



HAL
open science

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

Ghislaine Scelo, Carlos Torres-Duque, Jorge Maspero, Trung Tran, Ruth Murray, Neil Martin, Andrew Menzies-Gow, Mark Hew, Matthew Peters, Peter Gibson, et al.

► To cite this version:

Ghislaine Scelo, Carlos Torres-Duque, Jorge Maspero, Trung Tran, Ruth Murray, et al.. Analysis of comorbidities and multimorbidity in adult patients in the International Severe Asthma Registry. *Annals of Allergy, Asthma and Immunology*, 2023, 132 (42-53), <10.1016/j.anai.2023.08.021>. <hal-04190650>

HAL Id: hal-04190650

<https://hal.science/hal-04190650v1>

Submitted on 17 Jan 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



HAL Authorization

Analysis of comorbidities and multi-morbidity in adult patients in the International Severe Asthma Registry

Ghislaine Scelo¹, Carlos A Torres-Duque², Jorge Maspero³, Trung N Tran⁴, Ruth Murray⁵, Neil Martin⁶, Andrew N Menzies-Gow⁷, Mark Hew⁸, Matthew J Peters⁹, Peter G Gibson¹⁰, George C Christoff¹¹, Todor A Popov¹², Andréanne Côté¹³, Celine Bergeron¹⁴, Delbert Dorscheid¹⁵, J Mark FitzGerald¹⁶, Kenneth R Chapman¹⁷, Louis Philippe Boulet¹⁸, Mohit Bhutani¹⁹, Mohsen Sadatsafavi²⁰, Libardo Jiménez-Maldonado²¹, Mauricio Duran-Silva²², Bellanid Rodriguez²³, Carlos Andres Celis-Preciado²⁴, Diana Jimena Cano-Rosales²³, Ivan Solarte²⁴, Maria Jose Fernandez-Sanchez²⁴, Patricia Parada-Tovar²⁵, Anna von Bülow²⁶, Anne Sofie Bjerrum²⁷, Charlotte S Ulrik²⁸, Karin Dahl Assing²⁹, Linda Makowska Rasmussen³⁰, Susanne Hansen³¹, Alan Altraja³², Arnaud Bourdin³³, Camille Taille³⁴, Jeremy Charriot³³, Nicolas Roche³⁵, Andriana I Papaioannou³⁶, Konstantinos Kostikas³⁷, Nikolaos G Papadopoulos³⁸, Sundeep Salvi³⁹, Deirdre Long⁴⁰, Patrick D Mitchell⁴¹, Richard Costello⁴², Concetta Sirena⁴³, Cristina Cardini⁴³, Enrico Heffler⁴⁴, Francesca Puggioni⁴⁵, Giorgio Walter Canonica⁴⁴, Giuseppe Guida⁴⁶, Takashi Iwanaga⁴⁷, Mona Al-Ahmad⁴⁸, Désirée Larenas Linnemann⁴⁹, Ulises Garcia⁵⁰, Piotr Kuna⁵¹, João A Fonseca⁵², Riyadh Al-Lehebi⁵³, Mariko Siyue Koh⁵⁴, Chin Kook Rhee⁵⁵, Borja G Cosio⁵⁶, Luis Perez de Llano⁵⁷, Diahn-Warng Perng Steve⁵⁸, Erick Wan-Chun Huang⁵⁹, Hao-Chien Wang⁶⁰, Ming-Ju Tsai⁶¹, Bassam Mahboub⁶², Laila Ibraheem Jaber Salameh⁶³, David Jackson⁶⁴, John Busby⁶⁵, Liam G Heaney⁶⁶, Paul Pfeiffer⁶⁷, Amanda Grippen Goddard⁶⁸, Eileen Wang⁶⁹, Flavia Hoyte⁶⁹, Michael E Wechsler⁷⁰, Nicholas Chapman⁷¹, Rohit Katial⁶⁹, Victoria Carter¹, Lakmini Bulathsinhala¹, Neva Eleangovan¹, Con Ariti¹, Juntao Lyu⁷², David B Price⁷³, Celeste Porsbjerg⁷⁴

*Observational and Pragmatic Research Institute, Singapore ,Singapore

y Optimum Patient Care Global, Cambridge, United Kingdom

z CINEUMO, Respiratory Research Center, Fundacion Neumologica Colombiana, Bogota, Colombia

x Universidad de LaSabana, Chia, Colombia

Dr FitzGerald is included as posthumous author.

Address correspondence to:

David B. Price, MB BChir; Observational and Pragmatic Research Institute (OPRI) PteLtd ,22S in MingLane ,#06-76 Midview City ,Singapore 573969.

E-mail:

dprice@opri.sg.

- ¹ Observational and Pragmatic Research Institute, Singapore, Singapore; Optimum Patient Care Global, Cambridge, United Kingdom.
- ² CINEUMO, Respiratory Research Center, Fundación Neumológica Colombiana, Bogotá, Colombia; Universidad de La Sabana, Chia, Colombia.
- ³ Clinical Research for Allergy and Respiratory Medicine, CIDEA Foundation, Buenos Aires, Argentina.
- ⁴ BioPharmaceuticals Medical, AstraZeneca, Gaithersburg, Maryland.
- ⁵ Optimum Patient Care Global, Cambridge, United Kingdom.

