ORIGINAL RESEARCH

Characteristics and self-rated health of overlap syndrome

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Background and objective: Overlap syndrome shares features of both asthma and chronic obstructive pulmonary disease (COPD). The aim of this study was to investigate characteristics of overlap syndrome and their effect on self-rated health (SRH).

Methods: We analyzed data from the Fourth Korea National Health and Nutrition Examination Survey of 2007–2009. Subjects with acceptable spirometry and available wheezing history were included. Subjects were classified into four groups based on forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) results and the presence or absence of self-reported wheezing for the previous 12 months: 1) COPD group, defined as having FEV_1/FVC <0.7 without self-reported wheezing history; 2) asthma group, defined as having self-reported wheezing history without FEV_1/FVC <0.7; 3) overlap syndrome group, having both FEV_1/FVC <0.7 and wheezing history; and 4) non-obstructive disease (NOD) group, having neither FEV_1/FVC <0.7 nor self-reported wheezing. SRH was categorized as better or lower based on responses to a questionnaire.

Results: From a total 9,104 subjects, 700 were assigned to the COPD group, 560 to the asthma group, 210 to the overlap syndrome group, and 7,634 to the NOD group. Compared to the other groups, subjects in the overlap syndrome group were more likely to have low lung function, a high proportion of smokers, low socioeconomic status, short education duration, lower SRH, and past diagnosis of pulmonary tuberculosis or bronchiectasis. Multiple logistic regression analysis revealed that both overlap syndrome and asthma groups were independently associated with lower SRH after adjustment for age, sex, socioeconomic status, education level, smoking status, comorbidities, and lung function. Female, old age, low education level, low economic status, smoker and other comorbidities were also associated with lower SRH.

Conclusion: Overlap syndrome was accompanied by high morbidity and was associated with lower SRH, which needs more appropriate care.

Keywords: chronic obstructive lung disease, asthma, overlap syndrome, self-rated health, COPD

Introduction

Chronic obstructive pulmonary disease (COPD) and asthma are the most common airway diseases. While COPD patients are likely to be older, smokers, and have persistent and usually progressive airflow limitation, patients with asthma tend to be younger, non-smokers, and have atopy and/or allergies and reversible airway obstruction.[1] However, in practice, airflow limitation that is not fully reversible is insufficient to explain COPD. Since some patients with asthma also develop poorly reversible airway limitation, differential diagnosis is sometimes difficult for clinicians. In the elderly with COPD, variable airway obstruction is commonly observed. Approximately half of COPD patients have

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both COPD and asthma (overlap syndrome), and coexistence of the two diseases increases with age.[2] Increased airway hyper-responsiveness (AHR) is reported to be associated with increased COPD exacerbations and overall mortality.[3]

Overlap syndrome is defined as having both AHR and incompletely reversible airway obstruction.[4,5] In patients with overlap syndrome, forced expiratory volume in one second (FEV_1) does not return to normal and often worsens over time. Since these patients are generally excluded from studies examining either disease, the clinical implications of overlap syndrome remain poorly recognized.[4] Despite a high prevalence of COPD and asthma in the general Korean population,[6–8] clinical features of patients with overlap syndrome have not been well described.

The aim of our study was to characterize overlap syndrome and investigate its impact on self-rated health (SRH) by using the data from the Fourth Korea National Health and Nutrition Examination Survey of 2007–2009 (KNHANES IV survey).[8]

Methods
Subjects
Data from the KNHANES IV survey conducted between July 2007 and December 2009 were reviewed retrospectively. The survey was conducted as a cross-sectional observational study using complex, stratified multistage cluster sampling. It was designed as a rolling sample survey based on the 2005 Korean population and housing census; once subjects were

interviewed, they were not interviewed again. Data were obtained from independent samples for each year, representing the total non-institutionalized population of Korea. Among the 24,971 potential subjects, 18,406 were >19 years. We excluded subjects with unavailable respiratory symptoms and poor spirometry results; that is, results that did not meet an acceptable flow-volume loop or were not reproducible. Finally, 9,104 subjects were enrolled (Figure 1). The study was approved by the Korea Centers for Disease Control and Prevention Institutional Review Board, and informed consent was obtained from each participant.

