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International variation in severe exacerbation rates in patients with severe asthma

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Data availability statement:

In line with ISAR governance restrictions, sharing individual deidentified participant data is subject to the consent of the ISAR steering committee (ISC) members in accordance with patient consent, patient confidentiality, and ethical considerations. The study documents (protocol, statistical analysis plan, clinical study report) will be made available in accordance with the criteria of the European Network of Centres for Pharmacoepidemiology and

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Tae Yoon Lee, Wenjia Chen, and Mohsen Sadatsafavi are responsible for the content of the manuscript, including the data and analysis.

Author contributions:

Tae Yoon Lee, Wenjia Chen, and Mohsen Sadatsafavi conceptualized the study, developed the study design and statistical plan.

David Price, Eileen Wang, Michael E. Wechsler, David J. Jackson, John Busby, Liam G. Heaney, Paul E. Pfeffer, Bassam Mahboub, Diahn-Warng Perng (Steve), Borja G. Cosio, Luis Perez-de-Llano, Riyad Al-Lehebi, Désirée Larenas-LinnemannMona Al-Ahmad, Chin Kook Rhee, Takashi IwanagaEnrico Heffler, Giorgio Walter Canonica, Richard Costello, Nikolaos G. Papadopoulos, Andriana I. Papaioannou, Celeste M. Porsbjerg, Carlos A. Torres-Duque, George C. Christoff, Ted A. Popov, Mark Hew, Matthew Peters, Peter G. Gibson, Jorge Maspero, Celine Bergeron, Wenjia Chen, and Mohsen Sadatsafavi were involved in data acquisition.

Chandra Prakash Yadav, Rupsa Roy, and Wenjia Chen processed and prepared the data for analysis.

Tae Yoon Lee performed the analysis and interpreted the results.

Tae Yoon Lee wrote the first draft of the manuscript.

Laura Lim Huey Mien reviewed the codes and independently replicated the results.

Wenjia Chen and Mohsen Sadatsafavi supervised the study progress and provided regular feedback.

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Abstract

Background: Exacerbation frequency strongly influences treatment choices in patients with severe asthma.

Research Question: What is the extent of the variability of exacerbations rate across countries and its implications in disease management?

Study Design and Methods: We retrieved data from the International Severe Asthma Registry, an international observational cohort of patients with a clinical diagnosis of severe asthma. We identified patients aged ≥18 years who did not initiate any biologics prior to baseline visit. A severe exacerbation was defined as the use of oral corticosteroids for ≥3 days or asthma-related hospitalization/emergency room visit. A series of negative binomial models were applied to estimate country-specific severe exacerbation rates during 365 days of follow-up, starting from a naïve model with country as the only variable, to an adjusted model with country as a random-effect term and patient and disease characteristics as independent variables.

Results: The final sample included 7,510 patients from 17 countries (56% from the United States), contributing to 1,939 severe exacerbations (0.27/person-year). There was large between-country variation in observed severe exacerbation rate (min: 0.04 [Argentina], max:0.88 [Saudi Arabia], interquartile range [IQR]: 0.13–0.54), which remained substantial after adjusting for patient characteristics and sampling variability (IQR: 0.16–0.39).

Interpretation: Individuals with similar patient characteristics but coming from different jurisdictions have varied severe exacerbation risks, even after controlling for patient and disease characteristics. This suggests unknown patient factors or system-level variations at play. Disease management guidelines should recognize such between-country variability. Risk prediction models that are calibrated for each jurisdiction will be needed to optimize treatment strategies.

Clinical Trial Registration Number: N/A

Key Words: Asthma, severe exacerbation, heterogeneity, country, prediction

Abbreviations

ATS: American Thoracic Society

ERS: European Respiratory Society

GINA: Global Initiative for Asthma

ICS: inhaled corticosteroids

IQR: Interquartile range

ISAR: International Severe Asthma Registry

LABA: long-acting beta-agonists

LAMA: long-acting muscarinic antagonists

OCS: oral corticosteroids

UAE: United Arab Emirates

Sudden worsening of symptoms referred to as exacerbations or 'flare-ups' is a hallmark of the natural course of asthma.[1] As exacerbations are a major cause of morbidity and economic burden,[2] reducing their risk is key to contemporary disease management.[1] In particular, exacerbation frequency is considered a major determinant in treatment decision-making for patients with severe asthma.[1] However, frequency of exacerbations and their severity can vary across settings. Such variation can lead to inconsistent treatment escalation or de-escalation strategies.[3] As such, setting-specific influences on exacerbation risk should be taken into consideration in designing disease management strategies. While variations can be defined at different levels (e.g., regions, countries, local health systems), as the locus of decision-making

(e.g., guideline development, health policymaking) is often at the country level, we focus on between-country variability in this work.

