaccurate self-reported physician diagnosis criteria. So we just described these diseases and comorbidities according to a self-reported questionnaire through our available data on Table S1.

Spirometry
Pulmonary function testing was carried out by trained medical personnel using dry rolling seal spirometers (SensorMedics, Model 2130; Yorba Linda, CA, USA), which met the performance criteria of the American Thoracic Society/ European Respiratory Society (ATS/ERS).[5] We analyzed prebronchodilator data from subjects aged $\geq$40 years that performed spirometry adequately.

Definition of COPD and the severity of airflow limitation
Airflow limitation was defined as forced expiratory volume in 1 second/forced vital capacity FEV_1/FVC ($\%FEV_1$) <0.7.
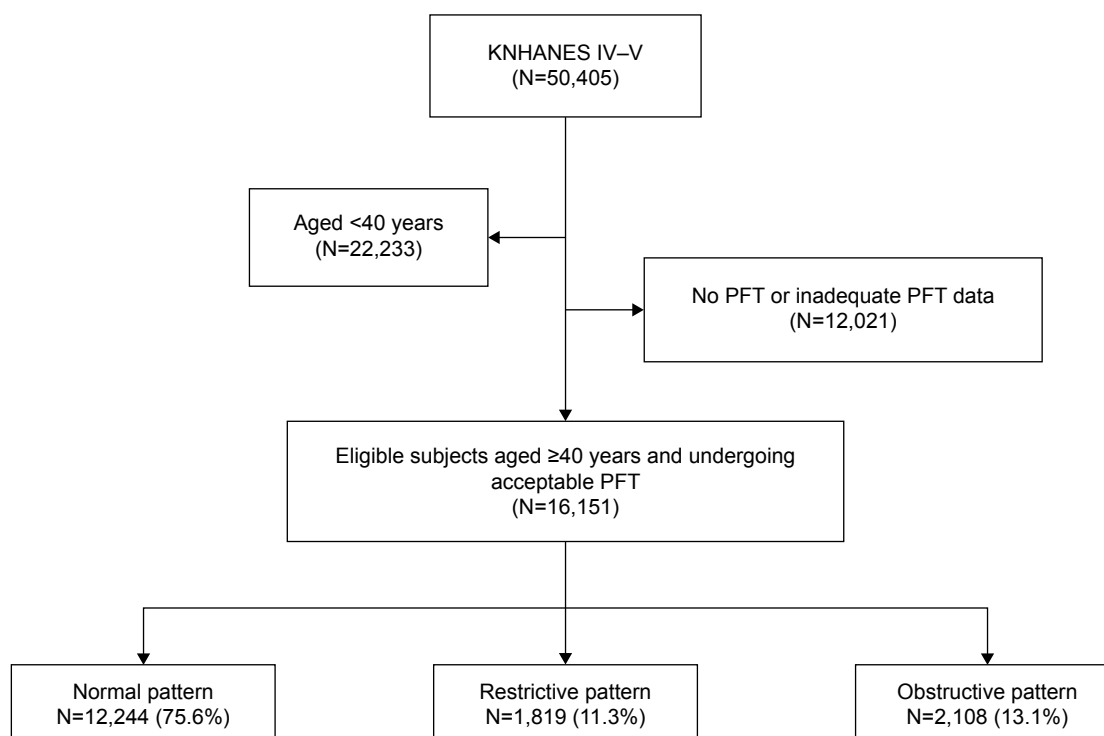

Figure 1 Flowchart for selection of study subjects.
Notes: Normal pattern = $FEV_1/FVC \geq$70% and $FEV_1 \geq$80% predicted; restrictive pattern = $FEV_1/FVC \geq$70% and $FEV_1 <$80% predicted; obstructive pattern = $FEV_1/FVC <$70%.
Abbreviations: KNHANES, Korean National Health and Nutrition Examination Survey; PFT, pulmonary function test; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

And COPD was defined as airflow limitation in subjects aged ≥40 years. The severity of airflow limitation was classified according to GOLD (Global Initiative for Chronic Obstructive Lung Disease)[1] criteria as follows:

- Mild: FEV_1 ≥80% predicted
- Moderate: 50% predicted ≤ FEV_1 <80% predicted
- Severe: FEV_1 <50% predicted.

Definition of comorbidities

Hypertension, diabetes mellitus (DM), anemia, dyslipidemia, obesity, osteopenia and osteoporosis, osteoarthritis were defined as follows:

1. Hypertension: systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, or on medication
2. DM: fasting blood glucose ≥126 mg/dL or on diabetes medication or insulin injections
3. Anemia: hemoglobin (Hb) <12 g/L in nonpregnant women aged ≥15 years; Hb <11 g/L in pregnant women and aged ≥15 years; Hb <13 g/L in men aged ≥15 years
4. Dyslipidemia: defined as inclusion of one or more of the following; hypercholesterolemia, hypertriglyceridemia, low HDL (high-density lipoprotein) cholesterol, and high LDL (low-density lipoprotein) cholesterol
   - Hypercholesterolemia: fasting total cholesterol ≥240 mg/dL or on medication
   - Hypertriglyceridemia: serum triglyceride level ≥200 mg/dL after fasting more than 12 hours
   - Low HDL cholesterol: serum HDL cholesterol level <40 mg/dL after fasting more than 8 hours
   - High LDL cholesterol: (total cholesterol – HDL cholesterol – triglyceride ×1/5) ≥130 mg/dL
5. Obesity: underweight (body mass index <18.5 kg/m^2), normal (18.5 kg/m^2 ≤ body mass index <23.0 kg/m^2), overweight (body mass index ≥ 23.0 kg/m^2) according to the Asian body mass index cutoff by WHO expert consultation[6]
6. Osteopenia (−2.5< T-score <−1.0) and Osteoporosis (T-score ≤−2.5): T-score was examined for the lumbar region, entire femur, and femoral neck in postmenopausal women and men aged ≥50 years
7. Osteoarthritis: ≥50 years old and Kellgren–Lawrence grade of knee or hip joint ≥2. The Kellgren–Lawrence grade system is a method of classifying the severity of knee osteoarthritis using five grades as follows: "grade 0" = no radiologic features of osteoarthritis are present; "grade 1" = doubtful joint space narrowing and possible osteophytic lipping; "grade 2" = define osteophytes and possible joint space narrowing on anteroposterior weight-bearing

