Original Article

# Comorbidities associated with adult asthma according to severity: analysis of data from the National Health Insurance Sharing Service

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**Background:** Asthma is a heterogenous disease having varied phenotypes. The comorbidities associated with asthma vary with age and disease severity. The well-known asthma related comorbid conditions include rhinitis, gastroesophageal reflux disease (GERD), hypertension, obstructive sleep apnea, hormonal disorders, and psychiatric disorders. However, comprehensive analyses of how asthma severity correlates with the prevalence and type of comorbidities remain limited. Understanding these relationships is essential for developing targeted management strategies. This study aims to analyze the comorbid conditions associated with adult asthma based on severity, using data from the National Health Insurance Sharing Service. By comparing non-severe asthma (NSA) and severe asthma (SA) groups, the study seeks to identify key differences in the prevalence and risks of comorbid diseases, thereby providing valuable insights for clinicians managing asthma patients.

**Methods:** National Health Insurance claim records from July 1, 2014 to June 31, 2016 were analyzed in a retrospective population-based study. We analyzed the frequent comorbidities in adult patients with asthma. Patients were divided into the following groups according to severity of asthma: NSA and SA. Risk of the developing major comorbid diseases conditions were analyzed according to the morbidity and severity of asthma.

**Results:** Vasomotor and allergic rhinitis, bronchitis, upper respiratory infection, and GERD were common comorbid conditions in all patients with asthma. chronic obstructive pulmonary disease was more common in SA than in NSA. In major comorbid diseases, patients with asthma had more risk in chronic diseases such as diabetes mellitus [odds ratio (OR) =1.13; 95% confidence interval (CI): 1.13, 1,14] and various types

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of psychiatric disorder (OR =1.49; 95% CI: 1.48, 1.49), as well as rhinitis (OR =1.94; 95% CI: 1.94, 1.95), GERD (OR =1.66; 95% CI: 1.66, 1.67), and osteoporosis (OR =1.40; 95% CI: 1.39, 1.41). Patients with SA experienced more comorbidities and higher incidence of cardiovascular disease, cerebrovascular disease, dementia, and several psychiatric disorders than patients with NSA.

**Conclusions:** Patients with asthma had a higher risk of chronic diseases than patients without asthma, and there was a tendency of higher risk of major comorbidities in SA. Clinicians should consider the impact of comorbid diseases in the asthma patient care.

**Keywords:** Asthma; comorbid diseases; severe asthma (SA)

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## Introduction

Asthma is one of the most commonly occurring airway disease in all ages and a major cause of morbidity and disability among adults, which is associated with increased emergency visits as well as hospitalizations (1-3). Since asthma is a heterogenous disease with varied phenotypes and clinical courses, comorbidities may vary with age and disease severity. The most frequently reported comorbid conditions of asthma include rhinitis, sinusitis, gastroesophageal reflux disease (GERD), hypertension, obstructive sleep apnea, hormonal disorders, and psychopathologies (4-7). These comorbid conditions are not only related with the severity and phenotype of asthma but also may impact the clinical outcome of the disease. Therefore, when creating a treatment plan for patients with asthma, tailored treatment regimen should be determined considering accompanying diseases as well as severity of the disease.

Korea has a unique National Health Insurance (NHI) system in which the governmental insurer covers insurance payment and claim management for the entire country population since 1989. NHI claims database include information regarding diagnosis, treatment, medical resource use, social economic state, and residence together with the cost of each healthcare service provided to the patients. Therefore, information on comorbidities and health care use can be tracked using longitudinal data from the NHI database for almost all patients with asthma in Korea, and analyzing these large-scale data is an optimal way to evaluate patterns of morbidities in real world practice (8-10).

Here, we investigated common comorbidities related to asthma in Korean adults and the associated differences according to the severity of asthma using NHI claims data. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1531/rc).

### Highlight box

**Key findings**

- This study found that patients with asthma have a higher risk of developing chronic diseases.
- Severe asthma (SA) was associated with a greater incidence of comorbidities, including cardiovascular and cerebrovascular diseases.

**What is known and what is new?**

- Asthma is associated with various comorbidities, including rhinitis, gastroesophageal reflux disease, and psychiatric disorders, which can impact the clinical outcome of the disease.
- This manuscript adds new insights by analyzing large-scale national health insurance data, demonstrating that the severity of asthma significantly influences the prevalence and risk of these comorbidities. SA patients have a notably higher risk compared to those with non-SA.

**What is the implication, and what should change now?**

- Clinicians should consider the impact of comorbid diseases when managing asthma patients, particularly those with SA. There is a need for a more comprehensive approach in treating asthma that includes screening and managing these associated comorbidities to improve patient outcomes.

## Methods

### *Study design and data source*

NHI claim records from July 1, 2014 to June 31, 2016 were analyzed in a retrospective population-based study. NHI claims data include sites of care as well as diagnoses

according to 10th revisions of the International Statistical Classification of Diseases and Related Health Problems (ICD-10), prescribed medications, and procedures concerning medical services. The NHI claims data were provided by the Korean National Health Insurance Service, an independent body established to review claims data and assess the quality of health care in Korea. The National Health Insurance Service database contains all information of claims and prescriptions data of the nation that they pay for. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Institutional Review Board of the Asan Medical Center (No. S2016-1254-0010) and the Ethics Committee of the National Health Insurance Sharing Service (No. NHIS-2016-4-016) and individual consent for this retrospective analysis was waived.

### *Definition of asthma and comorbid diseases*

We included patients with asthma who met the following criteria that were modified from the working definition of asthma in a previous study (8,11) (Appendix 1). To compare the comorbidities between patients with asthma and those without asthma, claim data of age and gender matching control were analyzed in the same way.

Patients were divided into the following groups according to severity of asthma: patients with severe asthma (SA) who were prescribed with a canister of inhaled ICSs equivalent to that of high-dose ICSs for >6 months of the year with asthma-related claims (they also had to be prescribed ICS canisters equivalent to greater than the sum of 12 months prescription of low-dose ICS) and patients with non-severe asthma (NSA) who were the remaining patients (table available at https://cdn.amegroups.cn/static/public/10.21037jtd-24-1531-1.docx). The primary outcome was the comparison between distribution and patterns of comorbidities in patients with SA and those of comorbidities in patients with NSA. The definitions of comorbid diseases are listed in table available at https://cdn.amegroups.cn/static/public/10.21037jtd-24-1531-1.docx.

### *Statistical analysis*

To investigate comorbidities associated with asthma, the odds ratios (ORs) of major comorbidities in patients with asthma and without asthma control groups were analyzed. The study population was divided according to age (18–44, 45–64, ≥65 years) and sex (male and female). Data for control group were matched 1:1 for age and gender with the patients with asthma group, and the OR was calculated using the logistic regression to present adjusted OR with age and sex corrected [95% confidence intervals (CIs)]. Frequencies and percentile distributions were used to describe categorical variables. Comparisons between groups were performed using the *t*-test for continuous variable and Chi-square test or Fisher exact test for proportions with <0.05 indicating a statistically acceptable significance level using a statistical software (SAS release 9.4; SAS Institute Inc., Cary, NC, USA)

## Results

### *Study subjects*

In 2015, there were 1,642,766 individuals aged ≥18 years (3.72% of the general population with the same age groups) who had been diagnosed with asthma in Korea. Among patients with asthma, female individuals accounted for 61.17% of the population, and the mean age was 55.86±17.58 years old.