Medical histories of respiratory symptoms and comorbidities, duration of education, and socioeconomic status were obtained by questionnaire. Height, weight, waist circumference, and blood pressure were measured in all subjects. Triglyceride and high-density lipoprotein (HDL) cholesterol levels were obtained after 12 hours of fasting. Spirometry was performed on all subjects >19 years. FEV_1 and forced vital capacity (FVC) were measured, and a predicted ratio for each parameter was calculated based on age, sex, height, and race.

Definitions
Subjects were assigned to one of four groups based on data reported for the previous 12 months: 1) the COPD group was defined as subjects having an FEV_1/FVC ratio <0.7 without history of self-reported wheezing; 2) the asthma
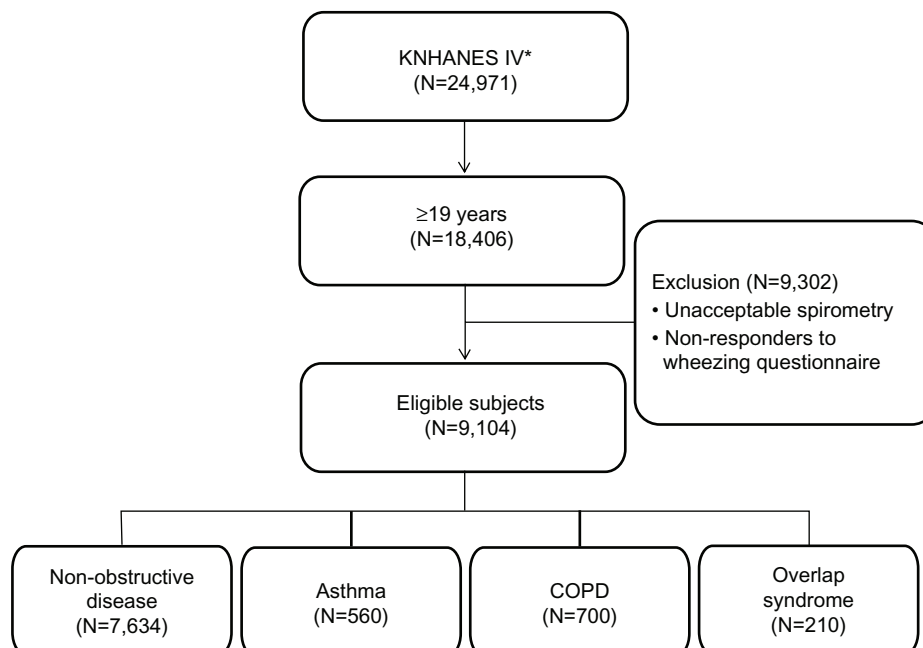

Figure 1 Study design.
Note: *KNHANES IV, Fourth Korea National Health and Nutrition Examination Survey, 2007–2009.[8]
Abbreviation: COPD, chronic obstructive pulmonary disease.

group was comprised of subjects with a history of wheezing without $FEV_1/FVC <0.7$; 3) the overlap syndrome group included subjects with both $FEV_1/FVC <0.7$ and a history of self-reported wheezing; the remaining subjects made up the non-obstructive disease (NOD) group.

SRH was assessed by asking the following question: "Would you say your general health status is excellent, very good, good, fair, or poor?" Based on responses, subjects were categorized into two outcome measures: better (excellent, very good, and good), and lower (fair and poor).[9] Standard questions were used to assess underlying disease such as, "Has a medical doctor ever told you that you had the following diseases: COPD, asthma, pulmonary tuberculosis, bronchiectasis, hypertension, diabetes mellitus, cerebrovascular disease, osteoarthritis, allergic rhinitis, or atopic dermatitis?" with the response alternatives "Yes" or "No" for each option. They were also asked about their wheezing history using the question: "Have you had wheezing or whistling in your chest at any time during the previous year?" Metabolic syndrome was diagnosed when more than three of the five criteria outlined by the National Cholesterol Education Program's Adult Treatment Panel III (NCEP/ATP III) were met.[10] Mean blood pressure was used for diagnosis of metabolic syndrome. Never-smoker was defined as having smoked less than five packs of cigarettes during their lifetime.