radiograph; "grade 3" = multiple osteophytes, definite joint space narrowing, sclerosis, possible bony deformity; "grade 4" = large osteophytes, marked joint space narrowing, severe sclerosis, and definite bony deformity.

Statistical analysis

All values are expressed as means ± standard deviation. The cross-sectional analysis and chi-square test were used to establish the prevalence of comorbid disease among subjects with and without COPD. A P-value of less than 0.05 was defined as statistically significant. Statistical analyses were carried out using SAS 9 (SAS Institute Inc. Cary, NC, USA).

Ethics statement

The Korea Center for Disease Control and Prevention (KCDC) Institutional Reviews Board approved all survey protocols (numbers 2007-02CON-04-P, 2008-04EXP-010C, 2009-01CON-03-2C, 2010-02CON-21-C, 2011-02CON-06-C, 2012-01EXP-01-2C), and participants provided informed consent before partaking in the study, which was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Results

Characteristics of the subjects

Among 50,405 subjects, a subgroup of 16,151 individuals aged ≥40 years who performed spirometry adequately were included in this study. Among these subjects, 13.1% had obstructive lung function, 11.3% had restrictive lung function, and 75.6% had normal lung function (Figure 1). Of the 16,151 subjects (43.2% male, 56.8% female; mean age: 57.1 years for men and 57.2 years for women), 21.0% were current smokers, 9.6% were ex-smokers, and 69.4% were never smokers. On average, all subjects smoked 6.6 pack-years. Subjects who were male, of older age, smokers, and reported having low income were more common in the COPD group than in the normal lung function group (Table 1).

Comorbidities of COPD subjects

When compared with the normal lung function group, subjects in the obstructive lung function group had a higher prevalence of hypertension, DM, hypertriglyceridemia, low HDL cholesterol, and low body mass index (BMI <18.5). Conversely, overweight (BMI ≥23.0), osteoarthritis, hypercholesterolemia, high LDL cholesterol, and anemia were less common in the obstructive lung function group than in the normal lung function group. In the case of osteoporosis, there was no great difference between the two groups (Table 2).

Table 1 Baseline characteristics of study population

Characteristics	Normal	Restrictive	Obstructive	Obstructive severity			Total
				Mild	Moderate	Severe	
	12,224 (75.6%)	1,819 (11.3%)	2,108 (13.1%)	954 (45.3%)	1,042 (49.4%)	112 (5.3%)	16,151 (100.0%)
Age (years)	55.8±10.7	60.4±10.9	64.5±10.2	65.8±10.1	63.2±10.3	65.9±9.2	57.5±11.1
Age group (years)							
40–49 (%)	4,066 (33.3)	350 (19.3)	203 (9.7)	72 (7.5)	125 (12.0)	6 (5.3)	4,619 (28.6)
50–59 (%)	3,826 (31.3)	481 (26.4)	433 (20.5)	182 (19.1)	230 (22.1)	21 (18.8)	4,740 (29.3)
60–69 (%)	2,741 (22.4)	559 (30.7)	730 (34.6)	315 (33.0)	378 (36.3)	37 (33.0)	4,030 (25.0)
≥70 (%)	1,591 (13.0)	429 (23.6)	742 (35.2)	385 (40.4)	309 (29.7)	48 (42.9)	2,762 (17.1)
Sex							
Male	4,695 (38.4)	849 (46.7)	1,434 (68.0)	664 (69.6)	695 (66.7)	75 (67.0)	6,978 (43.2)
Female	7,529 (61.6)	970 (53.3)	674 (32.0)	290 (30.4)	347 (33.3)	37 (33.0)	9,173 (56.8)
Smoking status[a]							
Never	7,920 (73.6)	1,057 (71.1)	667 (42.8)	284 (42.1)	355 (44.7)	28 (31.8)	9,644 (69.4)
Former	866 (8.1)	191 (12.8)	274 (17.6)	115 (17.0)	133 (16.8)	26 (29.6)	1,331 (9.6)
Current	1,973 (18.3)	329 (22.1)	616 (39.6)	276 (40.9)	306 (38.5)	34 (38.6)	2,918 (21.0)
Pack-year	5.3±12.9	7.5±16.5	15.5±20.7	14.8±19.9	15.8±20.9	19.7±25.0	6.6±14.6
Household income (quartile)[a]							
First quartile	2,491 (20.6)	505 (28.2)	698 (33.7)	332 (35.5)	316 (30.9)	50 (45.9)	3,694 (23.2)
Second quartile	3,012 (25.0)	423 (23.6)	546 (26.4)	223 (23.8)	297 (29.0)	26 (23.9)	3,981 (25.0)
Third quartile	3,041 (25.2)	422 (23.6)	418 (20.2)	180 (19.2)	219 (21.4)	19 (17.4)	3,881 (24.4)
Fourth quartile	3,522 (29.2)	440 (24.6)	407 (19.7)	201 (21.5)	192 (18.8)	14 (12.8)	4,369 (27.4)