Age and sex matched control patients without asthma diagnosis were randomly selected within the same year's claim data. Demographic characteristics of the study participants are presented in *Table 1*.

### *Major comorbidities in patients with asthma*

The prevalence of comorbidities in the study participants is described in *Table 2*, tables available at https://cdn.amegroups.cn/static/public/10.21037jtd-24-1531-2.docx, https://cdn.amegroups.cn/static/public/10.21037jtd-24-1531-3.docx according to sex and age groups. The prevalence of vasomotor and allergic rhinitis was 41.88% in patients without asthma and 81.20% in patients with asthma. The prevalence of gastric ulcer was 15.27% in patients without asthma and 25.41% in patients with asthma, whereas that of GERD was 26.90% in patients without asthma and 44.08% in patients with asthma. In the older age group comprising adults aged ≥65 years, the prevalence of osteoporosis was 20.08% in patients without asthma and 24.99% in patients with asthma. The prevalence of chronic conditions, such as hypertension (HTN), dyslipidemia, and diabetes mellitus (DM), increased with age in both the asthma and control groups. Additionally, the prevalence of age-

 

**Table 1** Demographic characteristic of study participants

| Characteristics | Control group | Patients with asthma |
|---|---|---|
| Total, n | 1,474,022 | 1,642,766 |
| Age (years), mean ± SD | 56.53±17.49 | 55.86±17.58 |
| Sex, n (%) | | |
| Male | 552,106 (37.46) | 637,934 (38.83) |
| Female | 921,916 (62.54) | 1,004,832 (61.17) |
| Population by age groups, n (%) | | |
| 18–44 years | 390,300 (26.48) | 468,401 (28.51) |
| 45–64 years | 546,956 (37.11) | 585,880 (35.66) |
| ≥65 years | 536,766 (36.42) | 588,485 (35.82) |
| Types of healthcare use (claim cases), n (%) | | |
| Less than 500 beds | 24,645,354 (89.39) | 86,559,914 (94.81) |
| 500 beds or more | 2,926,643 (10.61) | 4,736,533 (5.19) |
| Types of insurance, n (%) | | |
| Health insurance | 1,417,420 (96.16) | 1,483,465 (93.72) |
| Medical aid | 56,602 (3.84) | 99,446 (6.28) |
| Average income[†] | | |
| N | 1,356,071 | 1,455,885 |
| Grade, mean ± SD | 11.98±5.94 | 11.93±5.92 |

[†], annual income grades were defined with the lowest income as grade 1 and the highest income as grade 20. SD, standard deviation.

related diseases, such as cataracts, also rose with advancing age. However, unlike the control group, asthma patients aged ≥65 years exhibited a markedly higher prevalence of chronic obstructive pulmonary disease (COPD) compared to younger age groups, with a prevalence of 23.14%. Moreover, among individuals aged ≥45 years, the prevalence of anxiety disorders was significantly (P<0.001) higher in asthma patients (22.43%) compared to the control group (14.65%) (*Table 2*, table available at https://cdn.amegroups.cn/static/public/10.21037jtd-24-1531-2.docx). In male patients, the prevalence of benign prostate hyperplasia was 16.25% in patients without asthma and 22.84% in those with asthma. In female patients, the prevalence of anxiety disorders was 10.77% in patients without asthma and 17.17% in those with asthma (table available at https://cdn.amegroups.cn/static/public/10.21037jtd-24-1531-3.docx). Overall, 20.30% of the control group and 29.76% of the asthma group were identified with a recorded code for psychiatric disorders.

### *Association between comorbidities and asthma*

*Table 3* and table available at https://cdn.amegroups.cn/static/public/10.21037jtd-24-1531-4.docx show ORs for the associations between asthma and individual major comorbid conditions. Asthma appeared to be strongly associated with rhinitis (OR =1.944; 95% CI: 1.940–1.948), particularly vasomotor and allergic rhinitis (OR =7.153; 95% CI: 7.114–7.192) and COPD (OR =13.136; 95% CI:12.911–13.365). In addition, asthma was also associated with DM (OR =1.132; 95% CI: 1,126–1.137), hypertension (OR =1.086; 95% CI: 1.082–1.089), psychiatric disorders (OR =1.488; 95% CI: 1.482–1.494), GERD (OR =1.662; 95% CI: 1.657–1.668), osteoporosis (OR =1.402; 95% CI: 1.392–1.413), rheumatoid arthritis (RA) (OR =1.591; 95% CI: 1.571–1.612), and fatty liver disease (OR =1.366; 95% CI: 1.349–1.384). This tendency was observed even when the data were divided according to age or sex.

### *Major comorbidities according to asthma severity*

SA was associated with DM, hypertension, psychiatric disorder, GERD, osteoporosis and osteoporosis with fracture, and COPD when grouped according to the severity of asthma. Particularly, COPD prevalence was 38.09% in SA group and 11.14% in NSA group, with an OR of 6.75 (*Table 4*). Conversely, the prevalence of vasomotor and allergic rhinitis and RA in patients with NSA was 81.89% and 3.97%, respectively, compared to 63.64% and 3.23% in patients with SA, with ORs of 0.655 (95% CI: 0.639–0.671) for vasomotor and allergic rhinitis and 0.967 (95% CI: 0.918–1.018) for RA.

Patients with SA had more comorbidities and a higher prevalence of cardiovascular disorder (CVD), cerebrovascular disorder, dementia, dyslipidemia, endocrinologic disorder, obesity, psychiatric disorder and respiratory diseases than those of patients with NSA.

Focusing on patients with SA (table available at https://cdn.amegroups.cn/static/public/10.21037jtd-24-1531-5.docx), bronchitis was identified as the most common comorbidity across all groups, with a prevalence of 82.99% in the NSA group and 73.58% in the SA group. Among uncontrolled SA patients, bronchitis was observed in 79.35%, compared to 64.85% in controlled SA patients. Similarly, vasomotor and allergic rhinitis were prevalent in 81.89% of NSA patients, compared to 63.64% of SA

