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Original Article

# Analysis of comorbidities and multimorbidity in adult patients in the International Severe Asthma Registry

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ABSTRACT

**Background:** Investigation for the presence of asthma comorbidities is recommended by the Global Initiative for Asthma because their presence can complicate asthma management.
**Objective:** To understand the prevalence and pattern of comorbidities and multimorbidity in adults with severe asthma and their association with asthma-related outcomes.
**Methods:** This was a cross-sectional study using data from the International Severe Asthma Registry from 22 countries. A total of 30 comorbidities were identified and categorized a priori as any of the following: (1) potentially type 2–related comorbidities, (2) potentially oral corticosteroid (OCS)–related comorbidities, or (3) comorbidities mimicking or aggravating asthma. The association between comorbidities and asthma-related outcomes was investigated using multivariable models adjusted for country, age at enrollment, and sex (ie male or female).
**Results:** Of the 11,821 patients, 69%, 67%, and 55% had at least 1 potentially type 2–related, potentially OCS-related, or mimicking or aggravating comorbidities, respectively; 57% had 3 or more comorbidities, and 33% had comorbidities in all 3 categories. Patients with allergic rhinitis, nasal polyposis, and chronic rhinosinusitis experienced 1.12 ($P = .003$), 1.16 ($P < .001$), and 1.29 times ($P < .001$) more exacerbations per year, respectively, than those without. Patients with nasal polyposis and chronic rhinosinusitis were 40% and 46% more likely ($P < .001$), respectively, to have received long-term (LT) OCS. All assessed potential OCS-related comorbidities (except obesity) were associated with a greater likelihood of LTOCS use (odds ratios [ORs]: 1.23-2.77) and, except for dyslipidemia, with a greater likelihood of uncontrolled asthma (ORs: 1.29-1.68). All mimicking or aggravating comorbidities assessed were associated with more exacerbations (1.24-1.68 times more), all (except bronchiectasis) with increased likelihood of uncontrolled asthma (ORs: 1.57-1.81), and all (except chronic obstructive pulmonary disease) with increased likelihood of LTOCS use (ORs: 1.37-1.57). A greater number of comorbidities was associated with worse outcomes.
**Conclusion:** In a global study, comorbidity or multimorbidity is reported in most adults with severe asthma and is associated with poorer asthma-related outcomes.
**Clinical Trial Registration:** The International Severe Asthma Registry database has ethical approval from the Anonymous Data Ethics Protocols and Transparency (ADEPT) committee (ADEPT0218) and is registered with the European Union Electronic Register of Post-Authorization Studies (European Network Centres for Pharmacoepidemiology and Pharmacovigilance [ENCEPP]/DSPP/23720). The study was designed, implemented, and reported in compliance with the European Network Centres for Pharmacoepidemiology and Pharmacovigilance (ENCEPP) Code of Conduct (EMA 2014; EUPAS44024) and with all applicable local and international laws and regulations, and registered with ENCEPP (https://www.encepp.eu/encepp/viewResource.htm?id=48848). Governance was provided by ADEPT (registration number: ADEPT1121).
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## Introduction

Since 2014, the Global Initiative for Asthma (GINA) has focused on asthma control and personalized management of patients' modifiable risk factors, including comorbidities.[1,2] Investigation for the presence of comorbidities is recommended at every part of the asthma management journey, and multimorbidity is recognized as a common problem in patients with asthma.[1] Some of these comorbidities can complicate asthma treatment, considerably increase the risk of poor asthma-related outcomes,[3-5] and are associated with significant productivity losses.[6] Overall comorbidity-attributable health care costs are 5 times higher than costs attributable to asthma alone.[7]

The list of asthma comorbidities is extensive and broadly divided into 3 categories: (1) type 2 (T2) inflammatory comorbidities, (2) comorbidities potentially related to oral corticosteroid (OCS) exposure, and (3) comorbidities that mimic or aggravate asthma symptoms, with some overlap between categories.[1,8,9] The T2 inflammatory comorbidities (eg, allergic rhinitis [AR], chronic rhinosinusitis [CRS], and nasal polyposis [NP]), are markers of T2 inflammation and are associated with more severe asthma (eg, particularly CRS with NP). The OCS-related comorbidities include obesity, osteoporosis, diabetes, anxiety, and depression.[8,10,11] Anxiety and depression are associated with worse asthma symptom control, reduced medication adherence, and reduced asthma-related quality of life, and are also sometimes categorized as asthma-mimicking or aggravating comorbidities.[12] Comorbidities that mimic/aggravate asthma symptoms include gastroesophageal reflux disease (GERD) and chronic obstructive pulmonary disease (COPD). Gastroesophageal reflux disease is a common cause of dry cough and may be aggravated by the use of asthma medications such as β-agonists and theophylline.[1] Chronic obstructive pulmonary disease can present with asthma, a condition sometimes referred to as asthma-COPD overlap.[13] Asthma-COPD overlap is associated with a greater symptom burden, more frequent exacerbations, worse quality of life, a more rapid lung functional decline, a higher mortality rate, and a greater use of health care resources compared with either asthma or COPD alone.[13] Few large-scale studies have been published that assessed comorbidities in severe asthma, and little has been reported on the burden and impact of multimorbidity.[14-16]

The International Severe Asthma Registry (ISAR), the largest adult severe asthma registry in the world, includes data on more than 12,000 patients and collects information on comorbidities, asthma clinical characteristics, and outcome domains.[17-20] Its size and scope permit an in-depth look at comorbidity prevalence globally and by country, facilitating comorbidity categorization, assessment of presentation patterns, and investigation of the relationship between comorbidities and asthma. The aim of our study was to understand the global prevalence, distribution, and coexistence of comorbidities, including multimorbidities, in adults with severe asthma and investigate the association of comorbidities with clinical and asthma-related outcomes.