Notes: Data are presented as numbers (percentages) for categorical variables. Continuous variables are presented as means ± standard deviations. [a]The sums of some data do not equal the total due to missing data; normal = $FEV_1/FVC \geq 70\%$ and $FEV_1 \geq 80\%$ predicted; restrictive = $FEV_1/FVC \geq 70\%$ and $FEV_1 < 80\%$ predicted; obstructive = $FEV_1/FVC < 70\%$ predicted; mild = $FEV_1 \geq 80\%$ predicted; moderate =50% ≤ $FEV_1 < 80\%$ predicted; severe = $FEV_1 < 50\%$ predicted.
Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

Table 2 Comorbidities according to lung function

Comorbidity	Normal	Restrictive	Obstructive	Obstructive severity			P-value
				Mild	Moderate	Severe	
	12,224 (75.6%)	1,819 (11.3%)	2,108 (13.1%)	954 (45.3%)	1,042 (49.4%)	112 (5.3%)	
Hypertension	4,237 (35.2)	936 (52.2)	1,035 (49.6)	456 (48.2)	519 (50.4)	60 (54.1)	<0.001
DM	1,206 (10.5)	345 (20.4)	329 (16.8)	137 (15.6)	178 (18.2)	14 (13.9)	<0.001
Anemia	1,028 (8.7)	176 (10.2)	153 (7.6)	73 (8.0)	71 (7.1)	9 (8.5)	0.074
Dyslipidemia	6,982 (70.0)	1,128 (76.6)	1,253 (72.7)	557 (71.0)	642 (64.3)	54 (64.3)	<0.001
Hypercholesterolemia	1,964 (17.1)	354 (21.0)	305 (15.6)	122 (13.9)	170 (17.4)	13 (13.0)	<0.001
Hypertriglyceridemia	1,640 (17.0)	299 (21.6)	337 (19.7)	150 (19.3)	175 (20.8)	12 (13.3)	<0.001
Low HDL cholesterol	2,742 (25.1)	522 (32.9)	635 (34.0)	296 (35.1)	310 (33.3)	29 (31.2)	<0.001
High LDL cholesterol	3,846 (35.8)	515 (33.2)	554 (30.6)	232 (28.8)	294 (32.1)	28 (31.5)	<0.001
Obesity							
18.5 kg/m² > BMI	153 (1.2)	31 (1.7)	70 (3.3)	18 (1.9)	33 (3.2)	19 (17.4)	<0.001
18.5 kg/m² ≤ BMI <23.0 kg/m²	7,616 (62.4)	832 (46.2)	1,435 (68.2)	691 (72.4)	671 (64.4)	73 (67.0)	
23.0 kg/m² ≤ BMI	4,437 (36.4)	939 (52.1)	600 (28.5)	245 (25.7)	338 (32.4)	17 (15.6)	
Osteoporosis[a]							
Osteopenia	406 (5.0)	63 (4.3)	51 (2.7)	19 (2.2)	29 (3.2)	3 (2.8)	0.954
Osteoporosis	223 (2.7)	36 (4.3)	35 (2.7)	12 (1.4)	20 (2.2)	3 (2.8)	
Osteoarthritis[a]	1,040 (12.7)	200 (13.6)	226 (11.9)	121 (13.7)	98 (10.7)	7 (6.6)	<0.001

Notes: Data are presented as numbers (percentages) for categorical variables. [a]Data do not equal the total because evaluations for osteoporosis and osteoarthritis were only performed in subjects aged ≥50 years (normal =8,158; restrictive =1,469; obstructive =1,905; mild =882; moderate =917; severe =106); normal = $FEV_1/FVC \geq 70\%$ and $FEV_1 \geq 80\%$ predicted; restrictive = $FEV_1/FVC \geq 70\%$ and $FEV_1 < 80\%$ predicted; obstructive = $FEV_1/FVC < 70\%$ predicted; Mild = $FEV_1 \geq 80\%$ predicted; moderate =50% ≤ $FEV_1 < 80\%$ predicted; severe = $FEV_1 < 50\%$ predicted.
Abbreviations: BMI, body mass index; DM, diabetes mellitus; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; HDL, high density lipoprotein; LDL, low density lipoprotein.

Comorbidities according to sex and lung function in subjects with obstructive airflow limitation

We analyzed comorbidities according to sex and the severity of COPD. Among individuals with obstructive lung function, 45.3% had mild disease, 49.4% had moderate disease, and 5.3% had severe disease. Hypertension was more common as the airway limitation became more severe. Although the prevalence of DM, hypertriglyceridemia, hypercholesterolemia, and overweight were lower in subjects with severe airway obstruction, the prevalence of underweight increased, but low HDL cholesterol decreased with the severity of obstruction. On the other hand, the prevalence of osteoarthritis decreased with increasing severity of airway obstruction. Osteoporosis seemed to have a higher prevalence as the severity of obstruction increased, but the prevalence of osteopenia in the groups with more severe disease was lower than that in the normal lung function group (Table 2).