**Table 2** Top 20 comorbid diseases in patients with asthma in 2015

| Rank | Total (n=1,642,766), n (%) | Age groups, n (%) | | |
|---|---|---|---|---|
| | | 18–44 years (n=468,401) | 45–64 years (n=585,880) | ≥65 years (n=588,485) |
| 1 | Bronchitis: 1,356,075 (82.55) | Vasomotor and allergic rhinitis: 423,750 (88.12) | Bronchitis: 484,601 (82.71) | Bronchitis: 472,187 (80.24) |
| 2 | Vasomotor and allergic rhinitis: 1,333,983 (81.20) | URI: 407,829 (87.07) | Vasomotor and allergic rhinitis: 483,711 (82.56) | Vasomotor and allergic rhinitis: 437,522 (74.35) |
| 3 | URI: 1,297,507 (78.98) | Bronchitis: 399,287 (85.24) | URI: 462,946 (79.02) | URI: 426,732 (72.51) |
| 4 | GERD: 724,100 (44.08) | GERD: 158,324 (33.80) | GERD: 270,371 (46.15) | HTN: 381,196 (64.78) |
| 5 | HTN: 586,083 (35.68) | Contact dermatitis: 120,935 (25.82) | Dyslipidemia: 215,691 (36.81) | GERD: 295,405 (50.20) |
| 6 | Dyslipidemia: 554,368 (33.75) | Conjunctivitis: 112,916 (24.11) | HTN: 151,548 (27.71) | Dyslipidemia: 288,836 (49.08) |
| 7 | Contact dermatitis: 494,566 (30.11) | Chronic sinusitis: 99,114 (21.16) | Contact dermatitis: 173,888 (29.68) | Contact dermatitis: 199,743 (33.94) |
| 8 | Conjunctivitis: 464,592 (28.28) | Urticaria: 79,498 (16.97) | Conjunctivitis: 152,362 (26.01) | Conjunctivitis: 199,314 (33.87) |
| 9 | Gastric ulcer: 417,454 (25.41) | Gastric ulcer: 78,332 (16.72) | Gastric ulcer: 151,252 (25.82) | DM: 193,811 (32.93) |
| 10 | Functional intestinal disorders: 377,517 (22.98) | Functional intestinal disorders: 73,903 (15.78) | Functional intestinal disorders: 119,539 (20.40) | Gastric ulcer: 187,870 (31.92) |
| 11 | DM: 315,666 (19.22) | Irritable bowel syndrome: 60,386 (12.89) | Urticaria: 106,966 (18.26) | Functional intestinal disorders: 184,075 (31.28) |
| 12 | Urticaria: 296,624 (18.06) | Keratitis: 59,149 (12.63) | Irritable bowel syndrome: 101,202 (17.27) | Arthritis: 154,319 (26.22) |
| 13 | Irritable bowel syndrome: 288,071 (17.54) | Pneumonia: 55,373 (11.82) | DM: 82,294 (15.05) | Chronic bronchitis: 149,419 (25.39) |
| 14 | Chronic bronchitis: 286,159 (17.42) | Dyslipidemia: 49,841 (10.64) | Chronic sinusitis: 99,032 (16.90) | Osteoporosis: 147,035 (24.99) |
| 15 | Arthritis: 279,143 (16.99) | Candidiasis: 50,548 (10.79) | Chronic bronchitis: 93,837 (16.02) | Cataract: 140,653 (23.90) |
| 16 | Pneumonia: 270,514 (16.47) | Acute bronchiolitis: 48,299 (10.31) | Arthritis: 93,714 (16.00) | COPD: 136,193 (23.14) |
| 17 | Keratitis: 274,811 (16.73) | Chronic rhinitis: 44,385 (9.48) | Keratitis: 90,921 (15.52) | Anxiety disorder: 131,993 (22.43) |
| 18 | Chronic sinusitis: 267,167 (16.26) | Otitis media: 45,798 (9.78) | Pneumonia: 84,547 (14.43) | Pneumonia: 130.594 (22.19) |
| 19 | Anxiety disorder: 246,551 (15.01) | Chronic bronchitis: 42,903 (9.16) | Anxiety disorder: 82,567 (14.09) | Irritable bowel syndrome: 126,483 (21.49) |
| 20 | Sleep disorders: 214,488 (13.06) | Otitis externa: 40,506 (8.65) | Gingivitis: 76,390 (13.04) | Keratitis: 124,741 (21.20) |

COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; GERD, gastroesophageal reflux disease; HTN, hypertension; URI, upper respiratory infection.

patients, with significant reductions noted in controlled SA (56.48%) compared to uncontrolled SA (79.35%), (P<0.001). Notably, GERD was more frequently observed in NSA patients (44.30%) than SA patients (39.84%), with the highest prevalence in uncontrolled SA patients (51.48%). The prevalence of COPD and pneumonia was significantly higher in the uncontrolled SA group compared to the controlled SA group (P<0.001). Specifically, COPD was observed in 49.80% of uncontrolled SA patients compared to 32.75% in controlled SA patients, while pneumonia was prevalent in 35.47% of uncontrolled SA patients compared to 16.57% in controlled SA patients. These findings underscore the substantial burden of both respiratory and non-respiratory comorbidities in patients with SA, particularly those with uncontrolled disease. This trend was generally similar when stratified by sex. However, for type 2 diabetes, patients with SA showed a higher risk compared to those with NSA, with an OR of 1.513 (95% CI: 1.479–1.548). When analyzed by sex, the association was not significant in males (P=0.109) but was significant in

