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Diseases Concomitant With Asthma in Middle-Aged and Elderly Subjects in Korea: A Population-Based Study

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Purpose: Asthma is prevalent in many countries. Few studies have investigated the association between asthma and concomitant diseases. We retrospectively analyzed the fourth Korean National Health and Nutrition Survey database, performed in 2008 using nationwide stratified random sampling to obtain a representative cohort of the Korean population. **Methods:** We evaluated the association between both self-reported ever-asthmatics and wheezers and concomitant diseases such as arthritis, hypertension, gastrointestinal (GI) ulcers, dyslipidemia, diabetes mellitus, rhinitis, depression, stroke, and obesity in subjects aged ≥40 years. A multivariate analysis was performed to identify concomitant diseases independently associated with asthma, after adjustment for age, gender, income, cigarette smoking, and other chronic diseases. **Results:** Of the total of 4,445 subjects, 2,596 (58.4%) were female and the mean age was 58.3 years. Of the 4,445 subjects, 195 (4.4%) had been diagnosed with asthma at some point, and 444 (10%) were wheezers. Multivariate analysis showed that arthritis (odds ratio [OR] 1.74, 95% confidence interval [CI] 1.26-2.42), rhinitis (OR 1.78, 95% CI 1.14-2.78), depression (OR 1.45, 95% CI 1.05-2.07), and obesity (OR 1.61, 95% CI 1.08-2.40) were significantly associated with self-reported ever-asthma, and arthritis (OR 1.50, 95% CI 1.19-1.909), hypertension (OR 1.34, 95% CI 1.07-1.67), GI ulcers (OR 1.48, 95% CI 1.05-2.08), rhinitis (OR 1.60, 95% CI 1.16-2.19), depression (OR 1.94, 95% CI 1.51-2.48), and obesity (OR 1.56, 95% CI 1.17-2.09) were significantly associated with wheezers. **Conclusions:** These findings indicate that arthritis, rhinitis, depression, and obesity may be associated with both self-reported ever asthma and wheezers in the Korean population.

Key Words: Asthma; arthritis; rhinitis; depression; obesity

INTRODUCTION

Asthma is a common condition in many countries, with a prevalence of 6 to 10% in high-income countries.[1] Moreover, the prevalence of asthma in adults increases with age, suggesting that greater attention should be paid to middle-aged and elderly subjects, who are more likely to have concomitant diseases. Concomitant diseases in subjects with asthma typically include rhinitis, chronic obstructive pulmonary disease (COPD), and obesity-associated morbidity such as obstructive sleep apnea, gastro-esophageal reflux disease, and mood disorders.[2] Moreover, arthritis, dyslipidemia, diabetes mellitus (DM), cancer, and cardiovascular disease often co-occur with asthma.[3] The presence of concomitant diseases may decrease quality-of-life and asthma control, especially in older subjects. Treatment of concomitant diseases has been found to improve asthma outcome and overall health.[4,5]

Diseases co-occurring with asthma may not be related to asthma itself, but rather to other factors, such as gender, age, income, cigarette smoking, or other diseases. Little is known about diseases concomitant with asthma after taking these factors into account. We therefore investigated diseases concomitant with asthma after controlling for confounding factors.

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MATERIALS AND METHODS

Fourth Korean National Health and Nutrition Examination Survey

We retrospectively analyzed the fourth Korean National Health and Nutrition Survey database (4th KNHANES), which was performed in 2008 and consisted of a nationwide stratified random sampling based on the census of the Korean Statistical Office.[6] In this survey, trained interviewers administered questionnaires on chronic diseases, including arthritis, hypertension, gastrointestinal (GI) ulcers, dyslipidemia, DM, rhinitis, depression, stroke, obesity, and asthma. The questionnaires also included questions on health-related factors such as income and cigarette smoking history. In addition, spirometry was performed as recommended by the task force on pulmonary function testing of the American Thoracic Society and the European Respiratory Society.[7]

The survey was approved by the Institutional Review Board of the Korea Centers for Disease Control and Prevention (approval number, 2008-01EXP-01-C) and all study participants provided informed consent.

Subjects

A total of 4,445 subjects, all of whom were at least 40 years old, were analyzed.[6]

Definition of asthma and concomitant diseases

Asthma was ascertained using two separate definitions. In the first, we ascertained whether subjects were self-reported ever-asthmatics using the question, "Has a physician ever told you that you have asthma?" In the second, we ascertained whether subjects were wheezers, using the question, "Have you had wheezing or whistling in your chest at any time in the past 12 months?"[8]

Subjects answering affirmatively to questions about concomitant diseases, such as arthritis, GI ulcer, rhinitis, depression, or stroke (e.g., "Have you had [name of chronic disease] for 6 months or more that was diagnosed by a healthcare professional?") were regarded as having that disease.