When the subjects were divided into men and women, the numbers of ever smokers (50.9% vs 23.7%), DM (17.3% vs 12.0%), hypertriglyceridemia (17.6% vs 12.6%), and low HDL cholesterol (35.0% vs 19.7%) were higher in men with obstructive lung function than in women with obstructive lung function. In contrast, women with obstructive lung function more frequently had hypercholesterolemia (18.0% vs 12.8%), high LDL cholesterol (31.9% vs 23.6%), osteoarthritis (18.3% vs 8.9%), anemia (9.5% vs 6.2%), and osteoporosis (5.0% vs 1.0%) (Table 3). Hypertension, underweight, overweight, and osteoarthritis showed similar trends between men and women (Figure 2). However, there were differences in trends for dyslipidemia between men and women. In men, the prevalence of all kinds of dyslipidemia decreased in the severe obstructive lung function group; in women, the prevalence of dyslipidemia increased rather than decreased in the severe obstructive lung function group, with the exception of hypercholesterolemia (Figure 3A–D).

Discussion

Most COPD patients also show other diseases that may affect the prognosis. Compared with patients without COPD, patients with COPD had more than twice the number of comorbidities, longer hospital stays, and higher in-hospital mortality rates. Some of these diseases are independently generated, regardless of COPD, but some others share risk factors, such as smoking, or increase the risk of one another. Systemic inflammation, which is characteristic of COPD, is common in other comorbidities, and is thought to be the mechanism that connects COPD with other comorbidities.[7]

Because COPD often develops in long-time smokers in middle age, patients frequently have a variety of other diseases related to either smoking or aging.[8] COPD itself also has significant extrapulmonary effects including weight loss, nutritional abnormalities, and skeletal muscle dysfunction. It can contribute to exercise intolerance and poor health status in patients with COPD.[9]

In this study, as in the previous study, hypertension, DM, and dyslipidemia were more common in COPD patients. However, when we divided the subjects by severity and sex, the results of this study were rather dissimilar to those of the previous study.

In COPD subjects, the prevalence of obesity was 23%.[10–13] The mean BMI was >25 kg/m^2 in Western countries, including Austria, Germany, Canada, and the United States, whereas in the People's Republic of China and the Philippines, mean BMI of COPD subjects was 23.3 and 24.9 kg/m^2, respectively.[14] In a previous study in Korea, obesity (BMI ≥23 kg/m^2) was observed in 23.5% of COPD patients.[15] In our study, prevalence of obesity (BMI ≥23 kg/m^2) was 28.5%, and mean BMI was 24.2 kg/m^2. Prevalence of obesity and mean BMI can vary depending on country and race. However, most available data suggest that obesity is more prevalent in patients with COPD than in the general population, depending on the severity of chronic airflow limitation; an exception was the study by Steuten et al[16] who had reported that the rate of obesity decreased in subjects with severe airway obstruction. As in our study, a previous study reported in Korea showed that subjects with airway obstruction had lower BMI and fat free mass index values, and the reductions were prominent in subjects with severe airway obstruction.[17] These data showed the pathognomonic relationship between BMI and the degree of airway obstruction in Asians, including Koreans. Increased work of breathing, higher total daily energy expenditure, catabolic energy balances, and systemic inflammatory responses can be causes of low BMI.[18–20] Moreover, low BMI can also be an independent risk factor for mortality in patients with COPD.[21,22] Therefore, physicians should pay more attention to the nutritional and functional status of patients with COPD.

Cardiovascular disease is the most important and the most frequent comorbidity in COPD.[8] Hypertension is the most important factor in cardiovascular disease, and it has a major influence on prognosis.[7] In Western countries, approximately 17%–55% of COPD patients had hypertension;[12,23–28] a previous study in Korea reported a prevalence of 39.4%.[15] Although in COPD patients, the mechanism of cardiovascular disease – including hypertension – is not yet quite clear,

Table 3 Comorbidities according to sex and lung function in subjects with obstructive airflow limitation