**Table 3** Prevalence of major comorbidities in patients with asthma and the control group

| Comorbidities | Patients with asthma (n=1,642,766) | Patients without asthma (n=1,474,022) | Adjusted OR (95% CI)[†] | P value |
|---|---|---|---|---|
| Rhinitis | 1,342,863 (81.74) | 628,948 (42.67) | 1.944 (1.940, 1.948) | <0.001 |
| Chronic rhinitis | 128,166 (7.80) | 49,166 (3.34) | 2.494 (2.468, 2.521) | <0.001 |
| Vasomotor and allergic rhinitis | 1,333,983 (81.20) | 617,249 (41.88) | 7.153 (7.114, 7.192) | <0.001 |
| DM | 315,666 (19.22) | 253,925 (17.23) | 1.132 (1.126, 1.137) | <0.001 |
| T1DM | 6,651 (0.40) | 5,875 (0.40) | 1.031 (0.995, 1.068) | 0.002 |
| T2DM | 309,015 (18.81) | 248,050 (16.83) | 1.167 (1.160, 1.174) | <0.001 |
| Cardiovascular disease | 677,313 (41.23) | 551,354 (37.40) | 1.535 (1.507, 1.564) | <0.001 |
| HTN | 586,083 (35.68) | 491,487 (33.34) | 1.086 (1.082, 1.089) | <0.001 |
| AMI | 13,874 (0.84) | 9,156 (0.62) | 1.380 (1.344, 1.416) | <0.001 |
| Cerebrovascular disease | 138,102 (8.41) | 117,637 (7.98) | 1.423 (1.348, 1.503) | <0.001 |
| Stroke | 61,433 (3.74) | 57,482 (3.90) | 1.061 (1.017, 1.107) | 0.006 |
| Dementia-related diseases | 63,275 (3.85) | 68,874 (4.67) | 0.838 (0.829, 0.848) | <0.001 |
| Dementia | 54,829 (3.34) | 61,033 (4.14) | 0.818 (0.809, 0.827) | <0.001 |
| Alzheimer's disease | 5,945 (0.36) | 6,151 (0.42) | 0.880 (0.849, 0.912) | <0.001 |
| Parkinson's disease | 10,950 (0.67) | 11,632 (0.79) | 0.857 (0.835, 0.880) | <0.001 |
| Psychiatric disorders | 488,889 (29.76) | 299,155 (20.30) | 1.488 (1.482, 1.494) | <0.001 |
| Anxiety disorders | 246,551 (15.01) | 137,975 (9.36) | 1.742 (1.730, 1.755) | <0.001 |
| Bipolar disorders | 18,484 (1.13) | 14,597 (0.99) | 1.155 (1.130, 1.180) | <0.001 |
| Mood disorders | 36,074 (2.20) | 19,673 (1.33) | 1.685 (1.656, 1.715) | <0.001 |
| Schizophrenia | 9,855 (0.60) | 10,735 (0.73) | 0.835 (0.812, 0.858) | <0.001 |
| Sleep disorders | 214,488 (13.06) | 119,872 (8.13) | 1.728 (1.715, 1.741) | <0.001 |
| Somatoform disorders | 63,368 (3.86) | 34,224 (2.32) | 1.714 (1.692, 1.737) | <0.001 |
| Symptoms and signs involving emotional state | 26,449 (1.61) | 12,139 (0.82) | 2.000 (1.958, 2.044) | <0.001 |
| Depressive disorders | 154,622 (9.41) | 93,126 (6.32) | 1.567 (1.554, 1.580) | <0.001 |
| Obsessive compulsive disorders | 2,347 (0.14) | 1,493 (0.10) | 1.432 (1.342, 1.528) | <0.001 |
| Stress disorders | 16,055 (0.98) | 9,331 (0.63) | 1.572 (1.533, 1.613) | <0.001 |
| GERD | 724,100 (44.08) | 396,561 (26.90) | 1.662 (1.657, 1.668) | <0.001 |
| Osteoporosis-related disease | 201,846 (12.75) | 147,312 (10.22) | 1.402 (1.392, 1.413) | <0.001 |
| Osteoporosis | 192,714 (12.17) | 141,008 (9.79) | 1.391 (1.380, 1.402) | <0.001 |
| Osteoporosis with fracture | 19,017 (1.20) | 12,093 (0.84) | 1.501 (1.467, 1.536) | <0.001 |
| Rheumatoid arthritis | 64,679 (4.09) | 38,627 (2.68) | 1.591 (1.571, 1.612) | <0.001 |
| Fatty liver disease | 59,971 (3.79) | 40,861 (2.84) | 1.366 (1.349, 1.384) | <0.001 |
| Dyslipidemia | 554,368 (33.75) | 426,469 (28.93) | 1.183 (1.180, 1.187) | <0.001 |
| Endocrine disorder | 626,018 (38.11) | 491,535 (33.35) | 1.160 (1.156, 1.163) | <0.001 |

**Table 3** *(continued)*

**Table 3** *(continued)*

| Comorbidities | Patients with asthma (n=1,642,766) | Patients without asthma (n=1,474,022) | Adjusted OR (95% CI)† | P value |
|---|---|---|---|---|
| Obesity | 2,525 (0.15) | 1,248 (0.08) | 1.842 (1.721, 1.971) | <0.001 |
| Respiratory disease | 1,558,747 (94.89) | 967,664 (65.65) | 1.467 (1.465, 1.468) | <0.001 |
| COPD | 195,209 (11.88) | 13,529 (0.92) | 13.136 (12.911, 13.365) | <0.001 |
| Pneumonia | 270,514 (16.47) | 42,965 (2.91) | 5.732 (5.675, 5.789) | <0.001 |
| Influenza | 45,317 (2.76) | 15,682 (1.06) | 2.631 (2.584, 2.679) | <0.001 |
| Herpes zoster | 55,345 (3.37) | 36,615 (2.48) | 1.376 (1.358, 1.394) | <0.001 |
| Food allergy | 4,929 (0.30) | 2,595 (0.18) | 1.729 (1.649, 1.813) | <0.001 |
| Anaphylaxis | 2,083 (0.13) | 732 (0.05) | 2.591 (2.382, 2.818) | <0.001 |

Data are presented as mean ± SD or n (%). †, adjusted for age (18–44, 45–64, or ≥65 years) and sex groups. AMI, acute myocardial infarction; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; GERD, gastroesophageal reflux disease; HTN, hypertension; OR, odds ratio; SD, standard deviation; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; URI, upper respiratory infection.

**Table 4** Comorbidities according to asthma severity

| Comorbidities | Non-severe asthma (n=1,595,847) | Severe asthma (n=46,919) | Adjusted OR (95% CI)† | P value |
|---|---|---|---|---|
| Number of co-morbid diseases | 12.59±6.48 | 13.95±7.10 | – | – |
| Number of comorbidities | | | | |
| None | 3,225 (0.20) | 13,969 (1.55) | 0.019 (0.016, 0.022) | <0.001 |
| 1–2 | 21,419 (1.34) | 813 (1.73) | 1.952 (1.795, 2.123) | <0.001 |
| 3–4 | 81,152 (5.09) | 3,620 (7.72) | 1.116 (1.060, 1.174) | <0.001 |
| ≥5 | 1,486,715 (93.16) | 42,228 (90.00) | 0.745 (0.713, 0.778) | <0.001 |
| Rhinitis‡ | 1,312,821 (82.26) | 30,042 (64.03) | 0.645 (0.629, 0.661) | <0.001 |
| Chronic rhinitis | 125,879 (7.89) | 2,287 (4.87) | 0.716 (0.686, 0.748) | <0.001 |
| Vasomotor and allergic rhinitis | 1,304,123 (81.72) | 29,860 (63.64) | 0.655 (0.639, 0.671) | <0.001 |
| DM‡ | 305,278 (19.13) | 10,388 (22.14) | 1.513 (1.478, 1.548) | <0.001 |
| T1DM | 6,454 (0.40) | 197 (0.42) | 1.233 (1.070, 1.422) | 0.28 |
| T2DM | 298,824 (18.73) | 10,191 (21.72) | 1.513 (1.479, 1.548) | <0.001 |
| Cardiovascular disease‡ | 655,270 (41.06) | 22,043 (46.98) | 1.844 (1.806, 1.882) | <0.001 |
| HTN | 566,661 (35.51) | 19,422 (41.39) | 1.778 (1.743, 1.815) | <0.001 |
| AMI | 13,402 (0.84) | 472 (1.01) | 1.420 (1.297, 1.557) | 0.13 |
| Cerebrovascular disease‡ | 133,554 (8.37) | 4,548 (9.69) | 1.425 (1.381, 1.471) | 0.048 |
| Stroke | 59,342 (3.72) | 2,091 (4.46) | 1.422 (1.362, 1.483) | 0.02 |
| Dementia-related diseases‡ | 61,117 (3.83) | 2,158 (4.60) | 1.451 (1.388, 1.516) | 0.35 |
| Dementia | 52,994 (3.32) | 1,835 (3.91) | 1.397 (1.335, 1.462) | 0.08 |
| Alzheimer's disease | 5,694 (0.36) | 251 (0.53) | 1.219 (1.071, 1.382) | 0.002 |