Part of variability in exacerbation rates across countries can be attributable to differences in case-mix, i.e., salient patient and disease characteristics that are associated with exacerbations, such as lung function and symptom burden. Such differences can be potentially accounted for by including patient characteristics in treatment recommendations, typically via using multivariable risk scores. Observed differences in exacerbation rate can also be in part due to the finite sample sizes of the studies documenting exacerbation rates. This is an inevitable consequence of sampling, as an observed exacerbation rate is a noisy estimate of the actual rate when the sample size is small, generating spurious variability. Without considering case-mix and sampling variability, a naïve estimate of variation can be exaggerated. This has been shown, for example, in the context of short-term mortality after myocardial infarction, where the observed variability across countries was reduced by 87% after controlling for patient characteristics and finite sample sizes.[4]

Understanding the extent of true heterogeneity, after attempting to control for patient characteristics and finite samples, is of paramount importance for formulating generalizable clinical management algorithms. This is also critical for designing efficient randomized trials. Using a standardized international registry of severe asthma, this study aims to assess the magnitude of explained and unexplained variation in severe asthma exacerbation rates across countries. Our particular focus is on biologic-naïve patients with severe asthma as the

assessment of exacerbation risk in such patients is a major factor in the decision to initiate biologics.

Study Design and Methods

This study has obtained ethics approval from the Institutional Review Board of [XXX] and the Anonymized Data Ethics & Protocol Transparency Committee ([XXX]). XXX: anonymized for the peer review process

Data source

The International Severe Asthma Registry (ISAR; 2015-2021; https://isaregistries.org/) is a prospective international observational cohort of patients with a clinical diagnosis of severe, uncontrolled asthma over 19 countries (list provided in Table 1).[5] Details of the design and data collection strategy of ISAR is explained elsewhere.[6] In brief, there is a leading center in each country that oversees the data collection and quality assurance. The centers, ranging from 1 to 55 per country, are secondary or tertiary clinics for asthma.[7] Data are collected using medical charts and electronic report forms. Severe asthma is defined as asthma that requires treatment at inclusion according to the 2018 definitions of the Global Initiative for Asthma (GINA): GINA Step 5 or uncontrolled asthma status at GINA Step 4 (details in ***Supplementary Materials Section 1***).[8,9] The registry contains a rich set of demographic and clinical characteristics including asthma symptoms and treatment, lung function, type 2 inflammation biomarkers, comorbidities, and health services use.[5]

Study cohort

The study sample included patients with severe asthma who were at least 18 years old and had not initiated any therapeutic antibodies ("biologics") at baseline visit. We had access to the cohort recruited between 2015 and 2021. The *index date* was defined as the date of the baseline visit. Patients were followed up to 365 days. We excluded patients with a follow-up period of below 30 days or with missing visit dates. We also excluded countries with sample sizes less than 5 to prevent small-cell effects.

We used an intention-to-treat approach and did not adjust for changes in status of use of asthma medications or biologics during follow-up.[10] Only a small percentage of the included patients (8.2%) received treatment with biologics during follow-up. We carried out a sensitivity analysis with exclusion of those patients. All the ISAR patients were on medium or high doses of inhaled corticosteroids (ICS) and long-acting beta-agonists (LABA) at baseline.

Outcomes

The primary outcome was the rate of severe exacerbations in the next 365 days. Severe exacerbation was defined according to the American Thoracic Society (ATS) / European Respiratory Society (ERS) taskforce: use of oral corticosteroids (OCS) for at least 3 days, or an occurrence of asthma-related hospitalization or emergency room visit.[11] In two participating countries that recorded OCS-requiring exacerbations without the start and end dates of OCS use, we assumed 3 days and above of OCS use for each recorded OCS-requiring exacerbation.

Due to the study inclusion/exclusion criteria, there were no missing values in the outcome variable.