- ⁶ BioPharmaceuticals Medical, AstraZeneca, Gaithersburg, Maryland; University of Leicester, Leicester, United Kingdom.
- ⁷ AstraZeneca, Cambridge, United Kingdom; Royal Brompton and Harefield Hospitals, London, United Kingdom.
- ⁸ Allergy, Asthma, and Clinical Immunology Service, Alfred Health, Melbourne, Australia; Public Health and Preventive Medicine, Monash University, Melbourne, Australia.
- ⁹ Department of Thoracic Medicine, Concord Hospital, Sydney, Australia.
- ¹⁰ Australian Severe Asthma Network, Priority Research Centre for Healthy Lungs, University of Newcastle, Newcastle, Australia; Hunter Medical Research Institute, Department of Respiratory and Sleep Medicine, John Hunter Hospital, New Lambton Heights, Australia.
- ¹¹ Medical University, Sofia, Bulgaria.
- ¹² University Hospital Sv. Ivan Rilski, Sofia, Bulgaria.
- ¹³ Department of Medicine, Laval University, Quebec, Canada.
- ¹⁴ Vancouver General Hospital and University of British Columbia, Vancouver, Canada.
- ¹⁵ Center for Heart Lung Innovation, University of British Columbia, Vancouver, Canada.
- ¹⁶ Department of Medicine, The University of British Columbia, Vancouver, Canada.
- ¹⁷ University of Toronto, Toronto, Canada.
- ¹⁸ Québec Heart and Lung Institute, Université Laval, Québec City, Canada.
- ¹⁹ Division of Pulmonary Medicine, Department of Medicine, University of Alberta, Alberta, Canada.
- ²⁰ Respiratory Evaluation Sciences Program, Faculty of Pharmaceutical Sciences, The University of British Columbia, Vancouver, Canada.
- ²¹ Universidad de La Sabana, Chia, Colombia; Fundación Neumológica Colombiana, ASMAIRE Program, Bogotá, Colombia.
- ²² Fundación Neumológica Colombiana, ASMAIRE Program, Bogotá, Colombia.
- ²³ Instituto Neumológico del Oriente, Bucaramanga, Colombia.
- ²⁴ Pulmonary Unit, Hospital Universitario San Ignacio, Bogota, Colombia; Faculty of Medicine, Pontificia Universidad Javeriana, Hospital Universitario San Ignacio, Bogota, Colombia.
- ²⁵ CINEUMO, Respiratory Research Center, Fundación Neumológica Colombiana, Bogotá, Colombia.
- ²⁶ Respiratory Research Unit, Department of Respiratory Medicine and Infectious Diseases, Bispebjerg hospital, Copenhagen, Denmark.
- ²⁷ Department of Respiratory Medicine and Allergy, Aarhus University Hospital, Denmark.
- ²⁸ Department of Respiratory Medicine, Copenhagen University Hospital, Hvidovre, Denmark.
- ²⁹ Department of Respiratory Medicine, Aalborg University Hospital, Aalborg, Denmark.
- ³⁰ Allergy Clinic, Copenhagen University Hospital-Gentofte, Hellerup, Denmark.
- ³¹ Respiratory Research Unit, Bispebjerg University Hospital, Copenhagen, Denmark; Center for Clinical Research and Prevention, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark.
- ³² Department of Pulmonology, University of Tartu and Lung Clinic, Tartu University Hospital, Tartu, Estonia.

- ³³ PhyMedExp, Univ Montpellier, CNRS, INSERM, CHU Montpellier, Montpellier, France.
- ³⁴ Department of Respiratory Diseases, Bichat Hospital, AP-HP Nord-Université Paris Cité, Paris, France.
- ³⁵ Department of Respiratory Medicine, APHP-Centre University Paris Cité, Cochin Hospital and Institute (UMR1016), Paris, France.
- ³⁶ Second Respiratory Medicine Department, National and Kapodistrian University of Athens Medical School, Attikon University Hospital, Athens, Greece.
- ³⁷ Respiratory Medicine Department, University of Ioannina, Greece.
- ³⁸ Division of Infection, Immunity, and Respiratory Medicine, University of Manchester, Manchester, United Kingdom; Allergy Department, Second Pediatric Clinic, University of Athens, Athens, Greece.
- ³⁹ Pulmocare Research and Education Foundation, Pune, India.
- ⁴⁰ Department of Medicine, Beaumont Hospital, Dublin, Ireland.
- ⁴¹ School of Medicine, Trinity College, Dublin, Ireland.
- ⁴² Clinical Research Centre, Department of Respiratory Medicine, Smurfit Building Beaumont Hospital, RCSI, Dublin, Ireland.
- ⁴³ Severe Asthma Network Italy (SANI), Milano, Italy.
- ⁴⁴ Personalized Medicine, Asthma and Allergy, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy; Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy.
- ⁴⁵ Personalized Medicine, Asthma and Allergy, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy.
- ⁴⁶ Severe Asthma and Rare Lung Disease Unit, Department of Clinical and Biological Sciences, San Luigi Gonzaga University Hospital, University of Turin, Orbassano, Turin, Italy.
- ⁴⁷ Kindai University Hospital, Osakasayama, Japan.
- ⁴⁸ Microbiology Department, College of Medicine, Kuwait University, Kuwait City, Kuwait; Al-Rashed Allergy Center, Ministry of Health, Kuwait City, Kuwait.
- ⁴⁹ Centro de Excelencia en Asma y Alergia, Hospital Médica Sur, Ciudad de México, Mexico.
- ⁵⁰ Department of Allergy and Immunology, National Medical Center of Bajío, Professor of Allergy and Immunology in the University of Guanajuato, Guanajuato, Mexico.
- ⁵¹ Division of Internal Medicine Asthma and Allergy, Medical University of Lodz, Lodz, Poland.
- ⁵² CINTESIS@RISE, MEDCIDS, Faculty of Medicine of the University of Porto, Porto, Portugal.
- ⁵³ Department of Pulmonology, King Fahad Medical City, Riyadh, Saudi Arabia; Alfaisal University, Riyadh, Saudi Arabia.
- ⁵⁴ Department of Respiratory and Critical Care Medicine, Singapore General Hospital, Singapore.
- ⁵⁵ Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, St. Mary's Hospital, Seoul, South Korea; College of Medicine, The Catholic University of Korea, Seoul, South Korea.
- ⁵⁶ Son Espases University Hospital-IdISBa-Ciberes, Mallorca, Spain.
- ⁵⁷ Pneumology Service, Lucus Augusti University Hospital, EOXI Lugo, Monforte, Cervo, Spain.
- ⁵⁸ School of Medicine, National Yang Ming Chiao Tung University, Hsinchu, Taiwan; Department of Chest Medicine, Taipei Veterans General Hospital, Taipei, Taiwan.