**Table 4** *(continued)*

**Table 4** *(continued)*

| Comorbidities | Non-severe asthma (n=1,595,847) | Severe asthma (n=46,919) | Adjusted OR (95% CI)† | P value |
|---|---|---|---|---|
| Parkinson's disease | 10,536 (0.66) | 414 (0.88) | 1.080 (0.976, 1.191) | 0.12 |
| Psychiatric disorders‡ | 475,130 (29.77) | 13,759 (29.33) | 1.264 (1.237, 1.291) | <0.001 |
| Anxiety disorders | 239,700 (15.02) | 6,851 (14.60) | 1.187 (1.156, 1.219) | 0.61 |
| Bipolar disorders | 17,760 (1.11) | 724 (1.54) | 1.658 (1.538, 1.787) | <0.001 |
| Mood disorders | 35,154 (9.36) | 920 (1.96) | 1.058 (0.990, 1.130) | 0.09 |
| Schizophrenia | 9,499 (2.20) | 356 (0.76) | 1.517 (1.364, 1.688) | <0.001 |
| Sleep disorders | 207,631 (0.60) | 6,857 (14.61) | 1.406 (1.369, 1.443) | <0.001 |
| Somatoform disorders | 61,814 (13.01) | 1,554 (3.31) | 1.015 (0.964, 1.069) | 0.56 |
| Symptoms and signs involving emotional state | 25,907 (3.87) | 542 (1.16) | 0.842 (0.773, 0.918) | <0.001 |
| Depressive disorders | 149,440 (1.62) | 5,182 (11.04) | 1.462 (1.419, 1.506) | <0.001 |
| Obsessive compulsive disorders | 2,284 (0.14) | 63 (0.13) | 1.114 (0.867, 1.431) | 0.38 |
| Stress disorders | 15,685 (0.98) | 370 (0.79) | 0.952 (0.858, 1.056) | 0.36 |
| GERD | 705,407 (44.20) | 18,693 (39.84) | 1.136 (1.113, 1.159) | 0.04 |
| Osteoporosis-related disease‡ | 195,477 (12.25) | 6,369 (13.57) | 1.378 (1.341, 1.416) | <0.001 |
| Osteoporosis | 186,687 (11.70) | 6,027 (12.85) | 1.360 (1.322, 1.398) | <0.001 |
| Osteoporosis with fracture | 18,249 (1.14) | 768 (1.64) | 1.713 (1.592, 1.842) | <0.001 |
| Rheumatoid arthritis | 63,164 (3.96) | 1,515 (3.23) | 0.967 (0.918, 1.018) | 0.20 |
| Fatty liver disease | 58,568 (3.67) | 1,403 (2.99) | 0.966 (0.915, 1.019) | 0.20 |
| Dyslipidemia | 538,636 (33.75) | 15,732 (33.53) | 1.304 (1.277, 1.331) | 0.003 |
| Endocrine disorder | 608,008 (38.10) | 18,010 (38.39) | 1.369 (1.342, 1.398) | <0.001 |
| Obesity | 2,484 (0.16) | 41 (0.09) | 1.501 (1.103, 2.043) | >0.99 |
| Respiratory disease‡ | 1,521,716 (95.35) | 37,031 (78.93) | 0.450 (0.424, 0.477) | <0.001 |
| COPD | 177,339 (11.11) | 17,870 (38.09) | 6.754 (6.616, 6.895) | <0.001 |
| Pneumonia | 259,962 (16.29) | 10,552 (22.49) | 1.619 (1.582, 1.657) | <0.001 |
| Influenza | 44,080 (2.76) | 1,237 (2.64) | 0.883 (0.835, 0.933) | <0.001 |
| Herpes zoster | 53,855 (3.37) | 1,490 (3.18) | 1.008 (0.956, 1.062) | 0.77 |
| Food allergy | 4,817 (0.30) | 112 (0.24) | 0.938 (0.778, 1.132) | 0.54 |
| Anaphylaxis | 1,995 (0.13) | 88 (0.19) | 1.782 (1.439, 2.207) | <0.001 |
| Drug allergy | 4,356 (0.27) | 211 (0.45) | 1.960 (1.707, 2.252) | <0.001 |

Data are presented as mean ± SD or n (%). †, adjusted for age (18–44, 45–64, or ≥65 years) and sex groups; ‡, *t*-test for continuous variable/Chi-square test or Fisher exact test for proportions. AMI, acute myocardial infarction; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; GERD, gastroesophageal reflux disease; HTN, hypertension; OR, odds ratio; SD, standard deviation; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; URI, upper respiratory infection.