## Methods

### *Study Design and Data Sources*

This was a cross-sectional study using data from ISAR (https://isaregistries.org/), details of which have been described elsewhere.[20] We

included data from 22 countries that shared data from 2010 to 2022 with ISAR (Argentina, Australia, Bulgaria, Canada, Colombia, Denmark, Greece, India, Ireland, Italy, Japan, Kuwait, Mexico, Poland, Portugal, Saudi Arabia, South Korea, Spain, Taiwan, the United Arab Emirates, the United Kingdom, and the United States). Data were either retrospective (collected pre-ISAR launch [ie, May 1, 2017]) or prospective (collected post-ISAR launch). For patients who did not subsequently initiate biologics, the enrollment date was the visit closest to the ISAR launch for retrospectively enrolled patients, and the first visit date for prospectively enrolled patients. For patients who subsequently initiated biologics, the enrollment date was the biologic initiation date for both retrospectively and prospectively enrolled patients. The pre–biologic use period was used to avoid confounding potentially caused by biologics on asthma-related outcomes and biomarkers.

This study is exempt from the institutional review board. All ISAR data collection sites have obtained regulatory agreements in compliance with specific data transfer laws, country-specific legislation, and relevant ethic committees and organizations (eSupplement).

### *Patients*

Patients were aged 18 years and older, had severe asthma (ie, receiving treatment at GINA 2018 step 5) or with uncontrolled asthma at GINA step 4 (ie, treated with inhaled corticosteroid/long-acting $\beta_2$-agonist),[21] and had data on 1 or more comorbidity collected as part of this study. We included all eligible patients to assess individual comorbidity prevalence and predefined comorbidity categories and to explore comorbidity cooccurrence (prevalent series). Only prospectively enrolled patients were included in the association analysis (association series) because at the time of the analysis, clinical and functional end point data were scarce for the retrospectively enrolled patients. Patients with missing sex data were excluded from the association analysis.

### *Comorbidity Data Collection*

Data on core physician-assessed, clinically diagnosed comorbidities (ie, eczema, AR, CRS, NP, and obesity) were collected by all countries. Data on additional potentially related OCS comorbidities (maximum 16; eg, circulatory system diseases, ocular diseases) were collected by many countries. Some countries also elected to collect data on extra comorbidity variables (eg, food allergy, dyslipidemia, GERD) (Table 1 and eTable 1).[20,22]

### *Study Variables*

A total of 30 comorbidities were identified and categorized a priori as the following: (1) potentially T2-related comorbidities, (2) potentially OCS-related comorbidities, or (3) comorbidities mimicking or aggravating asthma. These categories were identified by extensive literature search and expert consensus. Because presence or

**Table 1**
Prevalence of 30 Comorbid Conditions in Patients With Severe Asthma

| Comorbidities | Number of contributing countries | Sample size[a] | N[b] | Prevalence |
|---|---|---|---|---|
| **Potentially T2-related categories** | | | | |
| Allergic rhinitis | 22 | 11,281 | 5525 | 49% |
| Chronic rhinosinusitis[c] | 21 (all −AU) | 11,223 | 5151 | 46% |
| Nasal polyposis | 22 | 11,613 | 2413 | 21% |
| Eczema or atopic dermatitis | 22 | 11,600 | 1199 | 10% |
| Urticaria | 4 (AU, ES, UK, USA) | 6849 | 243 | 3.5% |
| Food allergy | 5 (AU, ES, PT, UK, USA) | 6977 | 230 | 3.3% |
| Aspirin sensitivity | 7 (AU, CA, DK, ES, PT, UK, USA) | 7498 | 122 | 1.6% |
| Eosinophilic esophagitis | 3 (AU, UK, USA) | 6149 | 32 | 0.52% |
| **Potentially OCS-related comorbidities** | | | | |
| Obesity | 22 | 11,583 | 4893 | 42% |
| Hypertension | 12 (AU, ES, IT, JP, MX, PL, PT, SK, TW, UAE, UK, USA) | 9252 | 2104 | 23% |
| Sleep apnea | 21 (all −IT) | 10,094 | 2256 | 22% |
| Dyslipidemia | 4 (AU, ES, UK, USA) | 6849 | 1083 | 16% |
| Anxiety or depression[d] | 21 (all −DK) | 11,019 | 1565 | 14% |
| Osteoporosis | 21 (all −DK) | 10,742 | 1371 | 13% |
| Diabetes | 22 | 11,422 | 1336 | 12% |
| Coronary heart disease | 22 | 11,039 | 984 | 8.9% |
| Pneumonia | 20 (all −DK, −ES) | 10,300 | 877 | 8.5% |
| Other significant infections | 20 (all −IE, −PT) | 6918 | 560 | 8.1% |
| Peptic ulcer | 20 (all −DK, -ES) | 10,323 | 266 | 2.6% |
| Pulmonary embolism or VTE | 20 (all −DK, −ES) | 9972 | 246 | 2.5% |
| Cataract | 21 (all −DK) | 10,923 | 258 | 2.4% |
| Chronic kidney disease | 21 (all −DK) | 11,032 | 164 | 1.5% |
| Adrenal insufficiency | 3 (AU, UK, USA) | 6149 | 80 | 1.3% |
| Glaucoma | 21 (all −DK) | 10,888 | 139 | 1.3% |
| Cerebrovascular accident | 20 (all −DK, −ES) | 9968 | 63 | 0.63% |
| **Comorbidities mimicking** or **aggravating asthma** | | | | |
| GERD[e] | 7 (AU, CA, DK, ES, PT, UK, USA) | 7400 | 3243 | 44% |
| COPD | 7 (AU, CA, DK, ES, PT, UK, USA) | 7508 | 1045 | 14% |
| Bronchiectasis | 7 (AU, CA, DK, ES, PT, UK, USA) | 7509 | 799 | 11% |
| VCD or laryngeal spasms | 5 (AU, DK, ES, UK, USA) | 7199 | 758 | 11% |
| Dysfunctional breathing | 6 (AU, CA, DK, ES, UK, USA) | 7389 | 234 | 3.2% |

Abbreviations: AU, Australia; CA, Canada; COPD, chronic obstructive pulmonary disease; DK, Denmark; ES, Spain; GERD, gastroesophageal reflux disease; IE, Ireland; IT, Italy; JP, Japan; MX, Mexico; OCS, oral corticosteroid' PL, Poland; PT, Portugal; SK, South Korea; T2, type 2; TW, Taiwan; UAE, United Arab Emirates; UK, United Kingdom; USA, United States of America; VCD, vocal cord dysfunction; VTE, venous thromboembolism.
[a]Variations in sample size are because of missing values for individual patients and/or at the country level.
[b]Number of patients with comorbidity.
[c]With or without nasal polyposis.
[d]Can also mimic or aggravate asthma.
[e]Can also be OCS related.