Hypertension was defined as diastolic blood pressure ≥90 mmHg or taking anti-hypertensive agents; dyslipidemia as a low density lipoprotein (LDL) cholesterol concentration ≥130 mg/dL or taking lipid-lowering agents; and DM as a fasting blood glucose (FBG) concentration ≥126 mg/dL or taking glucose-lowering agents. Obesity was defined as a body mass index (BMI) ≥27.5 kg/m^2, the criterion for Koreans.[9] Subjects were classified as ever-smokers if they had consumed at least 100 cigarettes, or as never-smokers if they had consumed <100 cigarettes.

We focused on nine major chronic diseases: arthritis, hypertension, GI ulcers, dyslipidemia, DM, rhinitis, depression, stroke, and obesity. These diseases were selected because of their high prevalence in Korea and/or their high impact on healthcare service utilization.[10]

To determine the association between asthma and each of these chronic diseases, we adjusted for gender, age, income, cigarette smoking, and other chronic diseases. Income was classified by ranking according to gender and age group (5-year intervals), with each subject's income calculated by dividing the sum of the total household income by the square root of the number of members of the household.

Data analysis

Categorical variables were analyzed using a contingency table, with groups compared using Chi-square tests. Means were compared using *t*-tests. Multivariate logistic regression analysis was performed to identify variables independently associated with asthma, after adjusting for gender, cigarette smoking, income, and other chronic diseases. The same analyses were performed separately for middle-aged subjects (aged 40-64 years), elderly subjects (aged ≥ 65 years), subjects with normal pulmonary function, and never-smokers.

The results are reported as odds ratios (ORs) with 95% confidence intervals (CIs). A *P* value less than 0.05 was taken as indicating statistical significance. All analyses were performed using SPSS Version 14.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

Table 1 shows the demographic and clinical characteristics of the 4,445 subjects. Mean subject age was 58.3 years (inter-quartile range [IQR]: 48-68 years) and 2,596 (58.4%) of the subjects were female. Of the 4,445 subjects, 195 (4.4%), of mean age 64 years (IQR: 56-73 years), had been diagnosed with asthma at some point and 444 (10.0%), of mean age 64 years (IQR: 54-72 years), were wheezers.

Analysis of all subjects

Simple comparisons showed that subjects who had been diagnosed with self-reported ever-asthma were more likely to have arthritis, hypertension, DM, depression, and obesity than subjects who were never previously diagnosed with self-reported ever-asthma (Table 1). Wheezers were more likely to have arthritis, hypertension, GI ulcer, rhinitis, depression, and obesity than non-wheezers.

After adjusting for gender, age, income, cigarette smoking, and other chronic diseases, multivariate analysis revealed that arthritis (OR: 1.74, 95% CI: 1.26-2.42, *P*=0.001), rhinitis (OR: 1.78, 95% CI: 1.14-2.78, *P*=0.011), depression (OR: 1.45, 95% CI: 1.05-2.07, *P*=0.041), and obesity (OR: 1.61, 95% CI: 1.08-2.40, *P*=0.02) were independently associated with a diagnosis of self-reported ever-asthma (Figure). In addition, arthritis (OR: 1.50, 95% CI: 1.19-1.90, *P*=0.001), hypertension (OR: 1.34, 95% CI: 1.07-1.67, *P*=0.011), GI ulcers (OR: 1.48, 95% CI: 1.05-2.08, *P*=0.024), rhi-