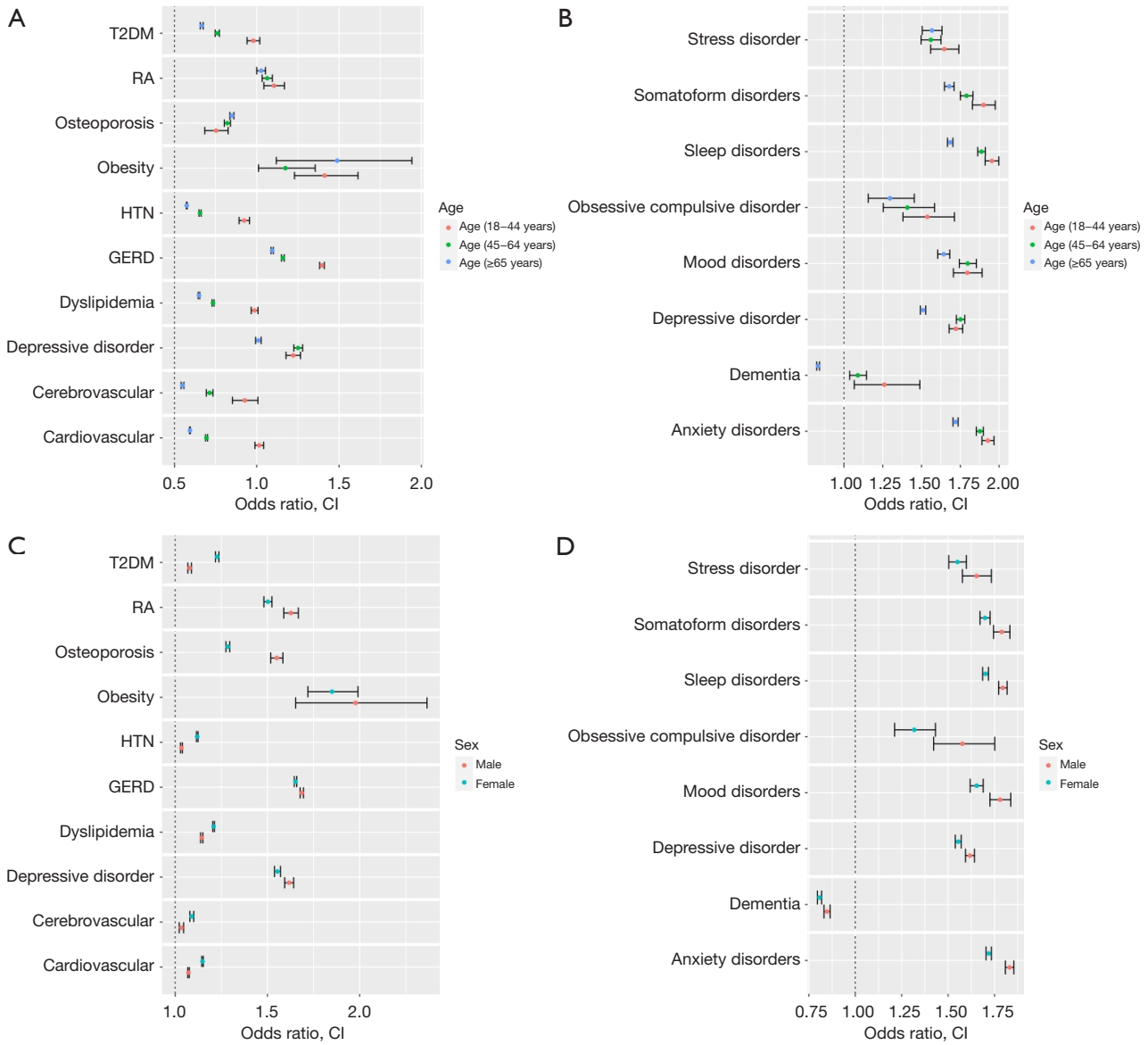


**Figure 1** Odds ratio of major comorbidities in adult patients with asthma and healthy control according to age (A,B) and sex groups (C,D). CI, confidence interval; GERD, gastroesophageal reflux disease; HTN, hypertension; RA, rheumatoid arthritis; T2DM, type 2 diabetes mellitus.

females (P<0.001) (table available at https://cdn.amegroups.cn/static/public/10.21037jtd-24-1531-6.docx).

### *Differences in comorbidities by age and sex*

When the control group and the patients with asthma were divided into age groups of 18–44, 45–64, and ≥65 years, the prevalence of various psychiatric disorders (ICD codes of anxiety disorder, bipolar disorder, depressive disorder, mood disorder, schizophrenia, sleep disorders, somatoform disorders, obsessive compulsive disorder, and stress disorder) by age group in the control group had statistically significant difference (P<0.001). In addition, the prevalence of CVD, cerebrovascular disease, DM, osteoporosis, endocrine disorder, dyslipidemia, RA, and herpes zoster by age group were also different (P<0.001). This tendency was almost similar in the NSA and SA groups of patients with asthma. *Figures 1,2* present the ORs

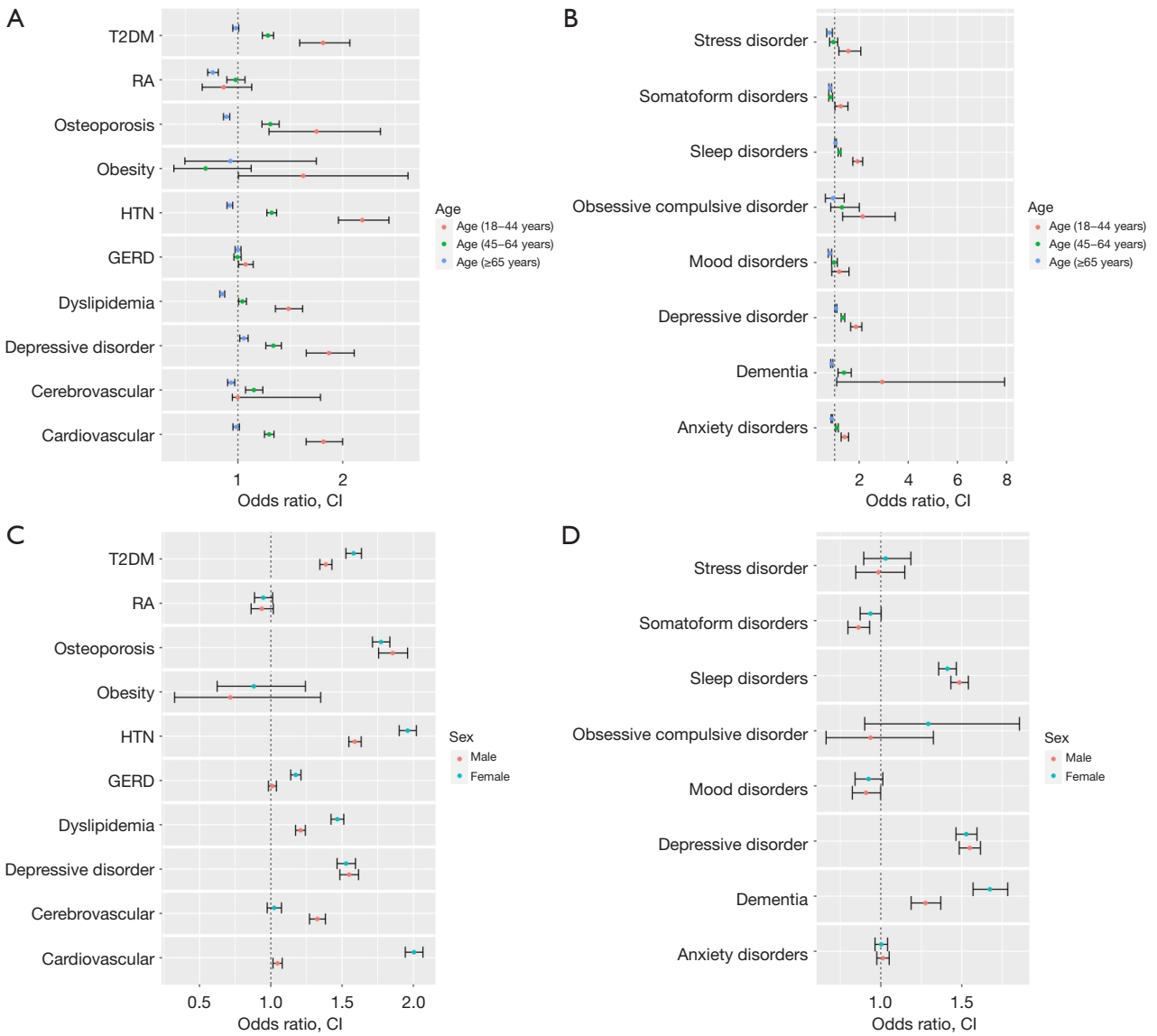


**Figure 2** Odds ratio of major comorbidities in patients with severe asthma and non-severe asthma according to age (A,B) and sex groups (C,D). CI, confidence interval; GERD, gastroesophageal reflux disease; HTN, hypertension; RA, rheumatoid arthritis; T2DM, type 2 diabetes mellitus.

for major comorbidities, with *Figure 1* comparing adult asthma patients to healthy controls stratified by age groups (*Figure 1A*,*1B*) and sex groups (*Figure 1C*,*1D*), and *Figure 2* comparing patients with SA to those with NSA using the same stratification. For dementia, the OR was 0.818 (95% CI: 0.809–0.827) in patients with asthma aged over 65 years, and this was continuously observed when grouped by sex (table available at https://cdn.amegroups.cn/static/public/10.21037jtd-24-1531-4.docx). Acute myocardial infarction (AMI) was associated with patients with asthma in all age (OR =1.380; 95% CI: 1.344–1.416) and sex groups, but there was no significant association according to the severity of asthma (P=0.13). Contrastingly, cerebrovascular stroke was significantly associated with patients with asthma aged over 45 years (P<0.001), but the difference according to sex showed significant association only in the male patients (table available at https://cdn.amegroups.cn/static/public/10.21037jtd-24-1531-4.docx).