**Table 2**
Definition and Timing of Collection for Demographic, Clinical, and Asthma Outcome Variables

| Variable | Definition/categorization | Timing of collection |
|---|---|---|
| Demographic characteristics | | |
| Sex | Male or female | At enrollment |
| Age groups (y) | 18-29; 30-39; 40-49; 50-59; 60-69; 70-79; 80+ | |
| Smoking status | Current, former, never | |
| Comorbidity | | |
| Potentially T2-related | AR, CRS, NP, eczema or AD, urticaria, food allergy, aspirin sensitivity, eosinophilic esophagitis | Before or after the time of enrollment |
| Potentially OCS-related | Obesity, HT, SA, diabetes, dyslipidemia, anxiety or depression, OP, CHD, PN, other significant infection, peptic ulcer, PE or VTE, cataract, glaucoma, adrenal insufficiency, CVA | |
| Potentially mimicking or aggravating asthma symptoms | GERD, COPD, bronchiectasis, VCD/LS, dysfunctional breathing | |
| Clinical characteristics | | |
| Age of asthma onset (y) | <12 and ≥12 | At enrollment |
| BEC (cells/μL) | Test result | Highest count before initiating biologics or highest count ever recorded for those not receiving biologics |
| Serum IgE (IU/mL) | | |
| FeNO (ppb) | | |
| Asthma outcomes | | |
| LTOCS use | Yes or no and defined as daily use of OCS as a background therapy for more than 3 mo | At enrollment |
| Exacerbation rate | Number of exacerbations requiring rescue steroids | In the 12-mo period preceding enrollment |
| $ppFEV_1$ | <80%; ≥80% | Measured as close as possible to enrollment |
| Asthma control | Well controlled, partly controlled, or uncontrolled defined by GINA 2023,[1] ACQ, or ACT | |

Abbreviations: ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; AD, atopic dermatitis; AR, allergic rhinitis; BEC, blood eosinophil count; CHD, chronic heart disease; COPD, chronic obstructive pulmonary disease; CRS, chronic rhinosinusitis; CVA, cerebrovascular accident; FeNO, fractional exhaled nitric oxide; GERD, gastroesophageal reflux disease; GINA, Global Initiative for Asthma; HT, hypertension; LS, least squares; LTOCS, long-term oral corticosteroid; NP, nasal polyposis; OCS, oral corticosteroids; OP, osteoporosis; PE, pulmonary embolism; PN, pneumonia; pp, parts per billion; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; SA, sleep apnea; T2, type 2; VCD, vocal cord dysfunction; VTE, venous thromboembolism.

absence information on comorbidities was not always available at each visit, we used all visits available (before or after enrollment) to compute a never or ever-present variable for each individual comorbidity. Demographic and clinical characteristics (eg, age of onset, biomarker levels) and also prebiologic asthma–related outcomes were also collected (ie, long-term OCS [LTOCS] use, exacerbation rate, percent predicted forced expiratory volume in 1 second [$ppFEV_1$],[23] and asthma control). Definitions and categorizations of variables and timing of collection are provided in Table 2 and eTable 2.

### *Study Outcomes*

The prevalence of individual comorbidities (by category and country), multimorbidity (1, 2, and 3+ comorbidities), and comorbidity co-occurrences across categories were calculated. Data on the number of countries collecting information on each type of comorbidity and how these data were collected (eg, categorially, check box, binary field, free text, International Classification of Diseases code) were also assessed. We assessed the association between the most common individual comorbidities (a priori threshold prevalence of ≥10%) and the number of comorbidities (overall and by comorbidity category) as well as the demographic characteristics, clinical characteristics, and asthma-related outcomes. Demographic characteristics, clinical characteristics, and asthma-related outcomes were assessed at the time of enrollment.

### *Statistics*

The statistical analysis plan was predefined. R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria) was used to conduct all statistical analyses.[24] Descriptive statistics were used to summarize comorbidity prevalence (individual and co-occurrences). For individual comorbidities, the denominator was computed as the number of patients with presence or absence information available on at least 1 visit (eSupplement). Comorbidity co-occurrence was assessed in patients with nonmissing data for at least 3 comorbidities and described as the prevalence of 1, 2, and 3 or more comorbidities, overall and by categories.

The prevalence of comorbidities by demographic characteristics was compared through univariate analysis. The association between clinical characteristics and asthma-related outcomeswith comorbidities was assessed through multivariable models. For the association of individual comorbidity with outcome, comorbidity (ever or never present) was the explanatory variable and clinical characteristics and asthma-related outcomes were the dependent variables. For the association between the number of comorbidities and outcomes, we used ordinal variables (0, 1, 2, or 3+ comorbidities), overall and within comorbidity categories. All models were adjusted for country, age at registry enrollment, and sex. For continuous dependent variables (age at asthma onset, biomarkers, and $ppFEV_1$), we used linear regression, and results were expressed as differences in means comparing patients with to those without the considered comorbidity. For binary dependent variables (LTOCS use [yes or no] and asthma control [uncontrolled or partly or well controlled]), we used logistic regressions, and the results were expressed as odds ratios (ORs). The comorbidity and exacerbation rate association was investigated using negative binomial regressions. All comparisons were 2-sided, and significance was considered at an $\alpha$ level of .05. Additional details on all statistical analyses are provided in the eSupplement.

## Results

### *Subject Disposition and Baseline Characteristics*

As of January 24, 2022, ISAR contained data from 22 countries including 12,099 adult patients with severe asthma (eFig 1). A total of 11,821 patients were included in the prevalence series and 8499 in the association series. Patients in both assessment cohorts were predominantly of the female sex (62%), aged 50 to 69 years at enrollment (50%), had later-onset asthma (ie, aged ≥12 years: ~80%) an eosinophilic phenotype (~87%), and evidence of atopy (>60%) (eTable 3A

and 3B). Baseline characteristics for both series are provided in the eSupplement (eTable 3A and 3B).