Table 1. Characteristics of subjects

Number of subjects	Total 4,445	Ever-asthma 195 (4.4)	Non-asthma control 4,250 (95.6)	Crude *P* value	Wheezer 444 (10.0)	Non-wheezer 4,001 (90.0)	Crude *P* value
Gender				0.001			0.44
Male	1,849 (41.6)	58 (29.7)	1,791 (42.1)		177 (39.9)	1,672 (41.8)	
Female	2,596 (58.4)	137 (70.3)	2,459 (57.9)		267 (60.1)	2,329 (58.2)	
Mean age (IQR)	58.3 (48-68)	64 (56-73)	58 (48-68)	<0.001	64 (54-72)	57 (47-67)	<0.001
Income				<0.001			<0.001
<25th percentile	1,169 (27.3)	86 (46.7)	1,083 (26.4)		182 (43.2)	987 (25.6)	
25-50th percentile	1,131 (26.4)	35 (19.0)	1,096 (26.8)		94 (22.3)	1,037 (26.9)	
50-75th percentile	982 (22.9)	33 (17.9)	949 (23.2)		75 (17.8)	907 (23.5)	
>75th percentile	998 (23.3)	30 (16.3)	968 (23.6)		70 (16.6)	928 (23.2)	
Smoking				0.24			<0.001
Never smoker	2,708 (61.1)	127 (65.1)	2,581 (60.9)		224 (50.9)	2,484 (62.2)	
Ever smoker	1,726 (38.9)	68 (34.9)	1,658 (39.1)		216 (49.1)	1,510 (37.8)	
Arthritis				<0.001			<0.001
No	3,173 (71.4)	98 (50.3)	3,075 (72.4)		260 (58.6)	2,913 (72.8)	
Yes	1,272 (28.6)	97 (49.7)	1,175 (27.6)		184 (41.4)	1,088 (27.2)	
Hypertension				0.001			<0.001
No	2,771 (62.3)	99 (50.8)	2,672 (62.9)		223 (50.2)	2,548 (63.7)	
Yes	1,674 (37.7)	96 (49.2)	1,578 (37.1)		221 (49.8)	1,453 (36.3)	
GI ulcer				0.13			<0.001
No	4,132 (93)	176 (90.3)	3,956 (93.1)		392 (88.3)	3,740 (93.5)	
Yes	313 (7.0)	19 (9.7)	294 (6.9)		52 (11.7)	261 (6.5)	
Dyslipidemia				0.26			0.18
No	2,990 (67.3)	124 (63.6)	2,866 (67.4)		286 (64.4)	2,704 (67.6)	
Yes	1,455 (32.7)	71 (36.4)	1,384 (32.6)		158 (35.6)	1,297 (32.4)	
Diabetes mellitus				0.01			0.52
No	3,887 (87.4)	159 (81.5)	3,728 (87.7)		384 (86.5)	3,503 (87.6)	
Yes	558 (12.6)	36 (18.5)	522 (12.3)		60 (13.5)	498 (12.4)	
Allergic rhinitis				0.25			0.04
No	3,964 (89.2)	169 (86.7)	3,795 (89.3)		383 (86.3)	3,581 (89.5)	
Yes	481 (10.8)	26 (13.3)	455 (10.7)		61 (13.7)	420 (10.5)	
Depression				<0.001			<0.001
No	3,709 (83.4)	145 (74.4)	3,564 (83.9)		323 (72.7)	3,386 (84.6)	
Yes	736 (16.6)	50 (25.6)	686 (16.1)		121 (27.3)	615 (15.4)	
Stroke				0.27			0.47
No	4,282 (96.3)	185 (94.9)	4,097 (96.4)		425 (95.7)	3,857 (96.4)	
Yes	163 (3.7)	10 (5.1)	153 (3.6)		19 (4.3)	144 (3.6)	
Obesity				0.004			0.002
No	3,914 (88.1)	159 (81.5)	3,755 (88.4)		370 (83.5)	3,544 (88.6)	
Yes	529 (11.9)	36 (18.5)	493 (11.6)		73 (16.5)	456 (11.4)	

Subjects at least 40 years of age were retrospectively selected from the database of the 4th Korean National Health and Nutrition Survey. Ever-asthma was ascertained by asking the question, "Has a physician ever told you that you had asthma?" Wheezers were ascertained by asking the question, "Have you had wheezing or whistling in your chest at any time in the past 12 months?" Arthritis, stroke, GI ulcer, allergic rhinitis, and depression were each defined as a disease lasting for 6 months or more after diagnosis by a health professional. Hypertension, diabetes mellitus, and dyslipidemia were diagnosed if a subject was relevant medication or met a criterion of diastolic blood pressure ≥90 mmHg, fasting blood glucose level ≥126 mg/dL, and low density lipoprotein level ≥130 mg/dL, respectively. Obesity was defined as a body mass index of 27.5 kg/m^2 or more. Data are presented as numbers of subjects, with percentages in parentheses, except for age, which is given in years with mean and interquartile range (IQR) in parentheses. *P* values were obtained by the chi-square test.
GI, gastrointestinal.