- ⁵⁹ Division of Pulmonary Medicine, Department of Internal Medicine, Shuang Ho Hospital, Taipei Medical University, New Taipei City, Taiwan.
- ⁶⁰ Department of Medicine, National Taiwan University Cancer Center, Taipei, Taiwan.
- ⁶¹ Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan; Department of Internal Medicine, School of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan.
- ⁶² Rashid hospital, Dubai Health Authority (DHA), Dubai, United Arab Emirates.
- ⁶³ Rashid hospital, Dubai Health Authority (DHA), Dubai, United Arab Emirates; College of Medicine, University of Sharjah, Sharjah, United Arab Emirates.
- ⁶⁴ Guy's Severe Asthma Centre, Guy's Hospital, King's College London, London, United Kingdom.
- ⁶⁵ Centre for Public Health, School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, Belfast, United Kingdom.
- ⁶⁶ Wellcome-Wolfson Institute for Experimental Medicine, Queen's University Belfast, Belfast, United Kingdom.
- ⁶⁷ Department of Respiratory Medicine, Barts Health National Health Service (NHS) Trust, London, United Kingdom; Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom.
- ⁶⁸ Allergy Partners of Albuquerque, Albuquerque, New Mexico.
- ⁶⁹ Division of Allergy and Clinical Immunology, Department of Medicine, National Jewish Health, Denver, Colorado.
- ⁷⁰ NJH Cohen Family Asthma Institute, Department of Medicine, National Jewish Health, Denver, Colorado.
- ⁷¹ Saint Joseph Hospital, Denver Colorado National Jewish Health, Denver, Colorado.
- ⁷² Centre for Applied Health Economics, Griffith University, Brisbane, Australia.
- ⁷³ Observational and Pragmatic Research Institute, Singapore, Singapore; Optimum Patient Care Global, Cambridge, United Kingdom; Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Aberdeen, United Kingdom. Electronic address: dprice@opri.sg.
- ⁷⁴ Research Unit, Department of Respiratory Medicine and Infectious Diseases, Bispebjerg Hospital, Copenhagen, Denmark.

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 multi-morbidity 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 multi-morbidity 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).

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 multi-morbidity 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 multi-morbidities, 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://isarregistries.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, Den-

mark, 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 b₂-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 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, bio-marker 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 [ppFEV₁],²³ and asthma control). Definitions and categorizations of variables and timing of collection are provided in Table 2 and eTable 2.

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.

^aVariations in sample size are because of missing values for individual patients and/or at the country level.

^bNumber of patients with comorbidity.

^cWith or without nasal polyposis.

^dCan also mimic or aggravate asthma.

^eCan also be OCS related.

Study Outcomes

The prevalence of individual comorbidities (by category and country), multi-morbidity (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 $\geq 10\%$) 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 non-missing 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 outcomes with 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 ppFEV₁), 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 α 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: $\gg 80\%$) an eosinophilic phenotype ($\gg 87\%$), 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 inter-category 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 Multi-morbidity

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 $\geq 10\%$) 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 bio- marker 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 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

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).

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/ μ L) 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	+32.3 (-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 +24.7)	-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.

^aEstimates 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.

^bStatistically significant.

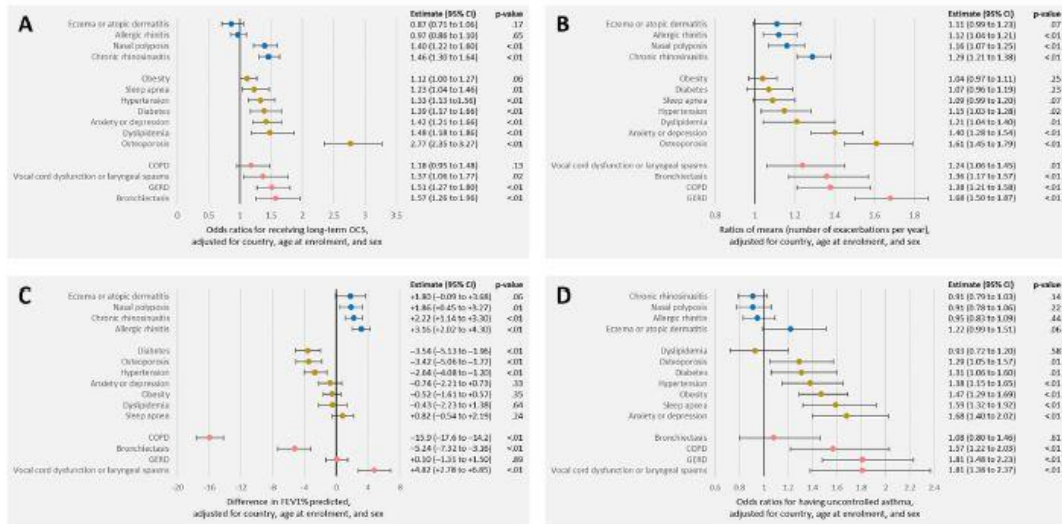


Figure 2. Association between comorbidities and (A) long-term OCS use, (B) asthma exacerbations, (C) lung function, and (D) asthma control. Long-term OCS: ORs and 95% CIs of receiving long-term OCS associated with presence of comorbidities. Exacerbations: ratios of means and 95% CIs of number of exacerbations in the year preceding enrollment associated with presence of comorbidities. Percent predicted FEV₁: averaged differences and 95% CIs of FEV₁% 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; FEV₁, forced expiratory volume in 1 second; GERD, gastroesophageal reflux disease; OCS, oral corticosteroid; OR, odds ratio.