*Comorbidity Data Collection*

Information on comorbidities was not uniformly collected by countries, depending on whether the comorbidity was core, additional, or extra (Table 1). Most potentially T2-related and OCS-related comorbidities were consistently collected. However, not all countries collected information on urticaria (collected in 4 countries), food allergy (n = 5), aspirin sensitivity (n = 7), eosinophilic esophagitis (n = 3), hypertension (n = 12), dyslipidemia (n = 4), and adrenal insufficiency (n = 3). Comorbidities mimicking or aggravating asthma symptoms were all infrequently collected (eg, GERD, COPD, and bronchiectasis were each collected by only 7 countries) (Table 1).

Comorbidity information was collected in different ways (eg, as categorical [eg, current, past or never] or binary [yes or no] data, or using check boxes, free text, or International Classification of Diseases codes from electronic medical records), and there was intercategory variability in the method of collection (eFig 2). Potentially T2-related comorbidity information was gathered predominantly categorically (eFig 2A), whereas the method of collection for potentially OCS-related comorbidities varied by comorbidity—collected mostly as categorical/binary data for sleep apnea, anxiety or depression, and osteoporosis, and as free text for hypertension (eFig 2B). Methods of collection for comorbidities mimicking or aggravating asthma symptoms exhibited the greatest heterogeneity (eFig 2C).[17]

*Prevalence of Comorbidities*

*Individual Comorbidities*

Patients with severe asthma had a wide range of comorbidities. The most prevalent reported individual comorbidities were AR (49%; n = 5525 of 11,281), CRS (46%; n = 5151 of 11,223), obesity (42%; n = 4893 of 11,583), and GERD (44%; n = 3243 of 7400) (Table 1). Of the 3745 patients with reported AR and available data on allergen tests (skin prick test or serum tests), 746 (19.9%) were not positive for any tested allergen. In addition, marked between-country variation was noted for each of these comorbidities (eFig 3). Reported AR prevalence ranged from 4.6% in the United Kingdom to 92.9% in Mexico, obesity prevalence ranged from 9.3% in South Korea to 64.2% in Kuwait, and GERD prevalence ranged from 3.4% in the United Kingdom to 56.8% in the United States.

*Comorbidity Categories*

Overall, the prevalence of at least 1 comorbidity was 92%. The estimates for at least 1 potentially T2-related comorbidity, at least 1 potentially OCS-related comorbidity, and at least 1 comorbidity mimicking or aggravating asthma were 69%, 67%, and 55%, respectively. These estimates were relatively stable in sensitivity analysis restricting the study population to patients with various thresholds of minimum numbers of comorbidities with available data (eTable 4).

*Comorbidity Counts and Multimorbidity*

Most patients (57.3%; n = 6761 of 11,794) had at least 3 comorbidities of any type (Fig 1). Of note, 39.5% (n = 4600 of 11,623) of patients had 2 or more potentially T2-related comorbidities, 39.9% (n = 4589 of 11,489) had 2 or more potentially OCS-related comorbidities, and 20.9% (n = 1567 of 7496) had 2 or more comorbidities mimicking or aggravating asthma (Fig 1). These proportions were relatively stable when explored by subgroups of patients with increasing numbers of comorbidities with available data (eTable 5). In a subpopulation of 7561 patients who had information available for 1 or more comorbidities in each category, 2477 (32.8%) had comorbidities in all 3 categories. We further explored the most frequent comorbidities and comorbidity combinations by number (1, 2, or ≥3) of reported comorbidities (eTable 6). The most common dual comorbidity patterns in patients with 2 reported comorbidities were AR and CRS (44.8%), obesity and sleep apnea (21.7%), and GERD and COPD (32.6%) for potentially T2-related, potentially OCS-related, and comorbidities mimicking or aggravating asthma symptom categories, respectively.

*Comorbidity Associations With Demographic Characteristics, Biomarkers, and Asthma Outcomes*

We focused on the 15 most common comorbidities (prevalence ≥10%) with restriction to prospectively enrolled patients (n = 8499; patient characteristics available in eTable 3B). The association of comorbidities with sex, age, and smoking status is provided in the eSupplement (eTables 7-9). The presence of comorbidities was significantly associated with asthma clinical characteristics and outcomes, and the pattern of the association was comorbidity dependent (Table 3; eTables 10-17; Fig 2).

*Biomarkers and Age at Asthma Onset*

Patients with potentially T2-related comorbidities had higher biomarker concentrations than those without (Table 3; eTables 11-13). Patients with CRS and NP had higher blood eosinophil count (BEC) and higher fractional exhaled nitric oxide concentrations, patients with AR had higher concentrations of all 3 biomarkers, and those with eczema or atopic dermatitis (AD) had higher IgE concentrations. In contrast, potentially OCS-related comorbidities were either not associated with this biomarker concentration elevation or were associated with lower concentrations, except for osteoporosis, which was associated with elevated BEC (Table 3; eTable 11). Comorbidities mimicking or aggravating asthma symptoms were also not associated with biomarker concentration elevation, with the exception of

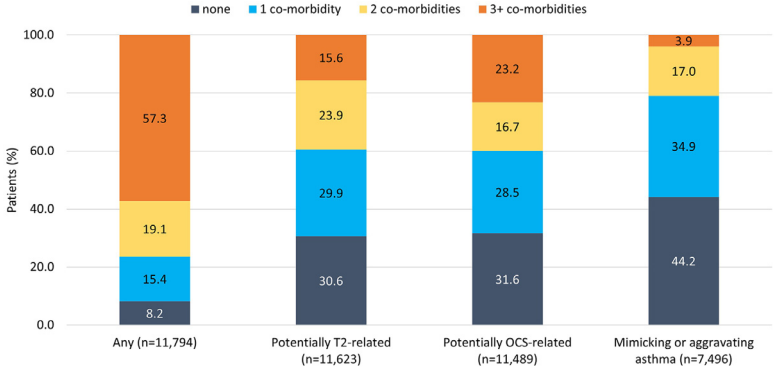


**Figure 1.** Proportion of patients with 1, 2, and 3 or more comorbidities overall and by comorbidity category in patients with available data for at least 3 comorbidities. OCS, oral corticosteroid; T2, type 2.