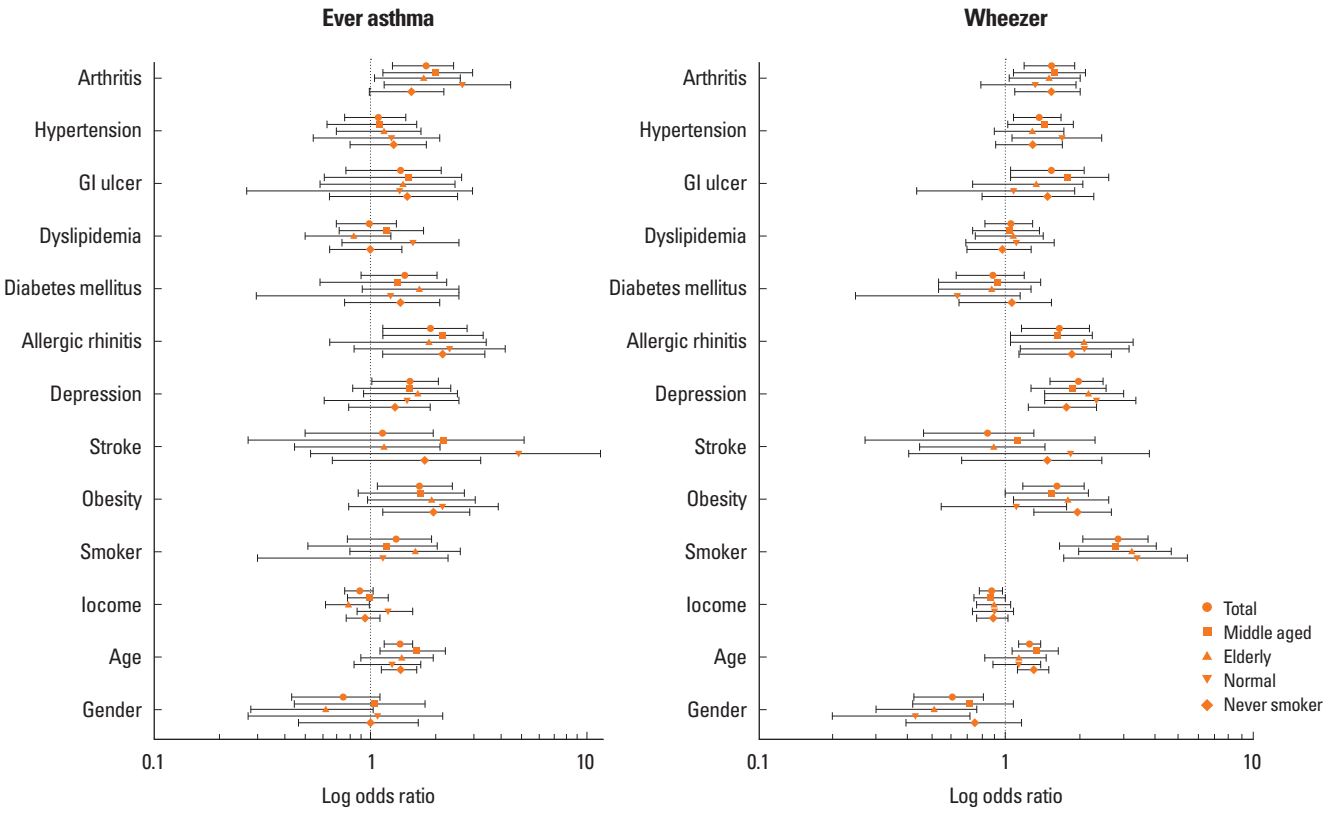

Figure. Odds ratios (ORs) of concomitant diseases for ever-asthma (left) and wheezer subjects (right). Data are shown as odds ratios with 95% confidence intervals derived from a fully adjusted logistic regression model including gender, age, income, cigarette smoking, and the other eight diseases. The OR of gender is for males compared to females. Ever-asthma was ascertained by the question, "Has a physician ever told you that you had asthma?" Wheezers were ascertained by the question, "Have you had wheezing or whistling in your chest at any time in the past 12 months?"Arthritis, stroke, GI ulcer, depression, and allergic rhinitis denote durative disease for 6 months or more after being diagnosed by a health professional. Hypertension, diabetes mellitus, and dyslipidemia denote the subjects on medication or meeting the criteria of diastolic blood pressure ≥90 mmHg, fasting blood glucose ≥126 mg/dL, and low density lipoprotein ≥130 mg/dL, respectively. Obesity denotes a body mass index of 27.5 kg/m^2 or more. GI, gastrointestinal.

nitis (OR: 1.60, 95% CI: 1.16-2.19, P=0.004), depression (OR: 1.94, 95% CI: 1.51-2.48, P<0.001), and obesity (OR: 1.56, 95% CI: 1.17-2.09, P=0.002) were independently associated with wheezing, after adjustment for gender, age, income, cigarette smoking, and other chronic diseases.

Analysis of middle-aged subjects

Of the 2,958 middle-aged subjects (age 40-64 years), 90 (3.0%) had been diagnosed with self-reported ever-asthma and 226 (7.6%) were wheezers (Tables 2 and 3). Arthritis (38.9% vs. 20.4%, P<0.001), rhinitis (21.1% vs. 13.2%, P=0.03), and depression (24.4% vs. 15.3%, P=0.02) were significantly more common in middle aged subjects with self-reported ever-asthma. Wheezers were significantly more likely to have arthritis (31.0% vs. 20.1%, P<0.001), hypertension (38.1% vs. 27.3%, P=0.001), GI ulcers (11.9% vs. 6.1%, P=0.001), depression (25.7% vs. 14.8%, P<0.001), and obesity (16.8% vs. 11.6%, P=0.02) than non-wheezers.