When divided by sex, except for dementia and schizophrenia, most comorbidities were more highly

prevalent in patients with asthma than in the control group, with an OR over 1.0. In patients with asthma, the OR for SA group was more than 1 in most comorbidities except rhinitis (*Table 4*). The OR of comorbidities, except vasomotor and allergic rhinitis and fatty liver disease, after adjusting for age was also increased based on asthma severity in both male and female patients (table available at https://cdn.amegroups.cn/static/public/10.21037jtd-24-1531-4.docx).

## Discussion

Previous studies showed that asthma is associated with high prevalence of comorbidities such as rhinitis (2-5), GERD (2,3,5,12,13), psychiatric disorders (3,14-24), CVD (2,3,12,18,25-27), cerebrovascular disease (18,25), DM (2,18,28-32), hyperlipidemia (33,34), and rheumatologic disease (35-37). In our study, we compared patients with asthma with those without asthma as the control group and found that asthma was associated with higher comorbidities in most age and sex groups. When we performed subgroup analysis according to severity of asthma, SA was also associated with most comorbidities.

There is a confirmational relationship between GERD and asthma: GERD is common in patients with asthma, and asthma is also reported more frequently in patients with GERD (38,39). This bidirectional association may be partially attributed to asthma medications such as β2-agonists, which cause relaxation of the lower esophageal sphincter (13). Other contributing factors include mechanical and reflexive mechanisms. Mechanical factors, such as increased negative intrathoracic pressure and diaphragmatic contractions associated with obstructive patterns in asthma, create a pressure gradient that facilitates gastroesophageal reflux. Additionally, micro-aspiration of gastric contents into the airways and the vagal reflex induced by esophageal acid exposure further contribute to airway hyperresponsiveness and inflammation. These mechanisms highlight the shared pathophysiology between GERD and asthma and emphasize the need for a comprehensive approach to managing these interconnected conditions (40). In previous studies, the prevalence of GERD in patients with asthma is 12–85% (39-41) and approximately 2.5–7% in Asia (42,43). Our study showed the prevalence of GERD of 26.94% in patients without asthma and 44.79% in patients with asthma. This difference might have occurred because the primary or secondary disease code for GERD was used in the previous analysis using similar data (43), and the principal or four additional diagnoses codes were used in our study. Additionally, GERD had a higher prevalence and hospital rate in patients with SA than those of patients with NSA, which could be considered a result indicating that GERD is a co-morbidity requiring management in uncontrolled asthma to control the symptomatic state of asthma.

Upper airway diseases such as allergic rhinitis, rhinitis, sinusitis, and rhinosinusitis are the well-known commonly occurring comorbidities in patients with asthma, and evidence clearly supports the correlation between upper and lower airway diseases (2-5,41,44).

Upper airway diseases such as allergic rhinitis, rhinitis, sinusitis, and rhinosinusitis are well-known comorbidities in asthma patients, with substantial evidence supporting the correlation between upper and lower airway diseases (2-5,41,44). Since our study analyzed claim data, we were unable to distinguish subtypes of rhinitis using claim codes alone, leading to a potential overestimation of the prevalence of vasomotor and allergic rhinitis as well as chronic sinusitis. In our study, vasomotor and allergic rhinitis were among the most prevalent conditions in asthma patients, ranking highest after bronchitis and upper respiratory infections (URI). However, bronchitis and URI are common diagnoses frequently used in primary care settings and may have been overrepresented in our analysis due to their broad and non-specific nature. Notably, nasal polyps, commonly associated with chronic rhinosinusitis (CRSwNP), also play a significant role in asthma as part of the 'united airway' concept. Patients with CRSwNP and asthma share common pathophysiological features, including type 2 inflammation, eosinophilia, and epithelial barrier dysfunction. CRSwNP is associated with more SA, characterized by increased exacerbation rates, greater airway obstruction, and more extensive eosinophilic inflammation (45,46). Furthermore, the prevalence of nasal polyps is higher in patients with nonallergic asthma and rhinitis compared to those with allergic respiratory diseases, suggesting that nonallergic respiratory disease may be a stronger contributor to nasal polyps development (46). These findings emphasize the importance of recognizing nasal polyps and CRSwNP as significant comorbidities in asthma management and their potential to influence disease severity and treatment outcomes. However, we were unable to separately analyze CRSwNP in this study, as this could have provided more detailed insights into its impact on asthma severity and comorbidities.

Psychiatric disorders, such as depressive disorder and anxiety disorders, are known to be more prevalent among patients with asthma (16,47,48). As psychological stress can

 

modulate asthma symptoms and patients with depressive disorder appeared to have a preference for Th2 immune response (21,49), psychological conditions are also associated with worsening asthma symptoms, acute exacerbation, higher healthcare utilization, and decreased quality of life and medication adherence (20,22,50). In a previous study, uncontrolled asthma showed an association with a higher productivity loss than controlled asthma, confirming that uncontrolled asthma and psychological distress are modifiable factors associated with substantial indirect costs in individuals with asthma. In this study, in terms of social policy, it was also shown that psychological distress should be actively monitored in patients with asthma (51). We found that patients with asthma had a higher prevalence of psychiatric disorders, which showed an association with asthma except for schizophrenia and bipolar disorder in all age and sex groups. SA was associated with several psychiatric disorders including depressive disorder, sleep disorder, bipolar disorder, and schizophrenia after adjusting for age and sex. Increased risk of bipolar disorder and schizophrenia spectrum disorders in patients with childhood asthma had also been reported in a previous study (52), and asthma alongside the psychological conditions appeared to share common genetic vulnerability and disturbance in the immune-inflammatory system (52,53).

Asthma is a well-known risk factor for developing CVD, with evidence suggesting that asthma exacerbations significantly increase the risk of acute myocardial infarction (AMI) and ischemic stroke (25,27). Hypertension, closely associated with asthma severity, particularly type 2-low asthma, is linked to inflammatory processes involving Interferon-γ and Th17 cells (54,55). Patients with asthma taking oral corticosteroids have an elevated risk of developing CVD.