**Table 3**
Association Between Comorbidities and Asthma Clinical Characteristics in Patients With Severe Asthma

| Comorbidity | Age at asthma onset (y) Difference[a] (95% CI) | BEC (cells/μL) Difference[a] (95% CI) | IgE (IU/mL) Difference[a] (95% CI) | FeNO (ppb) Difference[a] (95% CI) |
|---|---|---|---|---|
| **Potentially T2-related comorbidities** | | | | |
| AR | −2.95 (−3.98 to −1.92)[b] | +29.5 (+1.2 to +57.9)[b] | +100.3 (+50.3 to +150.2)[b] | +5.4 (+2.1 to +8.7)[b] |
| CRS | +1.70 (+0.75 to +2.64)[b] | +158.9 (+131.8 to +186.1)[b] | −5.6 (−53.3 to +42.1) | +12.6 (+9.5 to +15.7)[b] |
| NP | +1.10 (+0.12 to +2.08)[b] | +200.9 (+166.7 to +235.2)[b] | −20.7 (−79.7 to +38.3) | +17.7 (+14.0 to +21.5)[b] |
| Eczema or AD | −3.54 (−4.97 to −2.11)[b] | +37.3 (−9.1 to +83.6) | +271.2 (+191.9 to +350.4)[b] | −1.5 (−6.7 to +3.7) |
| **Potentially OCS-related comorbidities** | | | | |
| Obesity | −0.66 (−1.66 to +0.34) | −63.4 (−91.2 to −35.5)[b] | −47.9 (−96.8 to +1.0) | −9.3 (−12.4 to −6.2)[b] |
| Hypertension | +0.17 (−1.56 to +1.90) | −41.7 (−76.7 to −6.7)[b] | −14.7 (−82.2 to 52.8) | −7.6 (−11.7 to −3.5)[b] |
| Sleep apnea | −0.17 (−2.10 to +1.76) | −38.9 (−73.3 to −4.5)[b] | −67.0 (−130.8 to −3.2)[b] | −7.2 (−11.2 to −3.2)[b] |
| Dyslipidemia | −0.12 (−8.20 to +7.96) | −6.0 (−47.4 to +35.3) | −73.0 (−154.7 to +8.6) | −7.8 (−13.3 to −2.3)[b] |
| Anxiety or depression | −0.87 (−2.39 to +0.65) | −43.7 (−80.4 to −7.0) | −51.4 (−118.7 to +15.8) | −5.8 (−10.0 to −1.5)[b] |
| Osteoporosis | −0.49 (−2.09 to +1.11) | +43.2 (+1.8 to +84.6)[b] | +36.7 (−38.0 to +111.3) | −3.9 (−8.8 to +0.9) |
| Diabetes | −1.94 (−3.63 to −0.24)[b] | +3.23 (−36.9 to +43.3) | −43.8 (−116.8 to +29.3) | −6.8 (−11.8 to −1.9)[b] |
| **Potentially mimicking** or **aggravating asthma symptoms** | | | | |
| GERD | −2.61 (−5.40 to +0.17) | −46.4 (−80.4 to −12.4)[b] | −58.1 (−120.9 to +4.7) | −7.4 (−11.6 to −3.3)[b] |
| COPD | −2.15 (−7.33 to +3.03) | −93.0 (−134.9 to −51.1)[b] | +4.8 (−74.9 to +84.5) | −11.7 (−17.1 to −6.2)[b] |
| Bronchiectasis | −2.07 (−5.54 to +1.40) | +112.3 (+65.1 to +159.5)[b] | +114.4 (+30.8 to +198.0)[b] | −5.5 (−11.2 to +0.2) |
| VCD or laryngeal spasms | −0.52 (−6.34 to +5.31) | −50.8 (−98.7 to −3.0)[b] | −65.0 (−154.7 to +24.7) | −1.8 (−7.5 to +3.9) |

Abbreviations: AD, atopic dermatitis; AR, allergic rhinitis; BEC, blood eosinophil count; COPD, chronic obstructive pulmonary disease; CRS, chronic rhinosinusitis; FeNO, fractional exhaled nitric oxide; GERD, gastroesophageal reflux disease; NP, nasal polyposis; OCS, oral corticosteroid; T2, type 2; VCD, vocal cord dysfunction.
NOTE. Refer to eTables 10-13 for full data, sample sizes, and *P* values.
[a]Estimates were derived from linear regressions using absence of the considered individual comorbidity as the reference and adjusting for country, age at registry enrolment and sex.
[b]Statistically significant.

bronchiectasis, which was associated with elevated BEC and immunoglobulin (Table 3; eTables 11 and 12).

A few comorbidities were associated with age at asthma onset (Table 3; eTable 10). Patients with AR, eczema or AD, and diabetes were on average younger at asthma onset than patients without, whereas patients with CRS and NP were on average older at asthma onset.

*Individual Comorbidities and Asthma Outcomes*

Having a comorbidity was generally associated with receiving LTOCS and with higher exacerbation rates, with a variable impact noted on lung function and asthma control (Fig 2A-D; eTables 14-17). However, the extent of comorbidity association on asthma outcome was also comorbidity dependent.