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 ppFEV₁) and bronchiectasis (5.24 ppFEV₁) (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 ppFEV₁ and asthma control for potentially T2-related comorbidities (Table 4).

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 ^b		Percent predicted FEV ₁ ^c		Uncontrolled asthma ^d	
	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.

^aEstimates for LTOCS and uncontrolled asthma were obtained through logistic regressions.

^bEstimates for exacerbation rates were obtained through negative binomial regressions.

^cEstimates for ppFEV₁ were obtained through linear regressions.

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, multi-morbidity, 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 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.

Acknowledgments

The authors thank Joash Tan, BSc (Hons), and Andrea Lim, BSc (Hons), of the Observational Pragmatic Research Institute for their editorial and formatting assistance that supported the development of this article.

Disclosures

Dr Scelo and Dr Murray are consultants for the Observational and Pragmatic Research Institute (OPRI). Dr Torres-Duque has received fees as an advisory board participant and/or speaker from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, and Sanofi Aventis; has taken part in clinical trials from AstraZeneca, Novartis, and Sanofi-Aventis; and has received unrestricted grants for investigator-initiated studies at Fundacion Neumologica Colombiana from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Grifols, and Novartis. Dr Maspero reports receiving speaker fees, grants, or fees for serving on advisory boards for AstraZeneca, Sanofi, Glaxo Smith K-line, Novartis, Immunotek, Menarini, and Noucor. Dr Tran, Dr Menzies-Gow, and Dr Martin are employees of AstraZeneca and may own stock or stock options in AstraZeneca. Dr Hew reports receiving grants and other advisory board fees (made to his institutional employer) from AstraZeneca, GlaxoSmithKline, Novartis, Sanofi, Teva, and Seqirus for unrelated projects. Dr Peters reports receiving personal fees and nonfinancial support from AstraZeneca and Glaxomith Kline. Dr Gibson has received speaking fees and grants to his institution from AstraZeneca, GlaxoSmithKline,

and Novartis. Dr Popov reports receiving relevant research support from Novartis and Chiesi Pharma. Dr Côte reports receiving speaking fees and consultant fees from Sanofi, Regeneron, AstraZeneca, GlaxoSmithKline, and Valeo Pharma and reports receiving unrestricted grant support from GlaxoSmithKline; Dr Bergeron reports advisory board participation in Sanofi, AstraZeneca, Takeda, and Valeo Pharma and honorarium for presentations for GlaxoSmithKline, AstraZeneca, Amgen, Grifols, Sanofi, Regeneron, and Valeo Pharma. Dr Dorscheid is on faculty at the University of British Columbia and is supported by grants from the Canadian Institutes of Health Research, British Columbia Lung Association, and Michael Smith Foundation for Health Research. In addition, he has received speaking fees, travel grants, unrestricted project grants, and writing fees and is a paid consultant for Sanofi-Regeneron, Novartis Canada, AstraZeneca, GlaxoSmithKline, and ValeoPharma and is an active member of the Canadian Thoracic Society, American Thoracic Society, European Respiratory Society, and the Allergen Research Network. Dr FitzGerald previously reported receiving grants from AstraZeneca, GlaxoSmithKline, Sanofi-Regeneron, and Novartis paid directly to UBC and personal fees for lectures and attending advisory boards for AstraZeneca, GlaxoSmithKline, Sanofi-Regeneron, and Teva. Dr Chapman reports receiving grants from AstraZeneca, Boehringer Ingelheim, Bellus, CSL Behring, GlaxoSmithKline, Grifols, Inhibrx, Novartis, Regeneron, Sanofi, Takeda, and Vertex and consulting fees from AstraZeneca, CSL Behring, GlaxoSmithKline, Grifols, Inhibrx, Novartis, Sanofi, and Takeda; he has a leadership or fiduciary role in Alpha-1 Canada, the Canadian Thoracic Society, and Alpha-1 Foundation. Dr Boulet has received grants for participation in clinical studies from Amgen, AstraZeneca, GlaxoSmithKline, Merck, Novartis, Sanofi-Regeneron, and BioHaven; for consulting and advisory boards from AstraZeneca, Novartis, GlaxoSmithKline, Merck, and Sanofi-Regeneron; and lecture fees from AstraZeneca, Covis, Cipla, GlaxoSmithKline, Novartis, Merck, and Sanofi. Dr Bhutani has received speaker and consultant fees for AstraZeneca, GlaxoSmithKline, Sanofi, Covis, Boehringer Ingelheim, and Valeo. Dr Sadatsafavi has received honoraria from AstraZeneca, Boehringer Ingelheim, Teva, and GlaxoSmithKline for purposes unrelated to the content of this manuscript; and has received research funding from AstraZeneca and Boehringer Ingelheim directly into his research account from AstraZeneca for unrelated projects. Dr Jimenez-Maldonado has received fees as an advisory board participant and/or speaker from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, and Sanofi-Aventis and has participated in clinical trials for AstraZeneca, Novartis, and GlaxoSmithKline. Dr Duran-Silva has received fees as an advisory board participant and/or speaker from Boehringer Ingelheim, Novartis, and Sanofi-Aventis and has taken part in clinical trials from AstraZeneca, Novartis, and Sanofi-Aventis. Dr Solarte received fees from GlaxoSmithKline for participation on advisory boards. Dr Fernandez-Sanchez is a part-time employee of GlaxoSmithKline and does not hold shares in the company. Dr Bøulow reports receiving speakers fees and consultancy fees from AstraZeneca and Novartis outside the submitted work and has also attended the advisory board for Novartis and AstraZeneca. Dr Bjerrum has received lecture fees from AstraZeneca, GlaxoSmithKline, and Novartis. Dr Ulrik reports receiving personal fees for talks and participation in advisory boards, among others, from AstraZeneca, GlaxoSmithKline, Teva, Boehringer Ingelheim, Orion Pharma, Sanofi-Genzyme, TFF Pharmaceuticals, Covis Pharma, Berlin-Chemie, Takeda, Chiesi, and Pfizer outside the submitted work. Dr Rasmussen declares receiving speaker fees from AstraZeneca, Boehringer Ingelheim, Teva, ALK, and Mundipharma outside the submitted work and attended advisory board for AstraZeneca, Sanofi, and Teva. Dr Altraja has received lecture fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, MSD, Norameda, Novartis, Orion, Sanofi, and Zentiva; sponsorships from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, MSD, Norameda, Novartis, and Sanofi; and has participated in advisory boards for AstraZeneca, Boehringer