Covariates

In addition to country, we extracted 17 core prognostic patient characteristics for severe exacerbations from a larger set of potential candidates. This selection was conducted based on a survey of 70 leading experts in severe asthma care and management (***Supplementary Materials Section 2***).[12] We included 3 additional covariates for long-term use of asthma medications at baseline visit. The covariates were age, smoking status, body-mass index, asthma control, pre-bronchodilator measurement of forced expiratory volume at 1 second, fractional exhaled nitric oxide, blood eosinophil counts, total severe exacerbations in the past year (calculated in the same way as follow-up severe exacerbations), total hospital visits in the past year, total emergency room visits in the past year, total use of invasive ventilations in the past year, long-term OCS use, use of steroid sparing drugs, long-term use of long-acting muscarinic antagonists (LAMA), use of a combination therapy of LABA and LAMA, long-term use of macrolides, and presence of allergic rhinitis, chronic rhinosinusitis, nasal polyps, and obesity. System-level covariates such as access to biologics,[13] quality of care, or indices related to the development or wealth of a country, were not included. This is because such factors are currently not considered in guideline development and health policymaking. Correspondingly, we excluded them to describe the components of heterogeneity that are not considered in contemporary asthma management strategies.

Statistical Analyses

Extreme values of covariates were examined case by case, with outliers flagged if deemed implausible and recoded as missing values.[14] A robust, random forest-based non-parametric algorithm (MissForest) was performed to impute missing predictor values.[15]

To test for differences in individual covariates across countries, we used one-way analysis-of-variance for univariate associations and Pearson's chi-squared test for categorical covariates (asthma control and smoking status) with the Bonferroni correction to take multiple hypothesis testing into consideration.[16]

We used negative binomial regression modeling for evaluating the effect of case-mix and sampling on between-country variability. Based on diagnostic tests, we found that the negative binomial models without the zero-inflation component sufficiently captured the severe exacerbation pattern in the data (***Supplementary Materials Section 3***). To sequentially disentangle the effect of case-mix and sampling variability, we used a series of negative binomial models. First, we fitted a naïve fixed-effect model, with severe exacerbation count during the first 365 days of follow-up as the dependent variable and 17 dummy-coded indicators of countries as the fixed-effect terms. In case significant heterogeneity in severe exacerbation rates across countries were detected (based on the Wald chi-square test[17]), the second step involved the addition of baseline patient characteristics as independent variables in order to test whether the between-country variation remained significant. To capture potential non-linear relationships with the response variable, continuous covariates were modeled using

thin-plate splines.[18] If the between-country effect was removed by the covariate adjustment, the conclusion would be that all variability across countries could be explained by case-mix. Otherwise, a third step involved fitting an adjusted random-effects model to control for case-mix and variability in the country effects due to the sample size within each country.[19] We would extract the empirical Bayes estimates of the random-effects term (country) along with 95% confidence intervals.[19] In this context, the empirical Bayes estimate represents the shrinkage of a country effect towards the population mean depending on the relative magnitude of variance of the country effect and variance of between-country effects. We reported on country-specific severe exacerbation rates using the average marginal effect (details are provided in ***Supplementary Materials Section 4***).[20,21] We plotted the estimated 'country effect' for each of the naïve model, adjusted fixed-effect model, and adjusted random-effects model. In a sensitivity analysis, we carried out a nested random-effects analysis to investigate the effect of regions (details are provided in ***Supplementary Materials 5***).

All analyses were performed using R, version 4.3.1.[22]

Results

Study Cohort

The final cohort included 7,510 individuals from 17 countries, followed for an average of 353 days (***Figure 1***). The total number of severe exacerbations was 1,939, corresponding to an annual rate of 0.27 per person-year (***Table 1***; information on other covariates is provided in

Supplementary Materials Section 6). The crude annual severe exacerbation rates varied considerably across countries, with the average value of 0.32 (standard deviation: 0.25). Saudi Arabia and the United Kingdom had the highest values of 0.92 and 0.76, respectively, and Argentina and Colombia had the lowest values of, respectively, 0.04 and 0.08. We found significant between-country differences in all the covariates (*P*-value < 0.001) except for the long-term use of LABA and LAMA (*P*-value > 0.5).

<< Figure 1>>

<<Table 1>>

Between-country variability

In the naïve fixed-effect model, the between-country effect was statistically significant (Wald chi-squared test *P*-value < 0.001). The country-specific model-based severe exacerbation rates varied with the interquartile range (IQR) of 0.13–0.54 events per year (***Figure 2***).