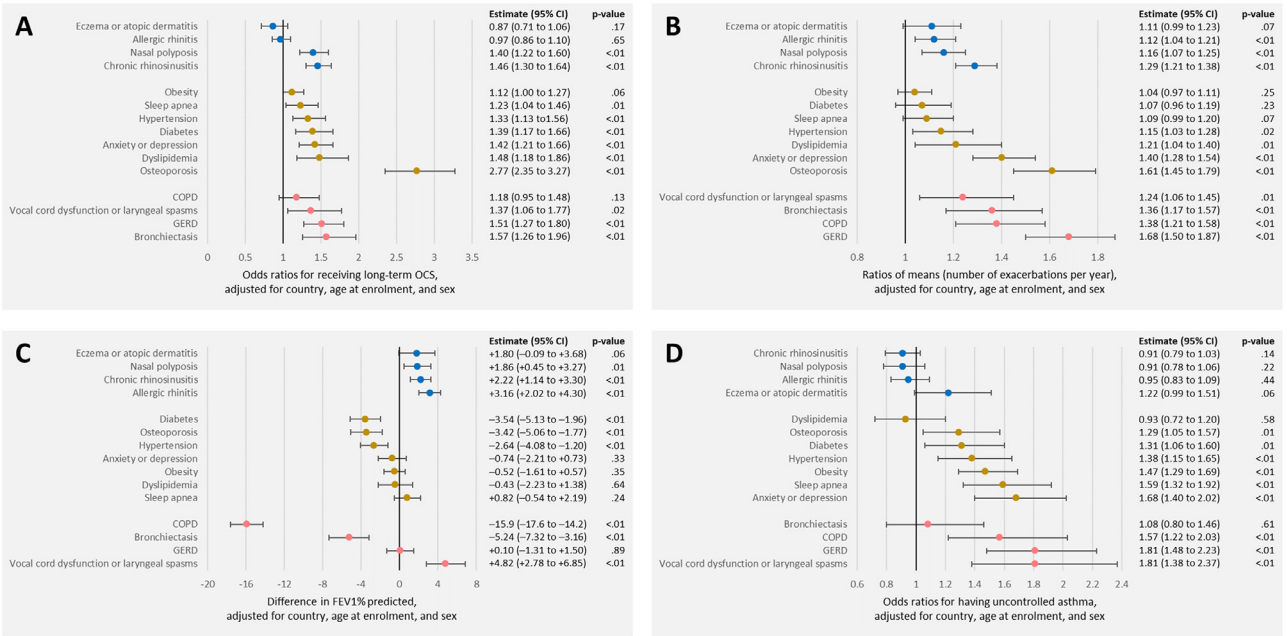


**Figure 2.** Association between comorbidities and (A) long-term OCS use, (B) asthma exacerbations, (C) lung function, and (D) asthma control. Long-term OCS: ORs and 95% CIs of receiving long-term OCS associated with presence of comorbidities. Exacerbations: ratios of means and 95% CIs of number of exacerbations in the year preceding enrollment associated with presence of comorbidities. Percent predicted $FEV_1$: averaged differences and 95% CIs of $FEV_1$% predicted at enrollment associated with presence of comorbidities. (D) Asthma control: ORs and 95% CIs of having uncontrolled asthma at enrollment associated with presence of comorbidities. All associations (ORs, ratios of means, and differences) were adjusted for country, age at registry enrollment, and sex. Potentially T2-related comorbidities are shown in blue, potentially OCS-related comorbidities are shown in yellow, and comorbidities mimicking or aggravating asthma are shown in pink. Full data, including sample sizes and *P* values are available in the eSupplement (eTables 14-17). COPD, chronic obstructive pulmonary disease; $FEV_1$, forced expiratory volume in 1 second; GERD, gastroesophageal reflux disease; OCS, oral corticosteroid; OR, odds ratio.

*Potentially Type 2–Related Comorbidities*

Chronic rhinosinusitis was associated with a poorer outcome for 2 variables: exacerbations and LTOCS use. Compared with those without CRS, patients with comorbid CRS had 29% more exacerbations and were 46% more likely to receive LTOCS (eTables 14 and 15). Nasal polyposis was also associated with a poorer outcome for these 2 variables. Allergic rhinitis was associated with higher exacerbation rates only, and AD was not associated with a significantly poorer asthma outcome for any variable assessed (Fig 2A-D). None of these potentially T2-related comorbidities were associated with poorer lung function, compared with those without; indeed, some of them were associated with better lung function (ie, AR, CRS, and NP) (eTable 16). In addition, none of these T2-related comorbidities were significantly associated with poorer asthma control (eTable 17).

*Potentially Non–Type 2-Related Comorbidities*

Having hypertension or osteoporosis was associated with a worse outcome in each of the 4 asthma outcomes assessed. Patients with osteoporosis were more than twice as likely to have used LTOCS (OR, 2.77; 95% CI, 2.35-3.27) (eTable 14) and experienced 61% more exacerbations (95% CI, 45%-79%) than those without osteoporosis (eTable 15; Fig 2A). Overall, 9 of 11 non–T2-related comorbidities were associated with higher odds of LTOCS use, and 8 of 11 were associated with higher exacerbation rates.

Most of the comorbidities that were potentially OCS-related or mimicking or aggravating asthma symptoms were also associated with worse asthma control. This was particularly the case for sleep apnea (OR, 1.59; 95% CI, 1.32-1.92), anxiety or depression (OR, 1.68; 95% CI, 1.40-2.02), GERD (OR, 1.81; 95% CI, 1.48-2.23), and vocal cord dysfunction or laryngeal spasm (OR, 1.81; 95% CI, 1.38-2.37) (Fig 2D; eTable 17). Some of them were also associated with worse lung function, particularly, COPD (−15.9 ppFEV$_1$) and bronchiectasis (−5.24 ppFEV$_1$) (Fig 2C; eTable 16).

*Number of Comorbidities and Asthma Outcomes*

Patients with a greater number of comorbidities, both overall and for each comorbidity category, had worse asthma outcomes, with the exception of ppFEV$_1$ and asthma control for potentially T2-related comorbidities (Table 4).

## Discussion

To our knowledge, our study is the first global analysis of comorbidity burden in patients with severe asthma, in terms of both prevalence and association with asthma clinical characteristics and outcomes. It included an in-depth exploration by category, multimorbidity, and co-occurrence patterns across categories and investigated the extent and method of comorbidity information collection—a reflection of the complexity of comorbidity presentation and reporting in real life. We found a differential association between comorbidities and asthma biomarkers, a comorbidity-specific association across multiple asthma outcomes, and a clear relationship between the number of comorbidities and the extent of outcome impairment. Having CRS and NP, in particular, was associated with more exacerbations and LTOCS use, whereas poor asthma control was associated with all potentially OCS-related comorbidities (with the exception of dyslipidemia). The use of LTOCS was associated with the largest number of comorbidities across the spectrum.