Ingelheim, GlaxoSmithKline, Novartis, Sanofi, and Teva. Dr Bourdin has received industry-sponsored grants from AstraZenecaMedImmune, Boehringer Ingelheim, Cephalon/Teva, GlaxoSmithKline, Novartis, and Sanofi-Regeneron and consultancies with AstraZeneca-MedImmune, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Regeneron-Sanofi, Med-in-Cell, Actelion, Merck, Roche, and Chiesi. Dr Taille has received lecture or advisory board fees and grants to her institution from AstraZeneca, Sanofi, GlaxoSmithKline, Chiesi, and Novartis for unrelated projects. Dr Charriot reports receiving advisory board and lecture fees from AstraZeneca, GlaxoSmithKline, Sanofi; consulting fees for Chiesi; and serving as a trial coinvestigator for AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, and Sanofi. Dr Roche reports receiving grants and personal fees from Austral, Biosency, Boehringer Ingelheim, Novartis, and Pfizer and personal fees from MSD, GlaxoSmithKline, AstraZeneca, Chiesi, Sanofi, Menarini, and Zambon. Dr Papaioannou has received fees and honoraria from Menarini, GlaxoSmithKline, Novartis, Elpen, Boehringer Ingelheim, AstraZeneca, and Chiesi. Dr Kostikas received honoraria for presentations and consultancy fees from AstraZeneca, Boehringer Ingelheim, CSL Behring, Chiesi, ELPEN, GILEAD, GlaxoSmithKline, Menarini, Novartis, Sanofi, Specialty Therapeutics, and WebMD; and received funding and grants from AstraZeneca, Boehringer Ingelheim, Chiesi, Innovis, ELPEN, GlaxoSmithKline, Menarini, Novartis, and NuvoAir (paid to the University of Ioannina). Dr Papadopoulos has been a speaker and/or advisory board member for Abbott, AbbVie, ALK, Asit Biotech, AstraZeneca, Biomay, Boehringer Ingelheim, GlaxoSmithKline, HAL, Faes Farma, Medscape, Menarini, MSD, Novartis, Nutricia, OM Pharma, Regeneron, Sanofi, Takeda, and Viatrix. Dr Salvi reports receiving research support and speaker fees from Cipla, Glenmark, and GlaxoSmithKline. Dr Mitchell has received speaker fees from GlaxoSmithKline, AstraZeneca, Teva, and Novartis and has received grants from AstraZeneca and Teva. Dr Costello has received honoraria for lectures from Aerogen, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, and Teva; is a member of advisory boards for GlaxoSmithKline and Novartis; has received grant support from GlaxoSmithKline and Aerogen; and has patents in the use of acoustics in the diagnosis of lung disease, assessment of adherence, and prediction of exacerbations. Dr Heffler declares receiving personal fees from Sanofi, Regeneron, GlaxoSmithKline, Novartis, AstraZeneca, Stallergenes, and Circassia. Dr Puggioni reports having received lectures or advisory board fees from Menarini, Mundipharma, Chiesi, Alk Abello, AstraZeneca, Boehringer Ingelheim, Guidotti, Malesci, GlaxoSmithKline, HAL Allergy, Novartis, Sanofi, Regeneron, Staller genes Greer, Valeas, and Almirall. Dr Canonica has received research grants and lecture or advisory board fees from A. Menarini, Alk- Abello, Allergy Therapeutics, Anallergo, AstraZeneca, MedImmune, Boehringer Ingelheim, Chiesi Farmaceutici, Circassia, Danone, Faes, Genentech, Guidotti Malesci, GlaxoSmithKline, HAL Allergy, Merck, MSD, Mundipharma, Novartis, Orion, Sanofi-Aventis, Sanofi, Genzyme/Regeneron, Stallergenes, UCB Pharma, Uriach Pharma, Teva, Thermo Fisher, and Valeas. Dr Iwanaga received lecture fees from Kyorin, GlaxoSmithKline, Novartis, Boehringer Ingelheim, and Astra- Zeneca. Dr Mona Al-Ahmad has received advisory board and speaker fees from AstraZeneca, Sanofi, Novartis, and GlaxoSmithKline and received a grant from the Kuwait Foundation for the Advancement of Sciences (KFAS). Dr Linnemann reports receiving personal fees from ALK-Abelo, AstraZeneca national and global, Bayer, Chiesi, Grunenthal, Grin, GlaxoSmithKline national and global, Viatrix, Menarini, MSD, Novartis, Pfizer, Sanofi, Siegfried, UCB, and Carnot and grants from AbbVie, Bayer, Lilly, Sanofi, AstraZeneca, Pfizer, Novartis, Circassia, UCB, and GlaxoSmithKline outside the submitted work. Dr Garcia Ramirez received fees as a speaker and advisory board participant from AstraZeneca, GlaxoSmithKline, Sanofi-Genzyme, Chiesi, and Novartis. Dr Kuna reports receiving personal fees from Adamed, AstraZeneca, Berlin-Chemie Menarini, FAES, Glenmark, Novartis, Pol-