Statistical analyses

Descriptive analysis was performed for all variables. Categorical variables were analyzed by chi-square test. Regression analysis for sampling survey data and Tukey's post hoc test were used to compare continuous numeric variables among the four groups. All estimates were calculated using the appropriate sampling weight provided in KNHANES IV, and standard errors (SE) were calculated reflecting complex design and survey weight. Simple logistic regression analysis was used to evaluate association between individual factors and lower SRH, and multiple logistic regression analysis of possible risk factors was performed using SAS version 9.2 statistical software (SAS institute Inc., Cary NC, USA). A P-value <0.05 was considered statistically significant.

Results
Subject characteristics

Of the 9,104 subjects with eligible spirometry and available wheezing history, 700 were admitted to the COPD group; 560 to the asthma group; 210 to the overlap syndrome group; and 7,634 to the NOD group. Epidemiological characteristics of the

subjects are summarized in Table 1 and comparisons between included and excluded subjects are shown in Table S1.

Table 1 shows that the mean age of all subjects was 44.4 years, whereas mean age of the COPD group was 60.7 years, and that of the overlap syndrome group 60.4 years. The overlap syndrome and COPD groups showed a higher proportion of males compared to the asthma group (67% and 69%, respectively, versus 46%). There were more smokers in the overlap syndrome group (73%) than in the COPD, asthma, and NOD groups (65%, 54%, and 44%, respectively). Subjects with overlap syndrome had the highest proportion of low socioeconomic status and fewer than 6 years of education, followed by the COPD and asthma groups. Metabolic syndrome and osteoarthritis were most prevalent in the overlap syndrome group. Except for metabolic syndrome, all comorbidities were more common in the COPD and overlap syndrome groups than the asthma group, which was likely due to their higher mean age. Despite higher mean age and prevalence of comorbidities (except for metabolic syndrome), the COPD group showed better SRH than the asthma group.

To identify factors associated with each airway disease, we performed multinomial logistic regression analysis; results are summarized in Table 2. While sex was associated with both asthma and COPD, old age increased the risks in both COPD and overlap syndrome groups. Low socioeconomic status was associated with overlap syndrome, and short education duration and smoking status were associated with all airway diseases. While lower body mass index (BMI) increased risk of both COPD and overlap syndrome, being overweight seemed to decrease risk of COPD. Except for osteoarthritis, other comorbidities were not associated with AHR.

Table 3 shows the lung function of subjects. FEV_1/FVC, FEV_1, and FVC were lowest in the overlap syndrome group. Table 4 shows the history of respiratory and allergic disease based on questionnaire responses. Subjects previously diagnosed with pulmonary tuberculosis or bronchiectasis were the most common subjects in the overlap syndrome group compared to the other three groups.

Factors associated with lower SRH

Independent factors associated with lower SRH are summarized in Table 5. In a multiple logistic regression analysis using NOD as a reference, overlap syndrome was the strongest factor associated with lower SRH (odds ratio [OR]: 2.31, 95% confidence interval [CI]: 1.51–3.55, $P<0.001$), followed by the asthma group (OR: 2.04, 95% CI: 1.58–2.65, $P<0.001$).