Patients with severe asthma presented with a wide variety of comorbidities, with some more prevalent than others (eg, AR, obesity, and GERD); more than 50% of patients with severe asthma had 3 or more comorbidities. Appropriate management of these multimorbid patients may be challenging because of the need for a multidisciplinary approach that may not be available in all countries. There also was marked intercountry variability in comorbidity prevalence estimates, possibly because of current gaps in comorbidity reporting, heterogeneity in reporting methodology, misclassification (eg, nonallergic rhinitis [NAR] many have been captured within the AR category), or intercountry demographic variability.[25] Although all countries collected the ISAR comorbidity core variables (ie, AR, CRS, NP, AD, and obesity) and many also collected the optional OCS-related comorbidities,[22] collection gaps were noted for certain T2-related comorbidities (eg, urticaria, food allergy, aspirin sensitivity, and eosinophilic esophagitis) and some OCS-related comorbidities (eg, sleep apnea, hypertension, dyslipidemia, and adrenal

**Table 4**
Association Between Comorbidity Counts and Asthma-Related Outcomes in Patients With Severe Asthma With Information Available on 3 or More Comorbidities

| Comorbidity count | Long-term OCS use[a] | | Exacerbations/y[b] | | Percent predicted FEV$_1$[c] | | Uncontrolled asthma[a] | |
|---|---|---|---|---|---|---|---|---|
| | Odds ratios (95% CI) | *P* value | Ratios of means (95% CI) | *P* value | Differences (95% CI) | *P* value | Odds ratios (95% CI) | *P* value |
| **Overall (any category of comorbidities)** | | | | | | | | |
| 0 | Reference | | Reference | | Reference | | Reference | |
| 1 | 1.07 (0.85 to 1.34) | .59 | 0.98 (0.87 to 1.12) | .81 | +0.84 (−1.43 to +3.11) | .47 | 1.08 (0.84 to 1.39) | .55 |
| 2 | 1.20 (0.96 to 1.50) | .12 | 1.09 (0.97 to 1.24) | .16 | +0.72 (−1.49 to +2.93) | .52 | 1.27 (0.99 to 1.63) | .06 |
| 3+ | 1.87 (1.51 to 2.31) | <.01 | 1.51 (1.34 to 1.70) | <.01 | +0.16 (−1.93 to +2.25) | .88 | 1.70 (1.35 to 2.15) | <.01 |
| **Potentially T2-related comorbidities** | | | | | | | | |
| 0 | Reference | | Reference | | Reference | | Reference | |
| 1 | 1.16 (0.99 to 1.34) | .06 | 1.14 (1.04 to 1.24) | <.01 | +3.73 (+2.40 to +5.07) | <.01 | 0.89 (0.76 to 1.05) | .18 |
| 2 | 1.31 (1.12 to 1.52) | <.01 | 1.26 (1.15 to 1.37) | <.01 | +4.39 (+2.96 to +5.82) | <.01 | 0.91 (0.77 to 1.08) | .28 |
| 3+ | 1.44 (1.20 to 1.72) | <.01 | 1.39 (1.25 to 1.55) | <.01 | +4.88 (+3.11 to +6.64) | <.01 | 1.05 (0.86 to 1.29) | .64 |
| **Potentially OCS-related comorbidities** | | | | | | | | |
| 0 | Reference | | Reference | | Reference | | Reference | |
| 1 | 1.37 (1.18 to 1.59) | <.01 | 1.18 (1.09 to 1.29) | <.01 | −0.77 (−2.17 to +0.63) | .28 | 1.31 (1.11 to 1.92) | <.01 |
| 2 | 1.69 (1.41 to 2.03) | <.01 | 1.28 (1.15 to 1.42) | <.01 | −2.60 (−4.26 to −0.94) | <.01 | 1.57 (1.28 to 1.92) | <.01 |
| 3+ | 2.50 (2.08 to 3.00) | <.01 | 1.62 (1.45 to 1.80) | <.01 | −2.75 (−4.37 to −1.14) | <.01 | 2.36 (1.92 to 2.90) | <.01 |
| **Comorbidities mimicking** or **aggravating asthma** | | | | | | | | |
| 0 | Reference | | Reference | | Reference | | Reference | |
| 1 | 1.38 (1.14 to 1.66) | <.01 | 1.56 (1.39 to 1.76) | <.01 | −1.97 (−3.55 to −0.40) | .01 | 2.06 (1.64 to 2.60) | <.01 |
| 2 | 1.73 (1.36 to 2.20) | <.01 | 1.82 (1.57 to 2.11) | <.01 | −7.00 (−8.92 to −5.09) | <.01 | 2.40 (1.82 to 3.18) | <.01 |
| 3+ | 2.66 (1.85 to 3.82) | <.01 | 2.66 (2.12 to 3.34) | <.01 | −10.48 (−13.71 to −7.25) | <.01 | 3.21 (2.04 to 5.04) | <.01 |

Abbreviations: FEV1, forced expiratory volume in 1 second; OCS, oral corticosteroids; T2, type 2.
NOTE. All models adjusted for country, age at registry enrollment, and sex. Refer to Table 1 for comorbidities included in each category.
[a]Estimates for LTOCS and uncontrolled asthma were obtained through logistic regressions.
[b]Estimates for exacerbation rates were obtained through negative binominal regressions.
[c]Estimates for ppFEV1 were obtained through linear regresssions.

insufficiency). In addition, most countries did not collect (or did not report) information on comorbidities mimicking or aggravating asthma symptoms, likely because these variables were not part of the original Delphi-agreed ISAR variables.[17] We also noted marked variation in how comorbidity information was recorded. These findings emphasize the need to focus on comorbidity assessment in clinical care, particularly those that are related to OCS considering the adverse event and socioeconomic impact associated with their use,[10,26,27] and the need for a "clinical protocol" to guide the assessment and management of severe asthma, and standardized tools to collect and report comorbidity data.

The position of T2-related comorbidities as drivers of continued exacerbations and their association with poor asthma control is well documented.[5,28,29] For example, among patients with asthma in UK primary care, those with 1 or 2 potentially T2-related comorbidities were significantly less likely to achieve asthma control (ORs: 0.95 and 0.86, respectively) compared with those without.[5] In our study, we noted higher exacerbation rates for those with comorbid AR, CRS, or NP and higher odds of LTOCS use for those with comorbid CRS and NP than those without; these results have been confirmed by others, albeit at the national level and not specifically in severe asthma.[30,31] However, we additionally found a marked cumulative negative effect of multiple T2-related comorbidities on exacerbation rate and LTOCS use that has not previously been reported; this is particularly important when one considers that approximately 40% of patients had at least 2 physician-assessed potentially T2-related comorbidities. The positive association noted in our study between nasal T2-comorbidities and lung function may be because of earlier diagnosis of asthma in these patients (because the association between these comorbidities and asthma is well documented),[32] earlier therapy intervention that may blunt lung function decline, and/or improved responsiveness to inhaled corticosteroids in T2-high asthma.[33,34]