After including covariates, between-country effect only reduced slightly overall and remained significant (*P*-value<0.001), implying the differences in the case-mix only partially explained the variation in severe exacerbation rates across countries. This was reflected by the modest changes in the IQR to 0.15–0.43 events per year. However, estimates from individual countries changed differently with the inclusion of covariates. For instance, Greece had a small change of <2% between the naïve and adjusted models. This implies the case-mix of severe asthma patients in Greece was close to the international average. On the other hand, controlling for

case mix changed the estimates substantially for Saudi Arabia (-49%) and United Kingdom (-43%).

Subsequently, we fitted an adjusted random-effects model to estimate country-specific effects. The estimates of country-specific severe exacerbation rates shrunk towards the overall mean at a modest level for most countries (***Figure 2; Supplementary Materials Section 7***). Consequently, it again led to small changes in the IQR to 0.16–0.39 events per year, indicating that sampling variability could only partially explain between-country heterogeneity.

<<Figure 2>>

Sensitivity analysis indicated that our overall results were largely insensitive to inclusion/exclusion of patients who received biologics during follow-up (***Supplementary Materials Section 8***) and that the there was no substantial regional effect over and beyond country-level effects (*P*-value: 0.56; ***Supplementary Materials 5***).

Discussion

In an international observational cohort of patients with severe asthma, we discovered substantial between-country differences in severe exacerbation rates. The inclusion of core prognostic covariates at patient-level could only modestly explain the between-country variation, as supported by small changes in the estimates of country-specific severe exacerbation rates when covariates were added. Using a random-effects model to account for sampling could modestly reduce the estimated variation. Considerable variation remained

unexplained, with the average of country-specific rates of severe exacerbation among the top 50% countries being 2.8 times than that of the bottom 50%.

There are several potential reasons for unexplained differences in the severe exacerbation rates across countries. The natural course of severe asthma might indeed be truly different across countries. However, the inclusion of several clinically relevant variables did not explain away between-country differences. As such, system-level factors are also likely to contribute to the observed variability. Differences in healthcare systems (e.g., access to biologics, biologic eligibility criteria, medication costs) can generate heterogeneity. Universal public coverage of essential medicines for asthma, particularly the combination therapy of ICS and LABA, can be another factor responsible for the unexplained heterogeneity. Affordability of these medicines remains a major barrier to asthma management (including severe exacerbations) for low-income and medium-income countries, such as Mexico.[26] Further, asthma management decisions in participating centers after recruitment of patients might be different, contributing to the variability in event rates. Examples include asthma education and training programs for inhaler use, treatment of comorbidity, and environmental control. Likely due to such interventions, the annual severe exacerbation rate generally decreased after enrollment in the study, albeit with varying degrees (e.g., from 0.79 to 0.13 in the UAE and from 0.29 to 0.25 in Italy). Moreover, environmental factors can play a role. For example, Saudi Rabia has a varied climate, and a large part of the country is often affected by regular sandstorms, which might explain part of the large differences in event rates comparted with its neighboring coastal countries such as Kuwait and UAE are.

The literature is sparse on the extent of between-country variability. Wang et al. provided descriptive statistics of clinical characteristics of severe asthma using an earlier version of the ISAR database.[27] They noted substantial differences across five groups of countries in asthma outcomes, including exacerbation rates, but could not make a definitive statement on the between-group heterogeneity, given that they did not adjust for case-mix and sampling variability. Using naïve estimates may exaggerate the between-country variability. For instance, Calverley et al. found substantial international differences in exacerbation rates of chronic obstructive pulmonary disease across 41 countries.[28] However, such findings and interpretations on between-country variability, while relevant for depicting an overall picture of heterogeneity, may change once they adjust for the uncertainty due to finite sample sizes. Similarly, findings by Vermeire et al. who used unadjusted estimates of between-country variability in asthma control and medication use among seven European countries, while varied, should be interpreted as not controlling for case-mix and finite sampling.[29]

Our study has important implications for practice and research. Our results question the merit of imposing unified treatment strategies for patients with severe asthma, without considering case-mix and country-specific effects. According to our findings, patients with similar characteristics and asthma histories but from different countries might be at different risk of future exacerbations. Thus, the benefit of treatments in terms of reduction in exacerbation rate (e.g., the number needed to treat prevent one exacerbation) may differ for otherwise similar patients across countries. We believe international initiatives such as GINA should emphasize multivariable risk calculations, which are further adapted to each setting (e.g., via country-specific risk correction).[30]