Table 1 Epidemiological characteristics

Variables	Overall (N=9,104)	NOD (N=7,634)	Asthma (N=560)	COPD (N=700)	Overlap syndrome (N=210)	P-value
Sex (%)						
Male	4,067	3,216 (49)	221 (46)	500 (69)	130 (67)	<0.001
Age, years						
Mean ± SE	44.4±0.3	42.9±0.3	44.8±0.9	60.7±0.9	60.4±1.9	<0.001*
19–39	2,410	2,223 (45)	150 (44)	28 (10)	9 (11)	<0.001
40–59	4,062	3,593 (40)	216 (34)	184 (30)	69 (34)	
≥60	2,632	1,818 (15)	194 (22)	488 (60)	132 (55)	
Socioeconomic status						
>75th percentile	2,354	1,999 (26)	151 (29)	163 (23)	41 (15)	0.025
25–75th percentile	4,597	3,893 (51)	256 (47)	351 (52)	97 (50)	
<25th percentile	2,153	1,742 (23)	153 (24)	186 (25)	72 (35)	
Education duration, years						
>12	2,270	2,048 (31)	116 (26)	90 (14)	16 (8)	<0.001
9–12	3,070	2,726 (42)	167 (39)	140 (23)	37 (20)	
6–9	1,196	972 (10)	64 (10)	127 (19)	33 (16)	
≤6	2,568	1,888 (17)	213 (25)	343 (44)	106 (54)	
Self-rated health						
Better	6,957	6,010 (83)	334 (67)	507 (76)	113 (53)	<0.001
Lower	2,147	1,624 (17)	226 (33)	193 (24)	104 (46)	
Smoking history						
Never-smoker	5,327	4,728 (57)	298 (46)	230 (35)	71 (28)	<0.001
Ex-smoker	1,696	1,348 (18)	44 (6)	252 (33)	52 (28)	
Current smoker	2,081	1,558 (26)	218 (48)	218 (32)	87 (45)	
BMI, kg/m²						
Mean ± SE	24.2±0.1	24.3±0.1	24.8±0.2	23.3±0.2	23.9±0.4	<0.001
<18.5	202	154 (2)	7 (2)	28 (5)	13 (5)	<0.001
18.5–25	5,518	4,604 (60)	282 (53)	499 (68)	133 (63)	
>25	3,384	2,876 (38)	271 (45)	173 (28)	64 (31)	
Waist circumference, cm						
Mean ± SE	82.7±0.2	82.6±0.2	84.5±0.7	82.9±0.5	84.9±1.0	>0.050**
Comorbidities						
Hypertension	1,892	1,446 (15)	158 (19)	217 (29)	71 (28)	<0.001
Diabetes mellitus	716	550 (6)	51 (6)	91 (13)	24 (13)	<0.001
Cerebrovascular disease	342	244 (2)	30 (4)	55 (6)	13 (6)	<0.001
Metabolic syndrome***	1,639	1,312 (25)	148 (34)	128 (32)	51 (39)	<0.001
Osteoarthritis	1,351	1,028 (10)	144 (17)	132 (18)	47 (23)	<0.001

Notes: Data are presented as mean ± SE or number (percentage). *$P<0.001$ were obtained except asthma versus NOD group ($P=0.173$) and COPD versus overlap syndrome group ($P=0.998$) by post hoc Tukey's method; **$P>0.05$ were obtained except asthma group versus NOD group, $P=0.021$ by post hoc Tukey's method. ***A total of 5,551 subjects were analyzed.
Abbreviations: NOD, non-obstructive disease; COPD, chronic obstructive pulmonary disease; N, number of subjects; BMI, body mass index; SE, standard error.

Adjusting for other factors such as sex, age, smoking, other comorbidities and FEV_1, the COPD group lost statistical significance. In addition, female sex, age >60 years, low socioeconomic status, education duration <9 years, presence of smoking history, and FEV_1 <50% were also associated with lower SRH. Neither obesity (BMI ≥25 kg/m²) nor low weight (BMI <18.5 kg/m²) were associated with lower SRH.

Discussion

The current study demonstrated that the overlap syndrome group makes up a significant portion of obstructive lung disease with high burden of morbidity based on data from a national population-based survey. Overlap syndrome was also independently associated with lower SRH. Subjects were classified into four groups using FEV_1/FVC results for airway obstruction and wheezing history as markers of AHR. These groups showed significant differences in variable individual factors during analyses, which provided validity to the study design. Each group represented a unique disease entity. For example, the COPD group had a greater number of clinical factors (increased age, higher prevalence of smoking, and comorbidities) compared to the asthma group. The overlap syndrome group showed a similar trend

Table 2 Multinomial logistic regression analysis to identify factors associated with airway diseases