After adjustment for gender, cigarette smoking, income, and other chronic diseases, multivariate analysis revealed that arthritis (OR: 1.83, 95% CI: 1.14-2.94, P=0.013) and rhinitis (OR: 1.95, 95% CI: 1.14-2.78, P=0.014) were independently associated with self-reported ever-asthma (Figure). In addition, arthritis (OR: 1.51, 95% CI: 1.08-2.10, P=0.016), hypertension (OR: 1.39, 95% CI: 1.02-1.88, P=0.036), GI ulcers (OR: 1.66, 95% CI: 1.05-2.62, P=0.029), rhinitis (OR: 1.53, 95% CI: 1.04-2.24, P=0.029), and depression (OR: 1.79, 95% CI: 1.27-2.53, P=0.001) were independently associated with wheezing (Figure).

Analysis of elderly subjects

Of the 1,487 elderly subjects (age ≥ 65 years), 105 (7.1%) were self-reported ever-asthmatics and 218 (15.7%) were wheezers (Tables 2 and 3). Unadjusted comparisons showed that arthritis (59.0% vs. 42.8%, P=0.001), depression (26.7% vs. 17.8%, P=0.02), and obesity (19.0% vs. 11.2%, P=0.02) were significantly more common in elderly subjects who were self-reported ever-asthmatics than those not diagnosed with this condition. Moreover, arthritis (52.3% vs. 42.5%, P=0.007), GI ulcers (11.5% vs. 7.5%, P=0.046), rhinitis (10.1% vs. 4.9%, P=0.002), depression

Table 2. Characteristics of ever-asthma subjects compared to non-asthma control subjects according to age group

Number of subjects (%)	Middle-aged subjects, 2,958 (66.5)			Elderly subjects, 1,487 (33.5)		
	Ever-asthma 90 (3.0)	Non- asthma control 2,868 (97.0)	Crude *P* value*	Ever-asthma 105 (7.1)	Non- asthma control 1,382 (92.9)	Crude *P* value*
Gender			0.133			0.003
Male	32 (35.6)	1,248 (43.5)		26 (24.8)	543 (39.3)	
Female	58 (64.4)	1,620 (56.5)		79 (75.2)	839 (60.7)	
Mean age (IQR)	53.9 (49-60)	51.1 (45-57)	<0.001	73.4 (69-77)	72.3 (68-76)	0.073
Income†			0.061			0.032
<25th percentile	18 (20.0)	395 (14.2)		68 (72.3)	688 (52.7)	
25-50th percentile	24 (26.7)	761 (27.3)		11 (11.7)	335 (25.7)	
50-75th percentile	30 (33.3)	808 (29.0)		3 (3.2)	141 (10.8)	
>75th percentile	18 (20.0)	827 (29.6)		12 (12.8)	141 (10.8)	
Smoking‡			0.257			0.595
Never smoker	60 (66.7)	1,739 (60.7)		67 (63.8)	842 (61.2)	
Ever smoker	30 (33.3)	1,124 (39.3)		38 (36.2)	534 (38.8)	
Arthritis			<0.001			0.001
No	55 (61.1)	2,284 (79.6)		43 (41.0)	791 (57.2)	
Yes	35 (38.9)	584 (20.4)		62 (59.0)	591 (42.8)	
Hypertension			0.268			0.177
No	60 (66.7)	2,065 (72.0)		39 (37.1)	607 (43.9)	
Yes	30 (33.3)	803 (28.0)		66 (62.9)	775 (56.1)	
GI ulcer			0.175			0.570
No	81 (90.0)	2,684 (93.6)		95 (90.5)	1,272 (92.0)	
Yes	9 (10.0)	184 (6.4)		10 (9.5)	110 (8.0)	
Dyslipidemia			0.279			0.957
No	58 (64.4)	2,001 (69.8)		66 (62.9)	865 (62.6)	
Yes	32 (35.6)	867 (30.2)		39 (37.1)	517 (37.4)	
Diabetes mellitus			0.507			0.070
No	79 (87.8)	2,579 (89.9)		80 (76.2)	1,149 (83.1)	
Yes	11 (12.2)	289 (10.1)		25 (23.8)	233 (16.9)	
Allergic rhinitis			0.030			0.639
No	71 (78.9)	2,490 (86.8)		98 (93.3)	1,305 (94.4)	
Yes	19 (21.1)	378 (13.2)		7 (6.7)	77 (5.6)	
Depression			0.019			0.024
No	68 (75.6)	2,428 (84.7)		77 (73.3)	1,136 (82.2)	
Yes	22 (24.4)	440 (15.3)		28 (26.7)	246 (17.8)	
Stroke			0.389			0.881
No	88 (97.8)	2,826 (98.5)		97 (92.4)	1,271 (92.0)	
Yes	2 (2.2)	42 (1.5)		8 (7.6)	111 (8.0)	
Obesity§			0.085			0.016
No	74 (82.2)	2,528 (88.2)		85 (81.0)	1,227 (88.8)	
Yes	16 (17.8)	338 (11.8)		20 (19.0)	155 (11.2)	

Middle-aged subjects were aged ≥40 years and <65 years; elderly subjects were aged ≥65 years. Data are presented as numbers of subjects, with percentages in parentheses, except for age, which is given in years with mean and IQR in parentheses.
*P values <0.05 were obtained by the chi-square test after comparisons of ever-asthma subjects and non-asthma controls. †,‡,§Some data were missing, but the proportion of such data was always<4%.
GI, gastrointestinal; IQR, inter-quartile range.