pharma, Boehringer Ingelheim, Teva, and Zentiva outside the submitted work. Dr Fonseca reports receiving grants from or has research agreements with AstraZeneca, Mundipharma, Sanofi-Regeneron, and Novartis and has received personal fees for lectures and attending advisory boards for AstraZeneca, GlaxoSmithKline, Mundipharma, Novartis, Sanofi-Regeneron, and Teva. Dr Lehebi has given lectures at meetings supported by AstraZeneca, Boehringer Ingelheim, Novartis, GlaxoSmithKline, and Sanofi and participated in advisory board fees from GlaxoSmithKline, AstraZeneca, Novartis, and Abbott. Dr Koh reports receiving grant support from AstraZeneca and honoraria for lectures and advisory board meetings paid to her hospital (Singapore General Hospital) from GlaxoSmithKline, AstraZeneca, Novartis, Sanofi, and Boehringer Ingelheim outside the submitted work. Dr Kook Rhee received consulting/lecture fees from MSD, AstraZeneca, GlaxoSmithKline, Novartis, Takeda, Mundipharma, Boehringer Ingelheim, Teva, Sanofi, and Bayer. Dr Cosio declares receiving grants from Chiesi and GlaxoSmithKline; personal fees for advisory board activities from Chiesi, GlaxoSmithKline, Novartis, Sanofi, Teva, and AstraZeneca; and payment for lectures/speaking engagements from Chiesi, Novartis, GlaxoSmithKline, Menarini, and AstraZeneca outside the submitted work. Dr de Llano reports receiving grants, personal fees and nonfinancial support from AstraZeneca, Teva, Faes, and Sanofi; personal fees and nonfinancial support from GlaxoSmithKline and Chiesi; personal fees from MSD, Techdow Pharma, GILEAD, and Leo Pharma; and grants and personal fees from GEBRO outside the submitted work. Dr Perng received sponsorship to attend or speak at international meetings, honoraria for lecturing or attending advisory boards, and research grants from the following companies: AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Daiichi Sankyo, Shionogi, and Orient Pharma. Dr Tsai has received grants from Boehringer Ingelheim and has received honoraria for lectures from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, and Orient EuroPharma. Dr Jackson has received speaker fees and consultancy fees from AstraZeneca, GlaxoSmithKline, Sanofi-Regeneron, and Boehringer Ingelheim and research funding from AstraZeneca. Dr Busby has received research grants from AstraZeneca and personnel fees from NuvoAir outside the submitted work. Dr Heaney has received grant funding, participated in advisory boards, and given lectures at meetings supported by Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Hoffmann la Roche, GlaxoSmithKline, Novartis, Theravance, Evelo Biosciences, Sanofi, and Teva; has received grants from MedImmune, Novartis UK, Roche/Genentech Inc, GlaxoSmithKline, Amgen, Genentech/Hoffman la Roche, AstraZeneca, Aerocrine, and Vitalograph; has received sponsorship for attending international scientific meetings from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, and Napp Pharmaceuticals; has taken part in asthma clinical trials sponsored by AstraZeneca, Boehringer Ingelheim, Hoffmann la Roche, and GlaxoSmithKline, for which his institution received remuneration; and is the Academic Lead for the Medical Research Council Stratified Medicine UK Consortium in Severe Asthma, which involves industrial partnerships with a number of pharmaceutical companies including Amgen, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Hoffmann la Roche, and Janssen. Dr Pfeffer has attended advisory boards for AstraZeneca, GlaxoSmithKline, and Sanofi; has given lectures at meetings supported by AstraZeneca and GlaxoSmithKline; has taken part in clinical trials sponsored by AstraZeneca, GlaxoSmithKline, Novartis, and Sanofi, for which his institution received remuneration; and has a current research grant funded by GlaxoSmithKline. Dr Goddard reports receiving lecture fees from Sanofi. Dr Wang has received honoraria from AstraZeneca, GlaxoSmithKline, and Genentech; and has been an investigator on studies sponsored by AstraZeneca, GlaxoSmithKline, Genentech, Sanofi, Novartis, and Teva, for which her institution has received funding. Dr Hoyte reports receiving honoraria from AstraZeneca and Genentech and has been an investigator on clinical trials sponsored by GlaxoSmithKline,