Variables	Asthma			COPD			Overlap syndrome		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Sex									
Male	1			1			1		
Female	1.81	1.28–2.58	0.0009	0.41	0.28–0.60	<0.0001	0.61	0.34–1.07	0.087
Age, years									
19–39	1			1			1		
40–59	0.88	0.66–1.17	NS	2.90	1.82–4.63	<0.0001	2.77	1.09–7.04	0.032
≥60	1.26	0.84–1.89	NS	14.53	8.83–23.90	<0.0001	9.50	3.39–26.63	<0.0001
Socioeconomic status, percentile									
>75th	1			1			1		
<25th	0.79	0.58–1.08	NS	1.12	0.83–1.50	NS	1.87	1.11–3.16	0.02
25–75th	0.75	0.57–0.99	0.04	1.07	0.81–1.41	NS	1.42	0.90–2.25	NS
Education duration, years									
>12	1			1			1		
≤6	1.45	1.00–2.09	0.048	2.16	1.46–3.20	0.0001	4.28	1.87–9.79	0.0006
6–9	1.15	0.75–1.76	NS	2.08	1.38–3.13	0.0004	2.58	1.00–6.62	0.049
9–12	1.03	0.75–1.42	NS	1.13	0.78–1.64	NS	1.32	0.65–2.68	NS
Smoking									
Never-smoker	1			1			1		
Ex-smoker	0.67	0.42–1.06	0.085	1.50	1.04–2.17	0.032	2.64	1.44–4.83	0.002
Current	4.06	2.92–5.64	<0.0001	1.99	1.39–2.87	0.0002	5.07	3.04–8.46	<0.0001
BMI, kg/m^2									
18.5–25	1			1			1		
<18.5	0.85	0.32–2.26	NS	2.14	1.05–4.35	0.036	2.57	1.18–5.57	0.02
≥25	1.25	0.99–1.58	0.056	0.65	0.51–0.83	0.0005	0.74	0.48–1.14	NS
Hypertension									
No	1			1			1		
Yes	1.02	0.77–1.35	NS	0.86	0.68–1.08	NS	0.86	0.57–1.30	NS
Diabetes mellitus									
No	1			1			1		
Yes	0.86	0.57–1.31	NS	1.05	0.77–1.44	NS	1.12	0.62–2.03	NS
Cerebrovascular disease									
No	1			1			1		
Yes	1.56	0.97–2.53	0.068	0.87	0.60–1.28	NS	0.92	0.43–1.95	NS
Osteoarthritis									
No	1			1			1		
Yes	1.61	1.19–2.17	0.002	1.09	0.78–1.52	NS	1.41	0.87–2.31	NS

Abbreviations: COPD, chronic obstructive pulmonary disease; OR, odds ratio; CI, confidence interval; NS, not significant; BMI, body mass index.

Table 3 Lung function

Variables	Overall (N=9,104)	NOD (N=7,634)	Asthma (N=560)	COPD (N=700)	Overlap syndrome (N=210)	P-value
Lung function						
FEV$_1$/FVC	0.80±0.0	0.82±0.0	0.81±0.0	0.64±0.0	0.60±0.0	<0.001**
FEV$_1$% predicted	92.0±0.2	93.6±0.2	90.4±0.7	77.2±0.7	69.4±1.5	<0.001
FVC% predicted	92.9±0.2	93.3±0.2	90.9±0.7	90.0±0.7	86.2±1.4	<0.050‡
FEV$_1$% predicted						
≥80	7,616	6,796 (89)	448 (81)	320 (45)	52 (27)	<0.001
50–80	1,422	835 (11)	110 (19)	351 (51)	126 (61)	
<50	66	3 (<1)	2 (<1)	29 (4)	32 (12)	

Notes: Data are presented as mean ± SE or number (percentage). **P<0.001 were obtained except asthma versus NOD group, P=0.004 by post hoc Tukey's method. ‡P<0.050 were obtained except COPD group versus asthma group (P=0.794), COPD group versus overlap syndrome group (P=0.060) by post hoc Tukey's method.
Abbreviations: NOD, non-obstructive disease; COPD, chronic obstructive pulmonary disease; N, the number of subjects; FEV$_1$, forced expiratory volume in one second; FVC, forced volume capacity; SE, standard error.