Sex	Male					Female				
Obstructive severity	Total	Mild	Moderate	Severe	P-value	Total	Mild	Moderate	Severe	P-value
Comorbidity	1,434	664 (9.5%)	695 (10.0%)	75 (1.1%)		674	290 (3.16%)	347 (3.78%)	37 (0.40%)	
Smoking status[a]										
Never	184 (12.8)	81 (20.1)	95 (20.7)	8 (0.2)	<0.001	483 (71.7)	203 (74.9)	260 (77.4)	20 (55.6)	<0.001
Former	214 (14.9)	93 (23.0)	102 (22.3)	19 (36.5)		60 (8.9)	22 (8.1)	31 (9.2)	7 (19.4)	
Current	516 (36.0)	230 (56.9)	261 (57.0)	25 (48.1)		100 (14.8)	46 (17.0)	45 (13.4)	9 (25.0)	
Hypertension	718 (50.1)	326 (49.6)	353 (51.3)	39 (52.7)	<0.001	317 (47.0)	130 (45.3)	166 (48.5)	21 (56.8)	<0.001
Diabetes Mellitus	248 (17.3)	101 (16.2)	136 (20.6)	11 (16.7)	<0.001	81 (12.0)	36 (14.0)	42 (13.2)	3 (8.6)	<0.001
Anemia	89 (6.2)	41 (6.4)	43 (6.4)	5 (7.0)	<0.001	64 (9.5)	32 (11.8)	28 (8.5)	4 (11.4)	0.409
Dyslipidemia										
Hypercholesterolemia	184 (12.8)	77 (12.4)	101 (15.3)	6 (9.1)	0.111	121 (18.0)	45 (17.7)	69 (21.7)	7 (20.6)	<0.001
Hypertriglyceridemia	252 (17.6)	108 (19.9)	138 (24.3)	6 (10.2)	0.009	85 (12.6)	42 (18.0)	37 (13.5)	6 (19.4)	0.015
Low HDL cholesterol	502 (35.0)	234 (38.4)	247 (38.2)	21 (33.3)	<0.001	133 (19.7)	62 (26.7)	63 (22.1)	8 (26.7)	<0.001
High LDL cholesterol	339 (23.6)	148 (25.9)	175 (28.3)	16 (25.8)	<0.001	215 (31.9)	84 (35.9)	119 (40.1)	12 (44.4)	<0.001
Obesity										
BMI <18.5 kg/m²	47 (3.2)	11 (1.7)	21 (3.0)	15 (18.9)	<0.001	24 (3.6)	7 (2.4)	12 (3.5)	5 (14.3)	<0.001
18.5 kg/m² ≤ BMI <23.0 kg/m²	980 (68.3)	492 (72.6)	440 (66.3)	48 (64.9)		465 (69.0)	209 (72.1)	231 (66.6)	25 (71.4)	0.015
23.0 kg/m² ≤ BMI	417 (29.1)	171 (25.8)	234 (33.7)	12 (16.2)		183 (27.2)	74 (25.5)	104 (30.0)	5 (14.3)	<0.001
Osteoporosis[b]										
Osteopenia	22 (1.7)	6 (1.0)	15 (2.4)	1 (1.4)	0.256	29 (4.9)	13 (4.9)	14 (4.7)	2 (5.9)	0.862
Osteoporosis	13 (1.0)	2 (0.3)	2 (0.3)	9 (12.5)		30 (5.0)	10 (3.8)	18 (6.0)	2 (5.9)	
Osteoarthritis[b]	117 (8.9)	65 (10.5)	47 (7.6)	5 (6.9)	<0.001	109 (18.3)	56 (21.3)	51 (17.0)	2 (5.9)	<0.001

Notes: Data are presented as numbers (percentages) for categorical variables. [a]The sums of some data do not equal the total due to missing data. [b]Data do not equal the total because evaluations for osteoporosis and osteoarthritis were only performed in subjects aged ≥50 years (male, obstructive =1,308; mild =619; moderate =617; severe =72; female, obstructive =300; severe =34); normal = FEV$_1$/FVC ≥70% and FEV$_1$ ≥80% predicted; restrictive = FEV$_1$/FVC ≥70% and FEV$_1$ <80% predicted; obstructive = FEV$_1$/FVC <70% predicted; mild = FEV$_1$ ≥80% predicted; moderate =50% ≤ FEV$_1$ <80% predicted; severe = FEV$_1$ <50% predicted. **Abbreviations:** BMI, body mass index; DM, diabetes mellitus; FEV$_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; HDL, high density lipoprotein; LDL, low density lipoprotein.
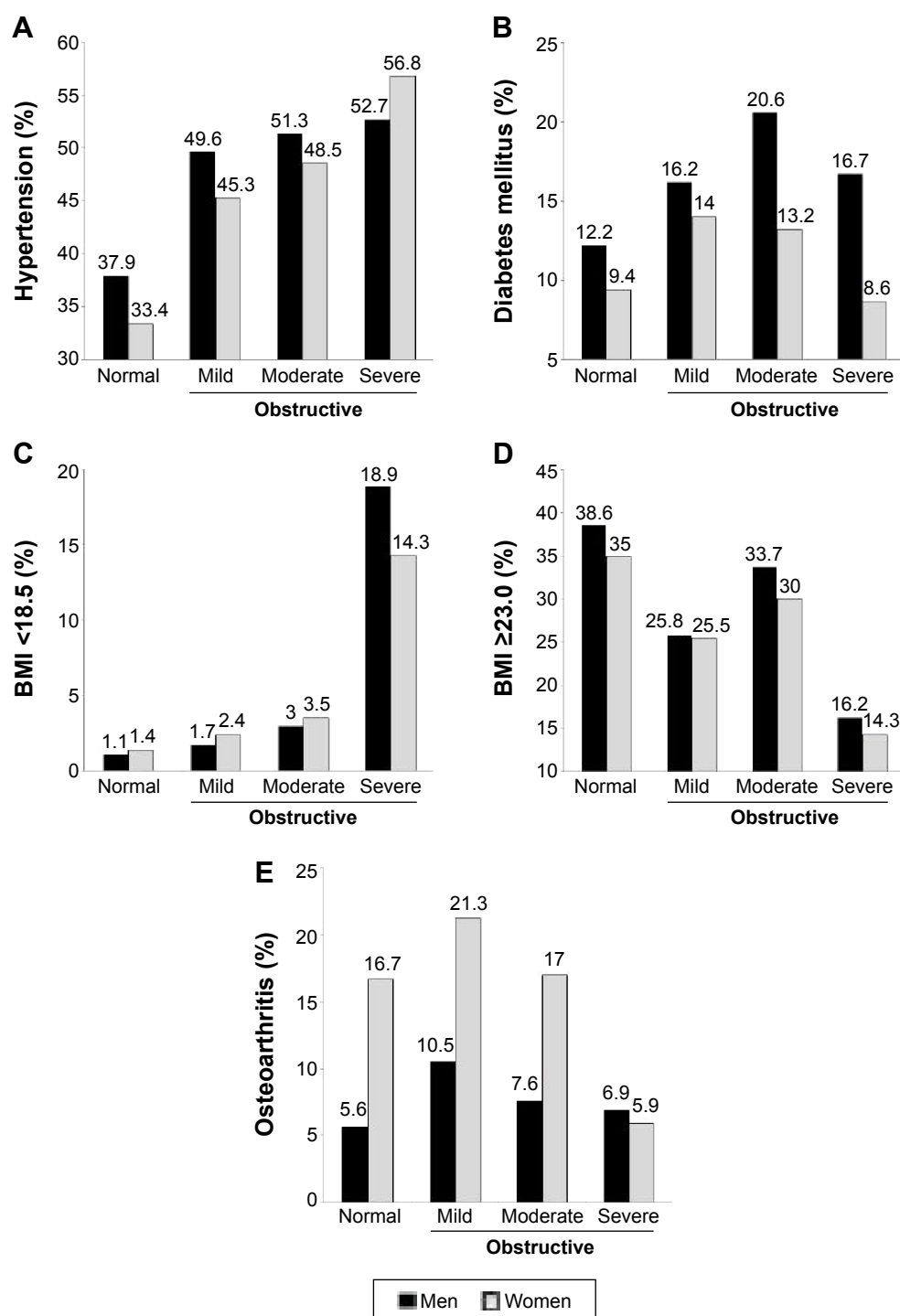
Figure 2 Prevalence of hypertension (**A**), DM (**B**), underweight (**C**) and overweight (**D**), and osteoarthritis (**E**) by sex and severity of obstructive airflow limitation.
Notes: Normal = $FEV_1/FVC \geq 70\%$ and $FEV_1 \geq 80\%$ predicted; obstructive = $FEV_1/FVC <70\%$; mild = $FEV_1 \geq 80\%$ predicted; moderate =$50\% \leq FEV_1 <80\%$ predicted; severe $FEV_1 <50\%$ predicted.
Abbreviations: BMI, body mass index; DM, diabetes mellitus; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