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Table 3. Characteristics of subjects who were wheezers compared to non-wheezer control subjects according to age group

Number of subjects (%)	Middle-aged subjects, 2,958 (66.5)			Elderly subjects, 1,487 (33.5)		
	Wheezer 226 (7.6)	Non-wheezer 2,732 (92.4)	Crude *P* value*	Wheezer 218 (14.7)	Non-wheezer 1,269 (85.3)	Crude *P* value*
Gender			0.31			0.085
Male	105 (46.5)	1,175 (43.0)		72 (33.0)	497 (39.2)	
Female	121 (53.5)	1,557 (57.0)		146 (67.0)	772 (60.8)	
Mean age (IQR)	53.3 (47-59)	51.0	<0.001	72.8 (68-76)	72.8 (68-76)	0.289
Income†			<0.001			0.069
<25th percentile	52 (24.0)	361 (13.6)		130 (63.7)	626 (52.4)	
25-50th percentile	61 (28.1)	724 (27.2)		33 (16.2)	313 (26.2)	
50-75th percentile	54 (24.9)	784 (29.4)		21 (10.3)	123 (10.3)	
>75th percentile	50 (23.0)	795 (29.8)		20 (9.8)	133 (11.1)	
Smoking‡			<0.001			0.003
Never smoker	112 (49.6)	1,687 (61.9)		112 (52.3)	797 (62.9)	
Ever smoker	114 (50.4)	1,040 (38.1)		102 (47.7)	470 (37.1)	
Arthritis			<0.001			0.007
No	153 (69.0)	2,183 (79.9)		104 (47.7)	730 (57.5)	
Yes	70 (31.0)	549 (20.1)		114 (52.3)	539 (42.5)	
Hypertension			0.001			0.083
No	140 (61.9)	1,985 (72.7)		83 (38.1)	563 (44.4)	
Yes	86 (38.1)	747 (27.3)		135 (61.9)	706 (55.6)	
GI ulcer			0.001			0.046
No	199 (88.1)	2,566 (93.9)		193 (88.5)	1,174 (92.5)	
Yes	27 (11.9)	166 (6.1)		25 (11.5)	95 (7.5)	
Dyslipidemia			0.52			0.597
No	153 (67.7)	1,906 (69.8)		133 (61.0)	798 (62.9)	
Yes	73 (32.3)	826 (30.2)		85 (39.0)	471 (37.1)	
Diabetes mellitus			0.986			0.873
No	203 (89.8)	2,455 (89.9)		181 (83.0)	1,048 (82.6)	
Yes	23 (10.2)	277 (10.1)		37 (17.0)	221 (17.4)	
Allergic rhinitis			0.078			0.002
No	187 (82.7)	2,374 (86.9)		196 (89.9)	1,207 (95.1)	
Yes	39 (17.3)	358 (13.1)		22 (10.1)	62 (4.9)	
Depression			<0.001			<0.001
No	168 (74.3)	2,328 (85.2)		155 (71.1)	1,058 (83.4)	
Yes	58 (25.7)	404 (14.8)		63 (28.9)	211 (16.6)	
Stroke			0.715			0.509
No	222 (98.2)	2,692 (98.5)		203 (93.1)	1,165 (91.8)	
Yes	4 (1.8)	40 (1.5)		15 (6.9)	104 (8.2)	
Obesity§			0.018			0.034
No	187 (83.1)	2,415 (88.4)		183 (83.9)	1,129 (89.0)	
Yes	38 (16.8)	316 (11.6)		35 (16.1)	140 (11.0)	

*P values <0.05 were obtained by the chi-square test after comparisons of wheezers and non-wheezing controls. †,‡,§Some data were missing, but the proportion of such data was always <4%.

(28.9% vs. 16.6%, P<0.001), and obesity (16.1% vs. 11.0% P=0.03) were significantly more common among wheezers than non-wheezers.

After adjustment for gender, cigarette smoking, income, and other chronic diseases, multivariate analysis showed that arthritis (OR: 1.64, 95% CI: 1.04-2.59, P=0.033) was independently associated with self-reported ever-asthma and that arthritis (OR: 1.44, 95% CI: 1.04-2.00, P=0.030), rhinitis (OR: 1.86, 95%

CI: 1.05-3.30, P=0.035), depression (OR: 2.08, 95% CI: 1.44-2.98, P<0.001), and obesity (OR: 1.67, 95% CI: 1.07-2.60, P=0.024) were significantly associated with wheezing in elderly subjects.