Table 4 Past history of respiratory or allergic diseases based on responses to questionnaires*

Diseases	Overall (N=9,104)	NOD (N=7,634)	Asthma (N=560)	COPD (N=700)	Overlap syndrome (N=210)
COPD	64 (1)	28 (<1)	9 (2)	11 (1)	16 (7)
Asthma	325 (3)	116 (1)	95 (14)	34 (6)	80 (40)
COPD and asthma	15 (<1)	1 (<1)	3 (1)	1 (<1)	10 (4)
Tuberculosis	533 (5)	365 (4)	31 (7)	94 (15)	43 (21)
Bronchiectasis	57 (1)	23 (<1)	7 (1)	10 (1)	17 (6)
Allergic rhinitis	862 (11)	726 (11)	75 (15)	41 (7)	20 (10)
Atopic dermatitis	216 (3)	180 (3)	24 (7)	8 (1)	4 (1)

Notes: Data are presented as number (percentage). *In all comparisons, $P<0.001$ by chi-square test.
Abbreviations: NOD, non-obstructive disease; COPD, chronic obstructive pulmonary disease; N, number of subjects.

Table 5 Factors associated with lower self-rated health (N=9,104)

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	P-value	OR	95% CI	P-value
Sex						
Male	1.00			1.00		
Female	2.04	1.78–2.34	<0.001	2.30	1.83–2.90	<0.001
Age, years						
19–39	1.00			1.00		
40–59	1.71	1.45–2.01	<0.001	1.16	0.97–1.39	0.105
≥60	3.99	3.32–4.79	<0.001	1.29	1.00–1.66	0.049
Socioeconomic status						
>75th percentile	1.00			1.00		
25–75th percentile	1.32	1.12–1.57	0.001	1.23	1.02–1.48	0.028
<25th percentile	1.69	1.39–2.04	<0.001	1.43	1.16–1.76	0.001
Educational duration, years						
>12	1.00			1.00		
9–12	1.39	1.15–1.67	0.005	1.15	0.95–1.39	0.145
6–9	2.26	1.79–2.85	<0.001	1.35	1.05–1.74	0.018
≤6	4.77	3.96–5.74	<0.001	1.91	1.52–2.40	<0.001
Smoking history						
Non-smoker	1.00			1.00		
Ex-smoker	0.84	0.70–1.00	0.055	1.42	1.09–1.84	0.009
Current smoker	0.70	0.60–0.82	<0.001	1.36	1.06–1.75	0.016
Airway disease						
NOD	1.00			1.00		
COPD	1.51	1.20–1.89	0.001	0.92	0.69–1.22	0.559
Asthma	2.33	1.84–2.95	<0.001	2.04	1.58–2.65	<0.001
Overlap syndrome	4.14	2.82–6.08	<0.001	2.31	1.51–3.55	<0.001
Comorbidities						
Hypertension	2.93	2.53–3.40	<0.001	1.53	1.29–1.83	<0.001
Diabetes mellitus	3.78	3.08–4.64	<0.001	2.33	1.83–2.97	<0.001
Cerebrovascular disease	5.64	4.33–7.34	<0.001	3.10	2.23–4.31	<0.001
Osteoarthritis	3.84	3.30–4.48	<0.001	1.86	1.57–2.19	<0.001
BMI, kg/m²						
18.5–25	1.00			1.00		
<18.5	0.97	0.63–1.48	0.877	0.97	0.62–1.51	0.895
≥25	1.25	1.09–1.45	0.002	1.12	0.95–1.32	0.161
FEV_1% predicted						
≥80	1.00			1.00		
50–80	1.45	1.23–1.71	<0.001	1.16	0.96–1.41	0.120
<50	4.91	2.69–8.96	<0.001	2.82	1.34–5.90	0.006

Abbreviations: OR, odds ratio; CI, confidence interval; NOD, non-obstructive disease; COPD, chronic obstructive pulmonary disease; BMI, body mass index; FEV_1, forced expiratory volume in one second; N, number of subjects.

as the COPD group, but most of the clinical factors were worse than those of the COPD group, except for comorbidities. Among subjects of overlap syndrome, almost half of them presented lower SRH, which is the highest rate among the four groups. These results were very similar to those from a previous study that demonstrated that adults with overlap syndrome, asthma, or COPD reported more health impairments compared to those with neither disease, and adults with overlap syndrome and COPD were more likely to have comorbidities.[11]

Despite these distinctive clinical characteristics, the physician diagnostic rate for obstructive disease was well below 20% in the COPD and asthma groups in that study. This suggests that disease severity in each group tended to be low in this population-based study, and/or that some subjects were considerably underdiagnosed. On the other hand, both difficulty in differential diagnosis and lack of comprehension of these diseases were likely to contribute to a low diagnosis rate.