Another important implication is for the design of future severe asthma trials, in which severe asthma exacerbation rate is often a key inclusion criterion (e.g., >1 exacerbations in the last 12 months[31]). To achieve desired sample sizes, international coordinated efforts are required in such trials.[32] Ignoring between-country variability can lead to inefficient clinical trial designs. As an illustration, we took three participating countries with the lowest, middle (median), and highest values of observed severe exacerbation rate and explored statistical power calculations (***Figure 3;*** details of the methodology are provided in ***Supplementary Materials Section 9***). To detect a 20% reduction in the severe exacerbation rate with 90% power, 12,699 patients per arm would be required in Argentina, whereas 2,503 patients would be needed in South Korea and only 1,432 patients per arm would be needed in Saudi Arabia. International clinical studies that recruit patients from specialty cares should therefore balance the efficiency of their trial design and the representativeness of countries and regions.

<<Figure 3>>

The strengths of this study include access to a multinational prospective severe asthma registry that provided large sample sizes and consistent inclusion criteria. Sequential modeling of severe exacerbations enabled us to examine, in a stepwise fashion, unexplained variability in severe exacerbation rates. Our sampling-adjusted exacerbation rates from the random-effects model provides objective baseline values for sample size calculations in future trials in severe asthma. However, limitations of our study should also be considered. Despite its wide acceptability, the ATS/ERS definition of exacerbation may underestimate the rate of true exacerbations among resource-constraint countries where patients have limited access to healthcare. We also cannot rule out that some of the observed variation can be due to the study protocol. Despite ISAR's

continuous efforts to unify the definition of severe asthma, the criteria still varied slightly across countries.[12] Standardization of definitions (e.g., training data providers to carefully distinguish exacerbation from loss of asthma control) can mitigate such induced variability. Another limitation is that ISAR is not a population-based registry. Most ISAR participants were recruited from specialty clinics and local registries in their respective participating countries, which are not necessarily representative of their respective severe asthma population. We note that the observed severe exacerbation rate in ISAR is notably low (0.27/year) in comparison with existing severe asthma trials (e.g., 1.84/year in the placebo arm of two multinational phase 3 trials of mepolizumab in severe eosinophilic asthma combined[33]). However, this is because trial samples are often highly enriched for patients at high risk of severe exacerbations, such as requiring a higher number of exacerbations and eosinophil count at baseline.[33] We did not have access to several potentially important patient-level variables, including health literacy and adherence.[34] Last but not least, COVID-19 which occurred during the recruitment period of ISAR could have contributed to the unexplained variability, as countries experienced COVID-19 waves at different time points.

Our study was aimed at documenting the extent of country-level heterogeneity in observed severe exacerbation rates beyond case-mix differences, and to that end, we intentionally did not include such country-level factors in the analysis. The inclusion of such factors would make our study less informative in demonstrating the extent of variability that is likely being missed by guidelines. Investigating the causes of such between-country heterogeneity is indeed a very relevant topic for future research. Such a study should consider multiple factors, such as quality of care (e.g., continuity of care, communications between general physicians and specialists,

the use of asthma action plans) as well as patients' experience of care and outcomes (through the use of patient-reported outcomes measures). To improve representativity and hence generalizability, future studies should expand the network of registries as well as consider collaboration with continental registries such as the pan-European Severe Heterogeneous Asthma Research Collaboration, Patient-centred.[35]

How can the field move forward? The considerable variability in exacerbation rates indicate the need for multivariable risk prediction. This research was indeed conducted as part of a larger study in developing and validating risk prediction models for severe asthma.[12] However, recent results show that 'no size fits all' if trying to apply a single risk scoring tool to different settings.[30,36] Instead, multivariable prediction models will likely need to incorporate a 'country effect'. Using a global multivariable model that is adapted to each country / setting is much preferred over country-specific models, as individual countries are unlikely to have sufficient sample sizes, and research has shown that the resulting risk calculator will have sub-optimal performance.[37] The ability to locally adapt a risk scoring algorithm is a key advantage of a regression-based risk modeling as opposed to simplistic tools (e.g., management based on asthma control and exacerbation history alone).[30]

Interpretation

There is considerable heterogeneity in severe exacerbation rates in patients with severe asthma across countries. Differences in observed patient characteristics, including exacerbation history, only partially account for such heterogeneity. This indicates unknown or unmeasured patient

factors or system-level variation at play, requiring further investigation. Our findings suggest that each country or jurisdiction adapt clinical recommendations for severe asthma to their setting for optimal treatment escalation strategies. Moreover, multivariable risk prediction models with setting-specific effects that are properly calibrated to their local settings should be promoted as part of our quest in improving the management of asthma and increasing the efficiency of severe asthma trials.