Mindful of the serious long-term adverse effects of OCS, GINA 2023 urges physicians to consider maintenance OCS as a "last resort" when other treatments have been optimized and no alternative is available.[1] However, globally some 20% to 60% of patients with severe asthma are still treated with LTOCS.[35] We found that 68% and 40% of patients had at least 1 and at least 2 potentially OCS-related comorbidities, respectively. Others have reported higher prevalence rates of conditions linked to OCS use in patients with severe asthma (93%), even in those with mild or moderate disease (78%).[11] Reassuringly, we found a strong association between potentially OCS-related comorbidities and LTOCS use at enrollment. Although our cross-sectional design prevents an assumption of any directional relationship, it is probable that LTOCS exposure caused the occurrence of comorbidities—a hypothesis strengthened by the greater odds of LTOCS use with a greater number of OCS-related comorbidities. Furthermore, the presence of an OCS-related comorbidity was generally associated with higher exacerbation rates and higher odds of uncontrolled asthma, with higher rates and odds noted with an increasing number of comorbidities. Others have reported an association between obesity, anxiety or depression, and diabetes and increased risk of experiencing multiple exacerbations,[36] as well as sleep apnea and poor asthma control even in patients who used their inhalers correctly.[37] Taken together, these results highlight the need for OCS stewardship to regulate OCS use.[38] A recently published expert consensus agreed that OCS use should be minimized, that OCS tapering should be attempted in every patient, that biologic therapies are useful OCS-sparing agents, and that patients should be systematically assessed for suitability for biologic therapy.[39]

Comorbidities mimicking or aggravating asthma were also relatively common in our study, with a strong association noted between these comorbidities and LTOCS use. The presence of COPD, GERD, and vocal cord dysfunction or laryngeal spasms was also associated with significantly greater odds of having poorly controlled disease and higher exacerbation rates. Other studies have found that patients with comorbid GERD were 3 times more likely to have uncontrolled asthma than their counterparts without GERD,[40] that these patients experienced 1.6 times more exacerbations per year,[41] and that GERD was predictive of future multiple exacerbations.[36] These results highlight the importance of a thorough comorbidity assessment to differentiate severe from poorly controlled disease caused by comorbidities, to treat the cause and not the symptoms, and to prevent inappropriate treatment and inadequate response.

Missing data were a limitation of our study—clinical variables were not available for all patients, particularly spirometry data during the COVID-19 pandemic. However, sensitivity analyses excluding patients with fewer collected comorbidities led to estimates of similar magnitudes, and sample sizes for all outcome measures were still large. In line with ISAR's current inclusion criteria, data were also not captured for those younger than 18 years; although, in the future, we hope to include children and adolescents in ISAR with the view of capturing the entire asthma life cycle. Although we included a long list of comorbidities, this was not exhaustive; for example, NAR was not included, although NAR may have been included in the AR categorization by some countries, evidenced by the fact that 19.9% of patients with reported AR were not positive for any tested allergen. In addition, information regarding comorbidity severity was not collected, results may have been confounded by asthma severity and phenotype, and there may have been some selection bias on the biomarkers collected. There was also marked intercountry variability in how comorbidity data were collected (although no clear pattern by data source was observed) and wide intercountry variability in the prevalence of certain comorbidities. The range of AR prevalence was particularly wide, lowest in the United Kingdom and highest in Mexico (eFig 3). This may have been because of underreporting in the former and the almost exclusive collection of data from allergist centers in the latter. Furthermore, although the inclusion of highly selective patients in some countries (eg, the United Kingdom and Denmark) may have positively selected for patients with multiple comorbidities, this is not true for all, and analyses were adjusted for each country. The data incompleteness inherent to real-world studies and the heterogeneity in data collection inherent to international studies led us to harmonize information on comorbidity into "ever or never present" variables using data available from all visits. Despite maximizing data on comorbidities, this compromise might have diluted the results from our association analysis if the comorbidity was resolved before the enrollment date or if the comorbidity occurred after the enrollment date. However, considering that many of the comorbidities included are chronic conditions for which diagnoses may be delayed, the potential bias might be minimal. Finally, the statistical power for the association analysis was directly linked to comorbidity prevalence; hence, power may have been lacking in some comorbidities (eg, eczema or AD). Comorbidities with a prevalence of less than or equal to 10% overall were not analyzed for this reason and will require further attention in larger studies.

Strengths of our study are its large size, incorporating a large, heterogeneous asthma cohort from 22 countries, and the generalizability of our findings to the global severe asthma population. We investigated the prevalence of 30 comorbidities, providing an in-depth analysis of prevalence patterns and permitting a comprehensive analysis of the association of individual and multiple comorbidities with multiple asthma outcomes. Future directions could include an assessment of comorbidity trajectory (ie, can biologics slow down the development of OCS-related comorbidities), the impact of the most prevalent comorbidity co-occurrences on asthma outcomes, a more detailed assessment of the clinical importance of the relationship of comorbidities and T2-related biomarkers, and the influence of comorbidities on biologic response. Addressing the relationship between comorbidities and patient behaviors (eg, adherence) would also be of interest.

In conclusion, comorbidities and multimorbidity are frequent in adults with severe asthma in real life, and their presence is associated

with poorer asthma-related outcomes. Our findings could (1) encourage a more systematic evaluation for comorbidities during routine asthma review, in line with GINA recommendations[1]; (2) promote standardized comorbidity data collection; (3) foster a multidisciplinary and holistic approach to asthma management; and (4) consequently improve outcomes for those with severe asthma.

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OPC Ltd (Australia and UK) and 74% of OPRI Pte Ltd (Singapore); has 5% shareholding in Timestamp, which develops adherence monitoring technology; is a peer reviewer for grant committees of the Efficacy and Mechanism Evaluation program and Health Technology Assessment; and was an expert witness for GlaxoSmithKline. Dr Porsbjerg has attended advisory boards for AstraZeneca, Novartis, Teva, and Sanofi-Genzyme; has given lectures at meetings supported by AstraZeneca, Novartis, Teva, Sanofi-Genzyme, and GlaxoSmithKline; has taken part in clinical trials sponsored by AstraZeneca, Novartis, MSD, Sanofi-Genzyme, GlaxoSmithKline, and Novartis; and has received educational and research grants from AstraZeneca, Novartis, Teva, GlaxoSmithKline, ALK, and Sanofi-Genzyme. The remaining authors have no conflicts of interest to report.

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