Some COPD patients have shown characteristics of asthma and have been diagnosed as asthmatics. Some asthma patients share the same features of COPD; yet, there has been no consensus on the definition and diagnostic criteria of overlap syndrome. According to the Dutch hypothesis, asthma, chronic bronchitis, and emphysema are different expressions of the same disease entity, and influenced by environmental and genetic influences.[12,13] A cohort study has suggested that asthma could be a risk factor for COPD development.[14]

The clinical features of the overlap syndrome group in the current study were remarkable. The group showed a greater rate of history of structural diseases such as pulmonary tuberculosis and bronchiectasis than the other groups. This could be linked to lower socioeconomic status, since both low economic status and shorter education duration were associated with overlap syndrome. Additionally, 40% of subjects in the overlap syndrome group had been diagnosed with asthma in the past. These results could support the hypothesis that asthma and AHR predispose individuals to develop COPD or fixed airway obstruction later in life.[12] Structural diseases can also be potential predisposing factors.[15–18] Childhood respiratory infection has been associated with airway obstruction and/or bronchiectasis.[19] Another explanation could be that overlap syndrome progressed under the influence of environmental factors like aging, smoking, or undertreatment due to low educational and socioeconomic status. These hypotheses could provide insights for further understanding of obstructive lung disease, including overlap syndrome.

Some degree of airflow obstruction of as much as FEV_1 25–30 mL/year is related to the natural aging process of lung function decrease. Airflow obstruction appears to be more of a fixed pattern in the elderly with asthma, whose symptoms worsen and respond poorly to treatment.[20] Similarly, the prevalence of AHR in COPD patients is increased as much as 3× in the elderly compared to non-elderly patients.[21] Studies have shown that 50% of the elderly with airway disease have airflow variability with some degree of irreversible airway obstruction.[4,22] Likewise, aging and cigarette smoking are other strong risk factors for obstructive lung disease. Smoking increases neutrophilic inflammation and interferes with the anti-inflammatory actions of corticosteroids, ie, steroid resistance.[23] Chronic inflammation and airway remodeling are influenced by smoking in both asthma and COPD patients.

Despite the fact that the COPD group had a greater number of subjects aged ≥60 years with comorbidities and asthma group subjects had more preserved lung function, the COPD group had relatively fewer subjects with lower SRH compared to the asthma group. The overlap syndrome group showed the highest association with lower SRH, followed by the asthma group. The COPD group did not show any associations with the other groups, despite significant association between low FEV_1 and lower SRH. These results support the hypothesis that subjective symptoms rather than objective airflow obstruction results can affect individual SRH.

Many studies have focused on symptoms. The presence of dyspnea has been shown to predict 5 year survival better than airway obstruction in patients with COPD.[24] The BODE Index is a better predictor of mortality than FEV_1 alone; it includes BMI, airflow obstruction, the Modified Medical Research Council Dyspnea Scale (MMRC), and the 6 minute walk distance test for exercise capacity.[25] The recent Global initiative for chronic Obstructive Lung Disease (GOLD) classification includes levels of daily symptoms, particularly self-reported dyspnea by MMRC scale, frequency of exacerbations, and level of lung function to stratify future risk.[1] Using this classification, a population-based study demonstrated the role of dyspnea in COPD even among individuals with relatively preserved FEV_1.[26]

While a previous study showed that patients with overlap syndrome had lower health-related quality of life compared to those with asthma,[27] the current study's asthma group rather than the COPD group showed lower SRH. This inconsistency could be due to differences in study subjects and the questionnaires used. Subjects were from a population-based survey, and most of them were more likely to have mild-to-moderate

airflow limitation, whereas the previous study used patients with a diagnosis of asthma or COPD or both.[27] In that study of search predictors of a decline in health-related quality of life in patients with asthma or COPD, respiratory symptoms were an important predictor of decline in health-related quality of life.[28]