increasing age and smoking are the most important factors in COPD. In this study, the prevalence of hypertension was 49.6%. Moreover, the findings showed that the prevalence of hypertension increases with the severity of obstruction, regardless of sex (Figure 2A).

DM occurs frequently in COPD and is being increasingly reported in many studies, and the prevalence is reported as approximately 10%–25%.[12,23,24,29] The association between the two diseases is not identified precisely, although it is believed to be a consequence of systemic inflammation.[30]
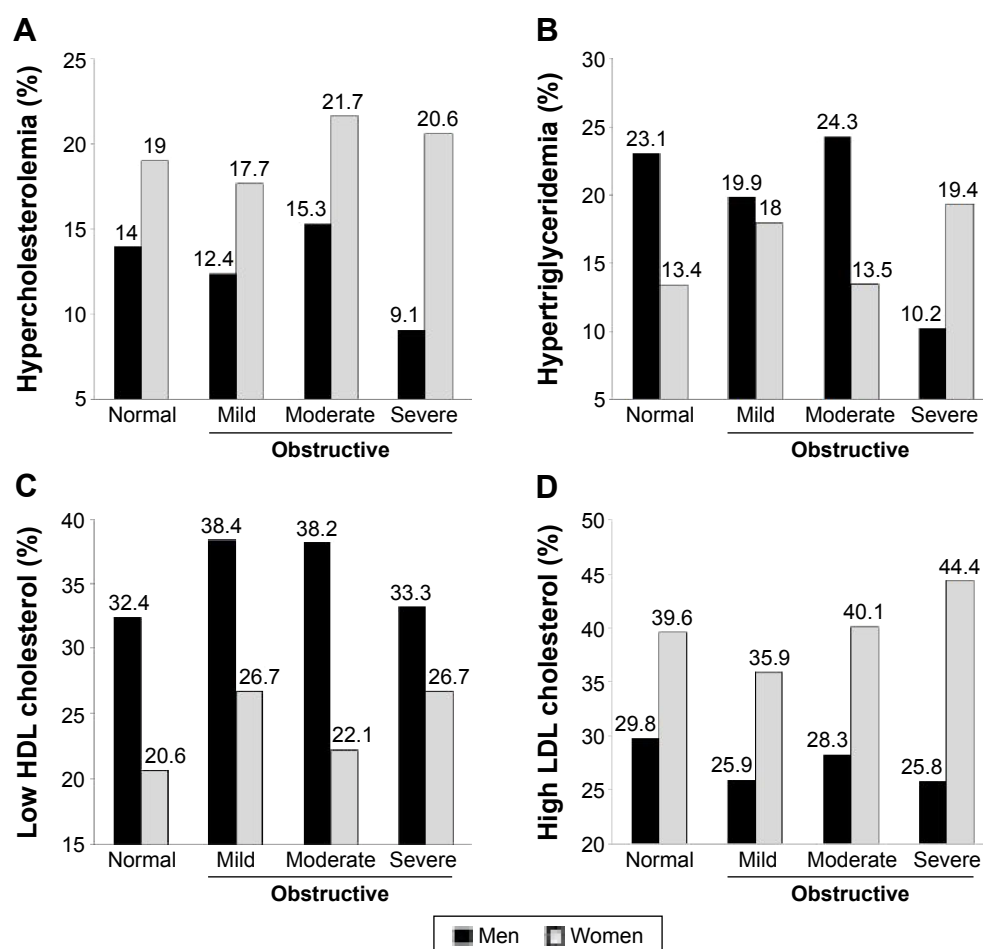
Figure 3 Prevalence of hypercholesterolemia (**A**), hypertriglyceridemia (**B**), low HDL cholesterol (**C**), and high LDL cholesterol (**D**), by sex and severity of obstructive airflow limitation.