The underlying mechanisms linking asthma to CVD may involve systemic inflammation, endothelial dysfunction, and prothrombotic states. Persistent asthma is associated with higher levels of systemic inflammatory markers such as C-reactive protein (CRP) and fibrinogen, which contribute to atherosclerotic plaque formation and increased cardiovascular risk (56,57). Additionally, asthma-related mortality due to CVD may be linked to leukotrienes, potent proinflammatory mediators that not only exacerbate asthma symptoms but also play a role in atherosclerotic plaque destabilization and thrombotic events (56). The association between asthma and CVD extends to asthma medications. While oral corticosteroids are critical for asthma management, their prolonged use has been linked to adverse cardiovascular outcomes (56,58). Furthermore, poor lung function and airflow obstruction, common in asthma, are significant predictors of cardiovascular mortality (58). Late-onset asthma has also been identified as a risk factor for increased CVD morbidity and mortality, possibly due to cumulative systemic inflammation and comorbidities such as hypertension and obesity (57,58). Nevertheless, the findings emphasize the importance of managing systemic inflammation and addressing comorbidities in asthma patients to reduce the risk of CVD-related mortality.

Previous meta-analyses have reported that asthma is associated with a hazard ratio (HR) of 1.32 for cerebral stroke (95% CI: 1.13–1.54) (59), However, stroke has diverse etiologies depending on subtypes and risk factors, making it challenging to evaluate the association between asthma and cerebrovascular stroke using claim data alone. While our study demonstrated a link between asthma and cerebrovascular disease, prior research that accounted for multiple confounding factors found no significant increase in the risk of hemorrhagic or ischemic stroke in asthma patients (60). These findings suggest that the relationship between asthma and stroke may be influenced by other underlying factors requiring further investigation.

Asthma and metabolic syndrome share a common pathophysiology characterized by chronic systemic inflammation, which may explain the observed associations between asthma and specific metabolic conditions, including diabetes mellitus (DM), obesity, and dyslipidemia (28,29,31,32,61). Previous studies have reported that DM is more prevalent in asthma patients, with SA requiring high doses of inhaled corticosteroids linked to worsening glycemic control (32). Insulin resistance and metabolic syndrome in patients with prediabetes or diabetes have also been suggested to contribute to increased asthma morbidity (29,62).

Obesity is another critical component of metabolic syndrome that has been strongly associated with asthma. Obesity-related increases in leptin and decreases in adiponectin are known to exacerbate systemic inflammation and airway hyperresponsiveness, thereby worsening asthma outcomes (29,63). However, in clinical practice, the coding for obesity may often be omitted when prescribing medications, potentially underestimating its prevalence in asthma patients.

Dyslipidemia, an independent risk factor for asthma exacerbations, also plays a role in the association between metabolic syndrome and asthma (64). Hypercholesterolemia has been shown to have a pro-inflammatory effect, promoting the release of inflammatory cytokines and driving eosinophilic inflammation. Changes in the lipid

 

profile may further enhance the innate immune response, contributing to airway inflammation in asthma (34,65).

In our study, DM, dyslipidemia, and obesity were significantly more prevalent in asthma patients, with SA showing a particularly strong association with dyslipidemia and type 2 DM. These findings highlight the intricate interplay between metabolic syndrome and asthma, underscoring the importance of addressing metabolic comorbidities in asthma management.

The association between asthma and RA has been reported in several previous studies, and it was thought to be caused by shared immunological mechanism such as Th17 inflammation, premature immune sensitization, or other inflammation mediators including tumor necrosis factor and leukotrienes (36,37,66,67). After adjusting for confounding factors such as smoking status, asthma, and atopic disease, the association between asthma and an increased risk of RA was observed (37). In our study, RA showed association with asthma in all age and sex groups, but association based on severity of asthma was not observed.

Asthma in the elderly represents a unique clinical phenotype, with distinct challenges arising from age-related physiological changes, higher comorbidity burdens, and polypharmacy. In our study, elderly patients with asthma exhibited a higher prevalence of chronic comorbidities such as hypertension, osteoporosis, and cardiovascular disease compared to younger counterparts. These findings align with previous research demonstrating an increased incidence of respiratory and systemic comorbidities in older adults, contributing to worse asthma outcomes and reduced quality of life (68,69). Age-related changes, including immunosenescence and structural alterations in the airways, exacerbate the severity of asthma symptoms in the elderly. A higher prevalence of asthma-COPD overlap (ACO) in this demographic further complicates diagnosis and management (68). Our data also indicate a notable association between asthma severity and comorbid conditions in older patients, emphasizing the need for a multidisciplinary approach to care. Polypharmacy is another critical consideration in elderly asthmatics, as it increases the risk of adverse drug interactions and complicates disease management. For instance, statin use has been associated with reduced asthma exacerbations, while proton pump inhibitors have been linked to an increased risk of exacerbations in older adults. These findings highlight the importance of careful medication review and optimization in this population (69). While comorbidities in elderly asthmatics may not always worsen asthma control (69), their presence necessitates individualized management strategies to mitigate the impact on overall health outcomes.

This large-scale, population-based database study, which covered approximately 99.4% of South Korea's population, provides significant insights into asthma and its associated conditions. However, the study has several limitations. First, as the analysis was retrospective and based on claim data, errors in diagnostic codes or omissions of claims may have occurred, a limitation inherent to most studies using such data. Diagnoses were made using operational definitions based on diagnostic codes and prescription histories rather than clinical diagnostic test results, which could impact accuracy. However, including asthma-related drug prescriptions likely improved diagnostic reliability, and South Korea's comprehensive national health insurance system minimized the risk of data omission compared to similar studies in other countries. Second, national health insurance policies may have influenced the input of diagnostic and treatment codes, potentially leading to conservative prevalence estimates for certain conditions, such as psychiatric disorders, which were counted only if treatment at a medical institution was sought. Third, asthma severity classification into SA and NSA relied on cumulative high-dose inhaled corticosteroid (ICS) prescriptions as a proxy for severity rather than clinical parameters like symptom scores or lung function. This approach may have misclassified patients treated with oral corticosteroids or biologics, which were not reimbursable at the time. While biologics were minimally used in 2015, their exclusion may have impacted the dataset. Nonetheless, this study is the first to define SA based on high-dose ICS using large-scale claim data, reducing discrepancies between clinical practice and claims data. Fourth, the study identified associations between asthma and specific comorbidities, but causal relationships remain unexplored. Further clinical studies are needed to investigate the mechanisms underlying these associations. Finally, the absence of clinical data on smoking history and the inclusion of ICD codes for COPD may raise questions about the specificity of the findings to asthma patients. However, excluding COPD codes would have removed the asthma-COPD overlap group, which was essential for this analysis. These limitations highlight the need for future studies incorporating detailed clinical data to validate and extend our findings.

## Conclusions

In conclusion, our study showed significant association

between several comorbidities and asthma using large-scale nationwide claim data, and clinicians should consider those comorbidities when treating patients with asthma. Although revealing causality in our study was difficult owing to limitation of the claim data, our findings substantiated previous studies with corresponding results using large-scale data and could be a foundation for prospective research.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1531/rc

*Data Sharing Statement:* Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1531/dss

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*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1531/coif). W.J.S. serves as an unpaid editorial board member of *Journal of Thoracic Disease*. The other authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board of the Asan Medical Center (No. S2016-1254-0010) and the Ethics Committee of the National Health Insurance Sharing Service (No. NHIS-2016-4-016) and individual consent for this retrospective analysis was waived.



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