Genentech, Teva, and Sanofi, for which her institution has received funding. Dr Wechsler reports receiving grants and/or personal fees from Novartis, Sanofi, Regeneron, Genentech, Sentien, resTORbio, Equillium, Genzyme, Cohero Health, Teva, Boehringer Ingelheim, AstraZeneca, Amgen, GlaxoSmithKline, Cytoreason, Cerecor, Sound biologic, Incyte, and Kinaset. Ms Carter is an employee of Optimum Patient Care (OPC) (OPC is a cofounder of the International Severe Asthma Registry and a cofounder of the APEX-COPD initiative). Ms Bulathsinhala is an employee of OPRI. Ms Eleangovan and Mr Ariti were employees of OPRI. Dr Lyu was an employee of OPC. Dr Price has advisory board membership with Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Mylan, Mundipharma, Novartis, Regeneron Pharmaceuticals, Sanofi-Genzyme, Teva Pharmaceuticals, Thermofisher; consultancy agreements with Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mylan, Mundipharma, Novartis, Pfizer, Teva Pharmaceuticals, Theravance; received grants and unrestricted funding for investigator-initiated studies (conducted through OPRI Pte Ltd) from AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Mylan, Mundipharma, Novartis, Pfizer, Regeneron Pharmaceuticals, Respiratory Effectiveness Group, Sanofi-Genzyme, Teva Pharmaceuticals, Theravance, and the UK National Health Service; received payment for lectures/speaking engagements from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Kyorin, Mylan, Mundipharma, Novartis, Regeneron Pharmaceuticals, Sanofi-Genzyme, Teva Pharmaceuticals; payment for the development of educational materials from Mundipharma, Novartis; payment for travel/ accommodation/meeting expenses from AstraZeneca, Boehringer Ingelheim, Mundipharma, Mylan, Novartis, Thermofisher; funding for patient enrollment or completion of research from Novartis; has stock/stock options from AKL Research and Development Ltd, which produces phyto-pharmaceuticals; owns 74% of the social enterprise 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.

Funding

This study was conducted by the Observational and Pragmatic Research Institute Pte Ltd and was partially funded by Optimum Patient Care Global and AstraZeneca Ltd. Observational and Pragmatic Research Institute Pte Ltd conducted this study in collaboration with Optimum Patient Care and AstraZeneca. No funding was received by Observational and Pragmatic Research Institute Pte Ltd for its contribution.

References

1. Global Initiative for Asthma. Global strategy for asthma management and prevention. 2023. Available at: <https://ginasthma.org/wp-content/uploads/2023/05/GINA-2023-Full-Report-2023-WMS.pdf>. Accessed September 22, 2023.
2. Global Initiative for Asthma. Global strategy for asthma management and prevention. Revised 2014. Available at: <https://ginasthma.org/wp-content/uploads/2019/01/2014-GINA.pdf>. Accessed September 22, 2023.
3. Patel GB, Peters AT. Comorbidities associated with severe asthma. *J Precis Respir Med*. 2019;2(1):5–9.
4. Chanoine S, Sanchez M, Pin I, Temam S, Le Moual N, Fournier A, et al. Multimorbidity medications and poor asthma prognosis. *Eur Respir J*. 2018;51(4):1702114.
5. Price D, Menzies-Gow A, Bachert C, Canonica GW, Kocks J, Khan AH, et al. Association between a type 2 inflammatory disease burden score and outcomes among patients with asthma. *J Asthma Allergy*. 2021;14:1173–1183.
6. Ehteshami-Afshar S, FitzGerald JM, Carlsten C, Tavakoli H, Rousseau R, Tan WC, et al. The impact of comorbidities on productivity loss in asthma patients. *Respir Res*. 2016;17(1):106.
7. Chen W, Lynd LD, FitzGerald JM, Marra CA, Balshaw R, To T, et al. Excess medical costs in patients with asthma and the role of comorbidity. *Eur Respir J*. 2016;48(6):1584–1592.
8. Chung KF. Defining phenotypes in asthma: a step towards personalized medicine. *Drugs*. 2014;74(7):719–728.
9. Porsbjerg C, Menzies-Gow A. Co-morbidities in severe asthma: clinical impact and management. *Respirology*. 2017;22(4):651–661.
10. Price DB, Trudo F, Voorham J, Xu X, Kerkhof M, Ling Zhi Jie J, et al. Adverse outcomes from initiation of systemic corticosteroids for asthma: long-term observational study. *J Asthma Allergy*. 2018;11:193–204.
11. Sweeney J, Patterson CC, Menzies-Gow A, Niven RM, Mansur AH, Bucknall C, et al. Comorbidity in severe asthma requiring systemic corticosteroid therapy: cross-sectional data from the Optimum Patient Care Research Database and the British Thoracic Difficult Asthma Registry. *Thorax*. 2016;71(4):339–346.
12. Lavoie KL, Cartier A, Labrecque M, Bacon SL, Lemi ère C, Malo JL, et al. Are psychiatric disorders associated with worse asthma control and quality of life in asthma patients? *Respir Med*. 2005;99(10):1249–1257.