Notes: Normal = $FEV_1/FVC \geq 70\%$ and $FEV_1 \geq 80\%$ predicted; Obstructive = $FEV_1/FVC <70\%$; Mild = $FEV_1 \geq 80\%$ predicted; moderate =$50\% \leq FEV_1 <80\%$ predicted; severe $FEV_1 <50\%$ predicted.

Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

DM in patients with COPD is caused partly by common genetic, lifestyle, and environmental factors, as well as the use of systemic corticosteroids, which are used to control lung inflammation in COPD.[31,32] In a previous study in Korea, the prevalence of DM was shown to be 16.6%.[15] DM has no correlation with the severity of airflow limitation, and is more common in men.[25] In this study, the prevalence of DM was 16.8%, and it was more common depending on the severity (except in the severe group), while it showed less prevalence in females (Figure 2B). Low prevalence of DM in COPD can be affected by low BMI,[33] which increases in patients with severe airway obstruction.

Dyslipidemia is one of several parameters employed to diagnose metabolic syndrome. A previous study reported that the prevalence of dyslipidemia in COPD was approximately 36%–52%.[23,27] Dyslipidemia is one of the major comorbidities in COPD; however, most studies have not demonstrated

differences in the prevalence of dyslipidemia between COPD and control subjects.[34] Otherwise, Joo et al[15] reported that the prevalence of dyslipidemia in COPD was 31.7%, which was lower than that in non-COPD subjects. They defined dyslipidemia as an LDL cholesterol level ≥ 130 mg/dL. In our study, the prevalence of dyslipidemia was 72.7%, which was higher than that in the normal lung function group. This difference is rooted in the definition of dyslipidemia. As in the previous study, our study showed that high LDL cholesterol was less common in the obstructive lung function group than in the normal lung function group. However, the prevalence of hypertriglyceridemia and low HDL cholesterol was higher in the obstructive lung function group than in the normal lung function group. Characteristically, the prevalence of all forms of dyslipidemia decreased in the severe group (Table 2). This phenomenon appears prominently in men. Low BMI would have a profound influence on results. A general increasing

trend marks the prevalence of dyslipidemia, with increasing BMI in both men and women with age.[35,36] However, in women, it increased rather than decreased in the severe group, despite a finding that underweight was predominant in the severe obstructive lung function group (Figure 3). This might be due to the mild severity of airway obstruction and racial/ethnic differences,[37] or the low percentage of smokers and old age in female COPD patients.

Anemia is usually seen in 10%–30% of COPD patients.[38] Anemia is a cause of dyspnea and contributes to functional limitation in anemic patients. The mechanism by which patients with COPD develop anemia remains unclear. Systemic inflammation, neurohormonal activation – both of which are associated with smoking – and cardio–renal syndrome, which involves activation of the renin–angiotensin–aldosterone system, were thought to be the mechanisms causing anemia in COPD patients.[39] In Korea, the prevalence of anemia in the obstructive lung function group was previously found to be 7.6%; our study also showed a prevalence of 7.6%. John et al[40] reported that, because of hypoxia, patients with advanced COPD showed significantly higher hemoglobin values and lower prevalence of anemia than did patients with COPD in stage 0. In our study, there was no association with severity in both men and women. Mean hemoglobin level was approximately 14.9–15.0 g/dL in men, and approximately 13.0–13.3 g/dL in women at all stages of obstruction. Moreover, there was no difference in the prevalence of anemia relative to the severity of COPD. These prevalence findings may be contingent upon patient characteristics and the diagnostic criteria used.[41] Women were significantly more likely than men to be anemic (6.2% vs 9.5%); when the subject population was divided into men and women, women from the obstructive lung function group did not show differences from the normal lung function group (men: 3.7% vs 6.2%; $P<0.001$, women: 11.8% vs 9.5%; $P<0.306$). We considered that the effects of other causes (eg, menopause, other chronic diseases) are more clinically important than those of systemic inflammation of COPD in women ≥40 years old. Further studies are needed on this topic. To our knowledge, this is the first study to have mentioned the relationship between anemia, severity of COPD, and sex.

Osteoporosis is a major comorbidity in COPD.[7] It is also associated with poor health status and prognosis. Osteoporosis is more common in subjects with low BMI and low fat-free mass.[42,43] A higher GOLD stage and a low FEV$_1$ have been shown to be related to osteoporosis in the presence of low bone mineral density (BMD).[44,45] Physical inactivity, smoking, poor diet, and systemic corticosteroids seem to have important effects on osteoporosis. Again, systemic inflammation in COPD patients can be a risk factor in osteoporosis.[46] The prevalence of osteoporosis in COPD is 8.4%–69%, and the prevalence of osteopenia is 28%–67%.[47] In Korea, an osteoporosis prevalence of 7.9% was reported in COPD patients.[15] This difference may be due to differences in patient characteristics and ethnicity. Our study also showed a high prevalence of osteoporosis among patients in the severe obstructive lung function group. However, the prevalence of osteopenia was lower than that in the normal lung function group (Table 2). Because the number of cases of osteopenia and osteoporosis in the severe obstructive lung function group was too small for accurate determination, it is necessary to perform studies with more subjects.

There are some studies that have reported the association between COPD and arthritis. The rate of osteoarthritis in patients with COPD has been shown to be 22%–70%.[48,49] In almost all of these studies, arthritis was defined via self-report, or the researchers studied only rheumatic arthritis. A previous study in Korea found no association between arthritis and COPD, although that study was dependent upon questionnaires.[15] Our study excluded the subjective symptoms of the patient, and diagnosed arthritis by using a radiological objective image; 11.9% of COPD subjects had osteoarthritis. More than half (61.1%) of these cases were accompanied by symptoms (data were not shown). To our knowledge, this is the first study that has mentioned the relationship between osteoarthritis, severity of COPD, and sex.