Analysis of subjects with normal pulmonary function

Of the 4,445 subjects in the survey, 1,820 (53.3%) had normal pulmonary function. Of these, 44 (2.4%) had been diagnosed with asthma at some point and 121 (6.6%) were wheezers. After adjustment for gender, age, income, cigarette smoking, and other chronic diseases, multivariate analysis revealed that arthritis (OR: 2.26, 95% CI: 1.15-4.43, P=0.018) was independently associated with self-reported ever-asthma and that hypertension (OR: 1.61, 95% CI: 1.06-2.45, P=0.025), rhinitis (OR: 1.90, 95% CI: 1.15-3.16, P=0.013), and depression (OR: 2.20, 95% CI: 1.43-3.38, P<0.001) were independently associated with wheezing in subjects with normal pulmonary function.

Analysis of never-smokers

Questionnaire results showed that 2,708 of the 4,445 subjects (60.9%) were never-smokers, defined as having consumed <100 cigarettes during their lifetimes. Among these never-smokers, 127 (4.7%) had been self-reported ever-asthmatics and 224 (8.3%) were wheezers. A multivariate analysis, after adjustment for gender, age, income, cigarette smoking, and other chronic diseases, showed that rhinitis (OR: 1.95, 95% CI: 1.14-3.36, P=0.016) and obesity (OR: 1.82, 95% CI: 1.15-2.88, P=0.011) were independently associated with self-reported ever-asthma (Figure) and that arthritis (OR: 1.48, 95% CI: 1.09-2.01, P=0.012), rhinitis (OR: 1.74, 95% CI: 1.14-2.68, P=0.011), depression (OR: 1.70, 95% CI: 1.24-2.33, P=0.001), and obesity (OR: 1.87, 95% CI: 1.30-2.68, P=0.001) were independently associated with wheezing in never-smokers.

DISCUSSION

This retrospective analysis of data obtained from the 4th KNHANES, a nationwide survey of South Korea in 2008, showed that arthritis, rhinitis, depression and obesity were independently associated with both self-reported ever-asthma and wheezing in adults ≥ 40 years old. To our knowledge, this is the first population-based study to identify an independent association between asthma and depression in an Asian population. The primary strength of our study was that comparisons were adjusted for covariables such as gender, age, income, smoking status, and other chronic diseases.

Aging is associated with the development of numerous chronic diseases.[11] Thus, as asthmatic subjects age, they are likely to develop additional chronic diseases, which may interfere with adherence to asthma treatments and the control of this condition.[12] Little is known, however, about the prevalence of concomitant chronic diseases in subjects with asthma. One study found that 10 major chronic diseases were significantly more prevalent in adults with asthma than in those without, including allergies, mental illness, non-asthma chronic respiratory diseases, arthritis/rheumatism, high blood pressure, diabetes, heart disease, stomach/intestinal ulcers, stroke, and thyroid conditions.[3] Moreover, a second study reported that six concomitant diseases were more common in adults with asthma than without: DM, arthritis, heart disease, stroke, cancer, and osteoporosis.[4] These studies, however, did not consider possible interactions between concomitant diseases and confounding factors such as, gender, age, income, and smoking status. We adjusted for confounding factors and other chronic diseases, finding that arthritis, rhinitis, depression, and obesity were independently associated with a lifetime diagnosis of asthma in Korean subjects over 40 years of age, whereas stroke, DM, hypertension, GI ulcers, and dyslipidemia were not.

Rhinitis is very common in patients with asthma.[12-15] Because of this, asthma and rhinitis have been considered a "one-airway disease" with a common pathogenesis.[10,11,15] Although we detected a close relationship between asthma and rhinitis in middle-aged subjects, this was not the case in elderly subjects, possibly due to the occurrence of immunosenescence, or deterioration of the immune system in elderly individuals. Asthma in older subjects has been characterized as being mostly non-atopic (intrinsic) rather than atopic (extrinsic).[16]

Evidence for an association between depression and asthma in elderly subjects is scant and inconsistent. Although depressive symptoms were reported to be more common in asthma subjects aged over 55 years,[17] the difference was not statistically significant, possibly due to the small sample size (40 asthma patients). Population-based sampling methods showed a significant association between adult asthma and depression.[18,19] However, these studies did not consider interactions with concomitant diseases. Similar to these studies, our population-based depression data indicated a significant association with adult asthma. Our result showed a stronger association than previous studies because we adjusted for confounding factors.

There is some support for an association between immune system activity and psychological state. Cytokines, including interleukins (IL)-1, -2, and -6, and tumor necrosis factor (TNF)-α are involved in the regulation of cognition, affect, and behavior.[20] An animal study indicated that an acute immune challenge has an effect similar to that of major depressive disorder. A fundamental aspect of the pathogenesis of depression implicates excessive macrophage-derived cytokine production. Aging is also associated with a chronic proinflammatory state, with increased concentrations of IL-1, IL-6, and TNF-α.[16] In addition to the significant association between depression and asthma in subjects over 40 years of age, we found that those aged ≥65 years with asthma were significantly more likely to have depression, after adjustment for other chronic diseases. Since asthma subjects with depression tended to have poor compliance with asthma treatments,[21] clinicians should pay

particular attention to elderly asthma patients with depression.