13. Tu X, Donovan C, Kim RY, Wark PAB, Horvat JC, Hansbro PM. Asthma-COPD overlap: current understanding and the utility of experimental models. *Eur Respir Rev.* 2021;30(159): 190185.
14. Nadeau M, Boulay M E, Milot J, Lepage J, Bilodeau L, Maltais F, et al. Comparative prevalence of co-morbidities in smoking and non-smoking asthma patients with incomplete reversibility of airway obstruction, non-smoking asthma patients with complete reversibility of airway obstruction and COPD patients. *Respir Med.* 2017;125:82–88.
15. Kauppi P, Linna M, Jantunen J, Martikainen JE, Haahtela T, Pelkonen A, et al. Chronic comorbidities contribute to the burden and costs of persistent asthma. *Mediators Inflamm.* 2015;2015: 819194.
16. Bisaccioni C, Aun MV, Cajuela E, Kalil J, Agondi RC, Giavina-Bianchi P. Comorbidities in severe asthma: frequency of rhinitis, nasal polyposis, gastroesophageal reflux disease, vocal cord dysfunction and bronchiectasis. *Clinics (S Paulo).* 2009;64(8):769–773.
17. Bulathsinhala L, Eleangovan N, Heaney LG, Menzies-Gow A, Gibson PG, Peters M, et al. Development of the International Severe Asthma Registry (ISAR): a modified Delphi study. *J Allergy Clin Immunol Pract.* 2019;7(2). 578-588.e2.
18. ISAR Study Group. International Severe Asthma Registry (ISAR): mission statement. *Chest.* 2020;157(4):805–814.
19. International Severe Asthma Registry (ISAR). Available at: <https://isaregistries.org/>. Accessed September 22, 2023.
20. FitzGerald JM, Tran TN, Alacqua M, Altraja A, Backer V, Bjermer L, et al. International Severe Asthma Registry (ISAR): protocol for a global registry. *BMC Med Res Methodol.* 2020;20(1):212.
21. Global Initiative for Asthma. Global strategy for asthma management and prevention. 2018. Available at: <https://ginasthma.org/wp-content/uploads/2019/01/2018-GINA.pdf>. Accessed September 22, 2023.
22. Cushen B, Koh MS, Tran TN, Martin N, Murray RB, Uthaman T. Adult severe asthma registries: a global and growing inventory. *Prag Obs Res.* 2023. Published online.
23. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. *Eur Respir J.* 1993;6(suppl 16):5–40.
24. R Core Team. A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing. Available at: <https://www.R-project.org/>. Accessed September 22, 2023.
25. Wang E, Wechsler ME, Tran TN, Heaney LG, Jones RC, Menzies-Gow AN, et al. Characterization of severe asthma worldwide: data from the International Severe Asthma Registry (ISAR). *Chest.* 2020;157(4):790–804.

26. Al Efraij K, Johnson KM, Wiebe D, Sadatsafavi M, FitzGerald JM. A systematic review of the adverse events and economic impact associated with oral corticosteroids in asthma. *J Asthma*. 2019;56(12):1334–1346.
27. Gurnell M, Heaney LG, Price D, Menzies-Gow A. Long-term corticosteroid use, adrenal insufficiency and the need for steroid-sparing treatment in adult severe asthma. *J Intern Med*. 2021;290(2):240–256.
28. Scadding G, Walker S. Poor asthma control?—then look up the nose. The importance of co-morbid rhinitis in patients with asthma. *Prim Care Respir J*. 2012;21(2):222–228.
29. Clatworthy J, Price D, Ryan D, Haughney J, Horne R. The value of self-report assessment of adherence, rhinitis and smoking in relation to asthma control. *Prim Care Respir J*. 2009;18(4):300–305.
30. Steppuhn H, Langen U, Scheidt-Nave C, Keil T. Major comorbid conditions in asthma and association with asthma-related hospitalizations and emergency department admissions in adults: results from the German National Health Telephone Interview Survey (GEDA) 2010. *BMC Pulm Med*. 2013;13:46.
31. Janson C, Lisspers K, Stållberg B, Johansson G, Thuresson M, Telg G, et al. Prevalence, characteristics and management of frequently exacerbating asthma patients: an observational study in Sweden (PACEHR). *Eur Respir J*. 2018;52(2):1701927.
32. Khan AH, Gouia I, Kamat S, Johnson R, Small M, Siddall J. Prevalence and severity distribution of type 2 inflammation-related comorbidities among patients with asthma, chronic rhinosinusitis with nasal polyps, and atopic dermatitis. *Lung*. 2023;201(1):57–63.
33. Price DB, Buhl R, Chan A, Freeman D, Gardener E, Godley C, et al. Fractional exhaled nitric oxide as a predictor of response to inhaled corticosteroids in patients with non-specific respiratory symptoms and insignificant bronchodilator reversibility: a randomised controlled trial. *Lancet Respir Med*. 2018;6(1):29–39.
34. Soremekun S, Heaney LG, Skinner D, Bulathsinhala L, Carter V, Chaudhry I, et al. Asthma exacerbations are associated with a decline in lung function: a longitudinal population-based study. *Thorax*. 2023;78(7):643–652.
35. Bleecker ER, Menzies-Gow AN, Price DB, Bourdin A, Sweet S, Martin AL, et al. Systematic literature review of systemic corticosteroid use for asthma management. *Am J Respir Crit Care Med*. 2020;201(3):276–293.
36. Price D, Wilson AM, Chisholm A, Rigazio A, Burden A, Thomas M, et al. Predicting frequent asthma exacerbations using blood eosinophil count and other patient data routinely available in clinical practice. *J Asthma Allergy*. 2016;9:1–12.

37. Ozden Mat D, Firat S, Aksu K, Aksu F, Duyar S,S. Obstructive sleep apnea is a determinant of asthma control independent of smoking, reflux and rhinitis. *Allergy Asthma Proc.* 2021;42(1):e25–e29.
38. Blakey J, Chung LP, McDonald VM, Ruane L, Gornall J, Barton C, et al. Oral corticosteroids stewardship for asthma in adults and adolescents: a position paper from the Thoracic Society of Australia and New Zealand. *Respirology.* 2021;26(12):1112–1130.
39. Suehs CM, Menzies-Gow A, Price D, Bleecker ER, Canonica GW, Gurnell M, et al. Expert consensus on the tapering of oral corticosteroids for the treatment of asthma. A Delphi study. *Am J Respir Crit Care Med.* 2021;203(7):871–881.
40. Liang B, Yi Q, Feng Y. Association of gastroesophageal reflux disease with asthma control. *Dis Esophagus.* 2013;26(8):794–798.
41. Denlinger LC, Phillips BR, Ramratnam S, Ross K, Bhakta NR, Cardet JC, et al. Inflammatory and comorbid features of patients with severe asthma and frequent exacerbations. *Am J Respir Crit Care Med.* 2017;195(3):302–313.