In this study, we investigated the relationship between COPD airflow limitation severity and comorbidities with objective measurements. Echave-Sustaeta et al[50] mentioned that severity is not an independent predictor of comorbidity. However, we showed that many comorbidities were associated with severity. Our study had several strengths. First, we used data from a nationwide survey, with a nationally representative stratified random sample that was comprised of various objective data points. Thus, we could use a much larger sample size than other studies. We also obtained the data on comorbidities (eg, arthritis, osteoroposis) by laboratory tests and image study, not only interviews. Second, to our knowledge, this is the first study that was analyzed separately for both sex and severity. Third, we did not exclude restrictive lung disease subjects. Therefore, our study showed characteristics of the subjects with restrictive lung disease.

However, this study had some limitations. First, although this was a prevalence study of comorbidities in COPD, there was no analysis about other important comorbidities such as

cardiovascular disease and cancer because no objective data were available regarding these diseases. While previous studies of COPD comorbidities were based on interviews, this study was carried out on the basis of laboratory tests, image studies, and physical examination. Even though questionnaires included questions on the history of cardiovascular disease, depression, lung cancer, pulmonary tuberculosis, asthma, and allergic rhinitis, they were not objective. For that reason, we did not use this information in our study. So we just described these comorbidities according to a self-reported questionnaire on Table S1. Second, we included subjects with airway obstruction caused by other diseases, such as pulmonary tuberculosis, bronchiectasis, and asthma. This could have overdetermined the number of subjects with airway obstruction. Third, our spirometry data were prebronchodilator spirometry data. Fourth, disease severity in most subjects with airway obstructive disease was classified as either mild or moderate. When divided into men and women, many parameters had fewer than five subjects in the severe airway obstructive lung disease group, a circumstance that could have affected the result.

Conclusion

In conclusion, this study showed that hypertension and underweight are common comorbid diseases in COPD patients, and are more increased as the severity of airflow obstruction increased in both men and women. DM, hypertriglyceridemia, and low HDL cholesterol are also more common in subjects with airway obstruction, although their prevalence is lower in subjects with severe airway obstruction.

Author contributions

Hee Jin Park, contributed to the study design, data analysis and interpretation, and writing of this manuscript.

Ah Young Leem, contributed to the study design, data analysis and interpretation, and review of this manuscript.

Sang Hoon Lee, contributed to the study design, data analysis and interpretation, and review of this manuscript.

Ju Han Song, contributed to the study design, data analysis and interpretation, and review of this manuscript.

Moo Suk Park, contributed to the study design, data analysis and interpretation, and review of this manuscript.

Young Sam Kim, contributed to the study design, data analysis and interpretation, and review of this manuscript.

Se Kyu Kim, contributed to the study design, data analysis and interpretation, and writing of this manuscript.

Joon Chang, contributed to the study design, data analysis and interpretation, and writing of this manuscript.

Kyung Soo Chung, contributed to the study design, data analysis and interpretation, and writing of this manuscript.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

Table S1 Comorbidities according to self-reported questionnaire

Comorbidity	Normal	Restrictive	Obstructive	Obstructive severity			P-value
				Mild	Moderate	Severe	
	12,224 (75.6%)	1,819 (11.3%)	2,108 (13.1%)	954 (45.3%)	1,042 (49.4%)	112 (5.3%)	
Cardiovascular disease							
Ischemic heart disease	321 (2.6)	82 (4.5)	80 (3.8)	33 (3.5)	43 (4.1)	4 (3.6)	<0.001
Angina pectoris	238 (1.9)	53 (2.9)	44 (2.1)	20 (2.1)	22 (2.1)	2 (1.8)	0.037
Myocardial infarction	101 (0.8)	33 (1.8)	38 (1.8)	14 (1.5)	22 (2.1)	2 (1.8)	<0.001
Stroke	118 (1.0)	64 (3.5)	63 (3.0)	28 (2.9)	30 (2.9)	10 (8.9)	<0.001
Depression	1,922 (15.7)	289 (15.9)	265 (12.6)	115 (12.1)	130 (12.5)	20 (17.9)	<0.001
Lung cancer	3 (0.0)	7 (0.4)	9 (0.4)	1 (0.1)	7 (0.7)	1 (0.9)	<0.001
Pulmonary tuberculosis	604 (4.9)	163 (9.0)	229 (10.9)	92 (9.6)	168 (16.1)	39 (34.8)	<0.001
Asthma	366 (3.0)	108 (5.9)	273 (13.0)	67 (7.0)	153 (14.7)	53 (47.3)	<0.001
Allergic rhinitis	415 (3.4)	74 (4.1)	67 (3.2)	24 (2.5)	41 (3.9)	2 (1.8)	0.734

Notes: Data are presented as numbers (percentages) for categorical variables. Normal = $FEV_1/FVC \geq 70\%$ and $FEV_1 \geq 80\%$ predicted; restrictive = $FEV_1/FVC \geq 70\%$ and $FEV_1 < 80\%$ predicted; obstructive = $FEV_1/FVC < 70\%$ predicted; mild = $FEV_1 \geq 80\%$ predicted; moderate = $50\% \leq FEV_1 < 80\%$ predicted; severe = $FEV_1 < 50\%$ predicted.
Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.