Various inflammatory mediators, including IL-1, IL-6, IL-8, TNF-α, and other cytokines, are elevated in subjects with osteoarthritis.[20] All of these cytokines can stimulate the production of reactive oxygen species.[22] However, the recovery process deteriorates with age. Dysregulation of cytokines is related to the production of inappropriate autoantibodies. Senescence may underlie the association between asthma and arthritis. Consistent with results showing that women are at greater risk of osteoarthritis than men,[23] we found that elderly subjects with asthma were significantly more likely to be female, suggesting a common association between the pathogenesis of arthritis and asthma. However, we are not completely sure about the relationship between arthritis and asthma, since almost all of our subjects with asthma used a corticosteroid inhaler, which can affect musculoskeletal diseases. Studies on the association between arthritis and asthma should include the monitoring of musculoskeletal symptoms in these individuals.

Inflammatory cytokines are also involved in the pathogenesis of atherosclerosis.[24] In addition, asthma may be associated with hypertension via pathways that modulate CRP.[25] Although one study found an epidemiological relationship between high CRP and incident hypertension, there was no proof of cause and effect.[26] In addition, subjects with chest wheezing may have confused cardiogenic events with asthmatic wheezing. Confounders, such as sympathomimetic agents to relieve bronchospasm, may also play a role. Even with our data, there was a discordance in hypertension between wheezers and self-reported ever-asthmatics. Further studies are needed to determine whether asthma is related to hypertension.

Significant racial and ethnic differences have been observed in the prevalence of asthma[27] and dyslipidemia[28] and the relationship between these two diseases. Total serum cholesterol and non-high density lipoprotein (non-HDL) cholesterol were found to be inversely related to the prevalence of asthma in a US population, with the effect observed chiefly among Mexican-Americans.[29] In Korean subjects, however, we found no association between asthma and the profiles of any lipids, including LDL-cholesterol, triglycerides, HDL-cholesterol, and total cholesterol (data not shown).

Although DM has been associated with COPD,[30] studies on the associations between asthma and DM have yielded inconsistent results.[31-33] Although most of these studies have suggested that asthma is associated with DM, both asthma and DM are related to obesity, suggesting that asthma and DM may be independently associated. Moreover, there are differences in the inflammatory pathogenesis of asthma and COPD. In COPD, inflammation is characterized by cellular infiltration of neutrophils and Th1 cells with increased expression of TNF-α, IL-6, and IL-8, similar to the inflammatory process in type 2 DM.[29,32-34] Asthma, however, is characterized by the infiltration of eosinophils and Th2 cells. Thus, at the molecular level, the inflammatory processes in diabetes and asthma may be very different.

The present study has a few limitations. First, we used a cross-sectional design; hence, causal relationships could not be firmly established. Second, we used a somewhat vague diagnosis of asthma. Wheezers were defined as subjects who have had wheezing or whistling in their chest at any point in the past 12 months. Wheezers were considered one of the standard methods of asthma diagnosis in a previous epidemiologic study.[8] Our study used data from a large-scale epidemiologic study in which asthma diagnosis was considered when a subject had a physician-told asthma ever or wheezed in the past 12 months. There could be a potential bias, due to misclassification of asthma due to the use of wheezing for its diagnosis. However, the sensitivity and specificity of wheezing for diagnosis of asthma were reported to be 69 and 91%,[35] respectively. We considered this definition as acceptable in our epidemiologic data.

It is difficult to differentiate COPD from chronic persistent asthma, or the poorly reversible airway obstruction that occurs in older patients with chronic asthma. Therefore, we attempted to exclude individuals with COPD by the analyses of two subgroups, subjects with normal lung function and never-smokers. The results of the subgroup analyses showed a similar tendency compared with that of the total subjects. Third, we used national survey data, which had many questions regarding chronic diseases that relied on patient recall. Errors in recall may therefore have led to under- or over-estimates of the prevalence of concomitant diseases. However, the Korean national survey database was designed to include stratified random sampling and was conducted by well-trained interviewers, suggesting that our results are representative of the overall South Korean population. In contrast to previous population-based studies, we used multivariate regression to adjust for confounders, enabling a reduction in the effects of confounding factors and interactions between comorbidities. In addition to asthma, we focused on nine major chronic diseases, because of their high prevalence and considerable impact on healthcare service utilization in Korea. We therefore did not include gastro-esophageal reflux disease and coronary heart disease, both of which are not as prevalent in Korea as in Western countries.[36]

In conclusion, our findings suggest that arthritis, rhinitis, depression, and obesity are associated with both wheezers and self-reported ever-asthma in the Korean population.

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