Take-Home Point

- **Study Question:** Exacerbation frequency strongly influences treatment choices in patients with severe asthma, but the rate of exacerbations is different across countries. Does such between-country variation in exacerbation rates remain substantial after controlling for patient characteristics and randomness due to finite sample?
- **Results**: We found substantial between-country variation in severe exacerbation rate, even after adjusting for observed patient characteristics and finite sample sizes. As such, differences in observed patient characteristics, including exacerbation history, only partially account for observed heterogeneity.
- **Interpretation**: Two similar patients with same characteristics (including exacerbation history) from two different countries might be at substantially different risk of future exacerbations. Asthma management guidelines should promote multivariable risk prediction, with country-level calibration, to optimize treatment strategies.

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Country	Sample size	Severe exacerbations during follow-up	Average follow-up (years)	Severe exacerbation rate (per year)	Baseline severe exacerbation rate (per year)	Use of biologics during follow-up (%)
Argentina	26	1	0.98	0.04	0.81	0
Australia	394	191	0.94	0.52	0.46	0
Bulgaria	180	74	0.76	0.54	1.08	1
Canada	149	25	1.00	0.17	0.81	7
Colombia	204	17	0.99	0.08	0.82	7
Denmark	229	25	0.99	0.11	0.03	9
Greece	94	18	0.92	0.21	0.67	9
Italy	800	186	0.95	0.25	0.29	13
Japan	107	14	1.00	0.13	0.89	14
South Korea	38	11	0.99	0.29	0.11	32
Kuwait	163	41	1.00	0.25	2.33	25
Saudi Arabia	45	33	0.80	0.92	4.60	11
Spain	209	108	0.94	0.55	1.00	14
Taiwan	141	48	0.93	0.37	0.99	29
United Arab Emirates	117	13	0.88	0.13	0.79	4
United Kingdom	434	328	1.00	0.76	4.86	22
United States of America	4,180	806	0.98	0.20	0.19	5
Total	**7,510**	**1,939**	**0.97**	**0.27**	**0.67**	**8**