The current study has several limitations. First, the examination survey was not solely designed for airway disease, and spirometry was not used in all participants. This resulted in selection bias. In addition, the overall participation rate was low, and only subjects with eligible spirometry results were enrolled. Subjects with no symptoms were excluded, and severely ill patients were excluded due to unsuitable data. Different sampling weights provided by KNHANES IV were used to minimize the healthy worker effect.[8] Second, the presence of AHR was not determined based on objective methods but on a subjective questionnaire. This could have led to a misdiagnosis and heterogeneity of subjects in each group. Some asthmatics who were uncontrolled or who had underlying structural disease might have been misclassified to the overlap syndrome group. Some COPD patients with recent exacerbations could also have been misclassified. In the setting of a general population-based study however, the use of objective methods was unfeasible and impractical; although self-assessment methods have been widely used in previous studies.[29,30] Third, there was no information about use of medications that could influence lung function such as inhaled corticosteroids and bronchodilators. Their potential use and effects were excluded, since pre-study omission was not implemented and questionnaires did not include regular medication use. However, most subjects were considered as not having been treated due to the low rate of physician diagnosis. Lastly, SRH is subjective and not a standardized item.

Health status is influenced by many other emotional and psychological factors. There were inter- and intra-individual differences in expression of SRH, even in the NOD group. Health status is not an appropriate marker to apply to all patients equally in practice. Nevertheless, a recent study reported that SRH was strongly associated with quality of life in asthma subjects.[31] SRH as a simple method for assessing health status related to disease has an advantage of being easier to explain to patients compared to a complicated respiratory questionnaire.

Conclusion

Obstructive lung disease is considered an aggregate of heterogeneous diseases with unique features. Compared to subjects with airway obstruction and no wheezing, subjects from our asthma and overlap syndrome groups showed lower SRH, although each subgroup did not represent a specific clinical disease entity. This study provides further evidence that overlap syndrome is an important and understudied disease, and that this population needs more appropriate care when considering the high burden of morbidity and lower SRH.

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Author contributions

Study concept and design, JH Lee; data acquisition and quality control, JW Chung, KA Kong, SJ Lee; analysis and interpretation: JW Chung, KA Kong, JH Lee; critical revision of manuscript, all authors. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

Table S1 Comparison of characteristics between included and excluded subjects

Variables	Included		Excluded		*P*-value
	N=9,104		**N=9,302**		
Males	4,067	44.7%	3,857	41.5%	<0.0001
Age, years					
19–39	2,410	26.5%	3,845	41.3%	<0.0001
40–59	4,062	44.6%	2,603	28.0%	
≥60	2,632	28.9%	2,854	30.7%	
BMI, kg/m^2					
Missing	0	0.0%	1,213	13.0%	<0.0001
<8.5	202	2.2%	598	6.4%	
18.5–25	5,518	60.6%	5,431	58.4%	
≥25	3,384	37.2%	2,060	22.1%	
Education duration, years					
Missing	0	0.0%	1,159	12.5%	<0.0001
≤6	2,568	28.2%	2,466	26.5%	
6–9	1,196	13.1%	730	7.8%	
9–12	3,070	33.7%	2,844	30.6%	
>12	2,270	24.9%	2,103	22.6%	
Socioeconomic status					
Missing	0	0.0%	546	5.9%	<0.0001
<25th percentile	2,153	23.6%	2,337	25.1%	
25–75th percentile	4,597	50.5%	4,295	46.2%	
>75th percentile	2,354	25.9%	2,124	22.8%	
Smoking history					
Missing	0	0.0%	1,158	12.4%	<0.0001
Never-smoker	5,327	58.5%	5,195	55.8%	
Ex-smoker	1,696	18.6%	1,268	13.6%	
Current smoker	2,081	22.9%	1,681	18.1%	
Self-rated health					
Missing	0	0.0%	1,152	12.4%	<0.0001
Better	6,957	76.4%	6,035	64.9%	
Lower	2,147	23.6%	2,115	22.7%	

Abbreviations: N, number of subjects; BMI, body mass index.