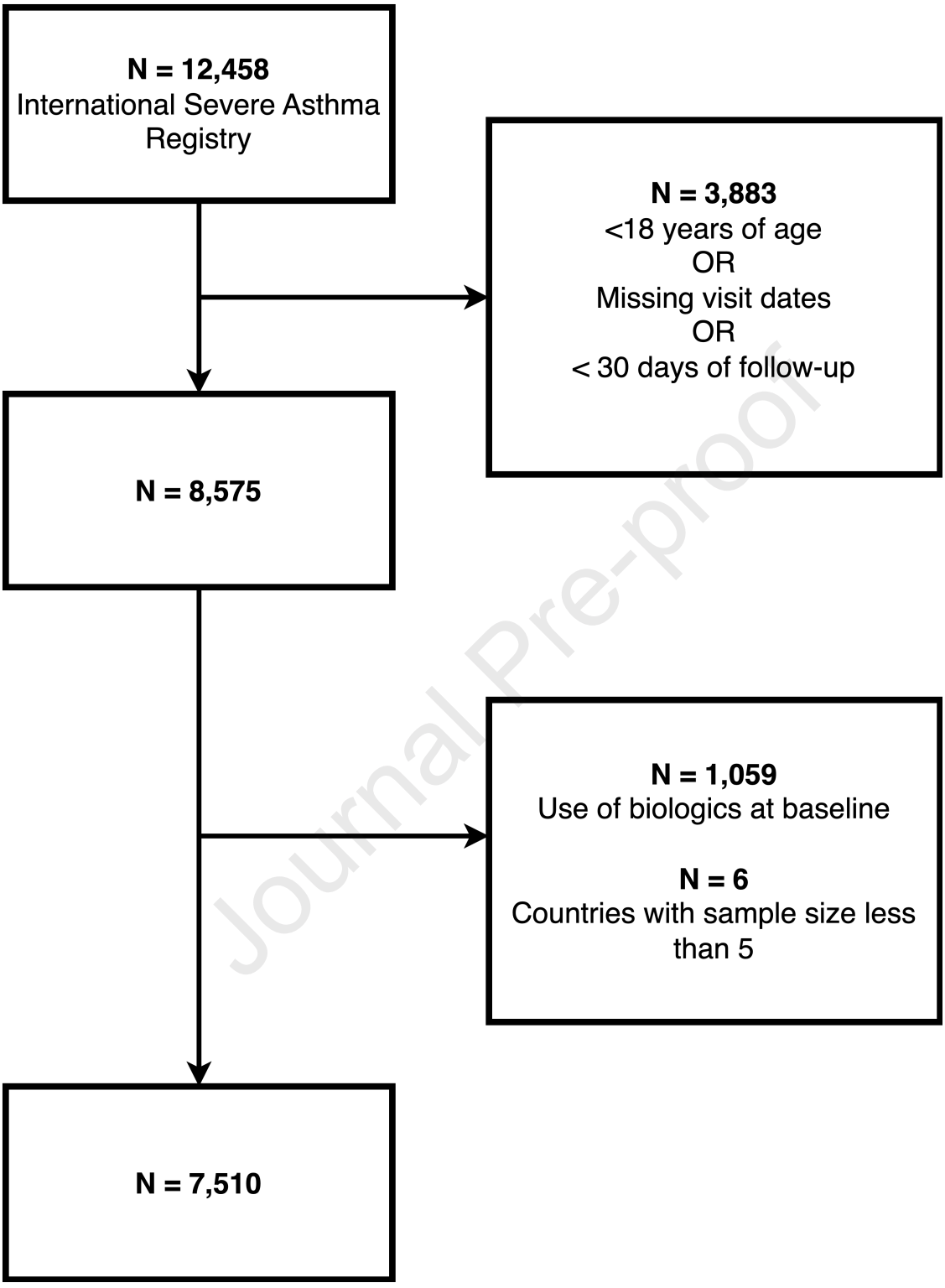
Table 1. Heterogeneity in patient characteristics (average values) and severe exacerbation rates between countries.

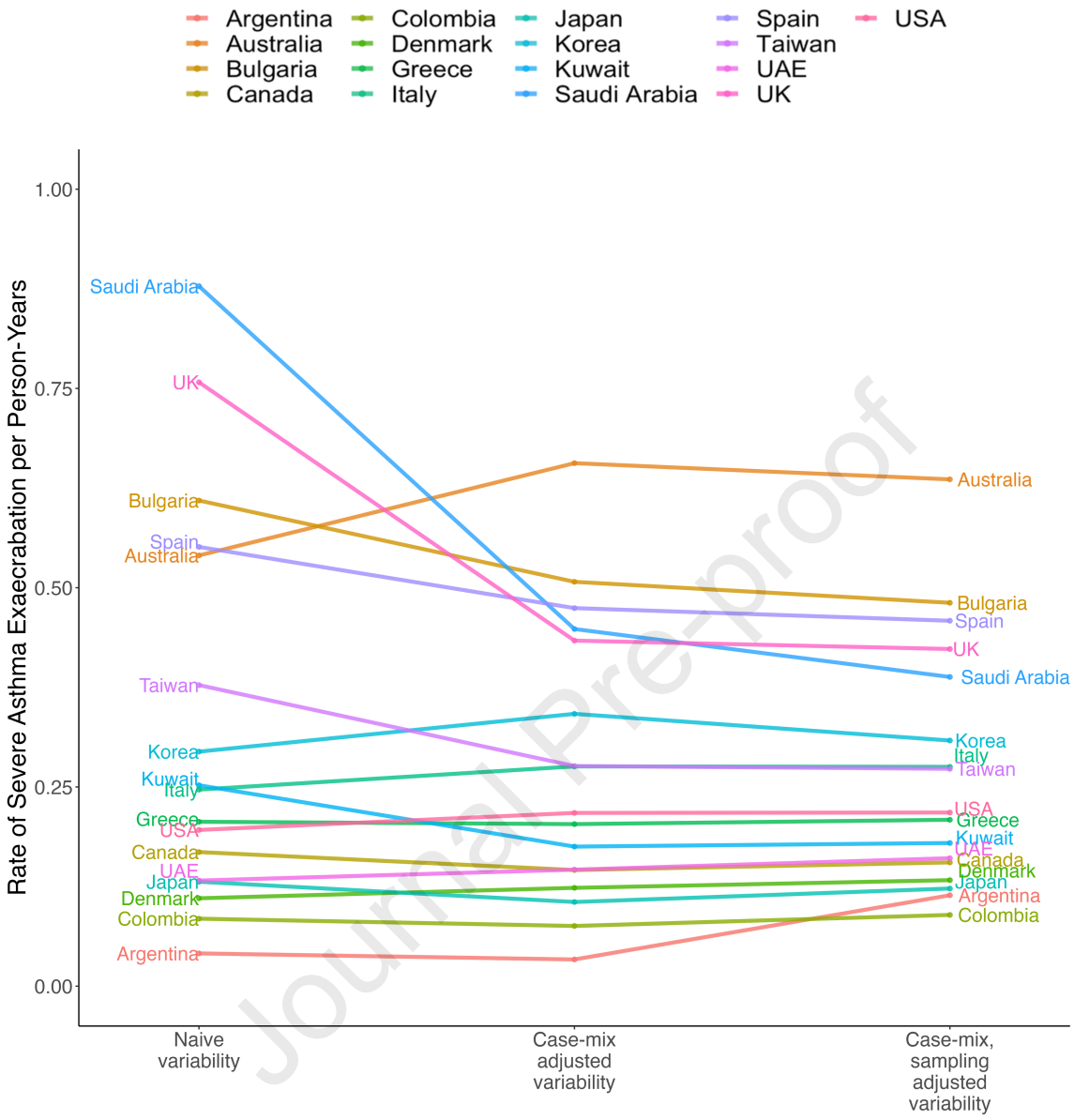
Figure legends

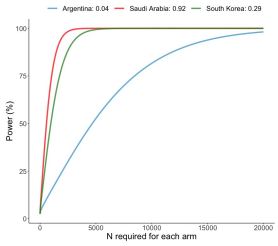
Figure 1. Flow diagram of the International Severe Asthma Registry cohort.

Figure 2. Estimates of country-specific severe asthma exacerbation rates (per person-years) using the average marginal effect framework for naïve, case-mix adjusted (fixed-effect), and case-mix & sampling adjusted (random-effects) models. *UK: United Kingdom; USA: United States of America; UAE: United Arab Emirates*.

Figure 3. Power analysis for the lowest, median, and highest severe exacerbation rates (per person-years) observed in the International Severe Asthma Registry to detect a reduction of 20% in severe exacerbation rates from the comparator.







International variation in severe exacerbation rates in patients with severe asthma

Supplementary Materials

Table of Contents

1. Diagnostic criteria for asthma and definition of severe asthma across countries in the International Registry of Severe Asthma

Country	Diagnostic criteria for asthma	Severe Asthma Definition
Argentina	• Bronchodilator response (BDR) > 200mL and/or > 12% of FEV1 baseline • FEV1 variability > 12% (between two FEV1 values measured within 2 months of each other)	• Lack of asthma control despite regular treatment with the combination of highest dose ICS and LABA • Or asthma that becomes uncontrolled when highest doses are reduced
Australia	• Variable airflow obstruction demonstrated within the last 10 years (any of the following). • Bronchodilator response (BDR) > 200mL and/or > 12% of FEV1 baseline • Airway hyper-responsiveness (AHR) in response to any standard challenge agent e.g. methacholine, histamine, hypertonic saline, mannitol, adenosine monophosphate, exercise • Peak flow variability > 12% when monitored over at least 1 week • FEV1 variability > 12% (between two FEV1 values measured within 2	• Confirmed Asthma Diagnosis with variable airflow obstruction • Maximal ICS Therapy with 2nd Controller • Optimised asthma management skills (inhaler technique, adherence, education, written asthma action plan) • Poor asthma control with 1 or more of the following: • Poor symptom control: ACQ6 consistently >1.5, ACT <20 (or "not well controlled" by NAEPP/GINA guidelines) • Frequent severe exacerbations: 2 or more bursts of systemic CSs (>3 days each) in the previous year • Serious exacerbations: at least one hospitalisation, ICU stay or mechanical ventilation in the previous year; or • Persistent airflow limitation: FEV1 < 80% predicted (in the face of reduced FEV1/FVC) following a withhold of short and long-acting bronchodilators (i.e. PRE-bronchodilator).

	months of each other)	
Bulgaria	• GINA and ERS confirmed asthma diagnosis.[1]	• As per ISAR protocol criteria for including asthmatics in the registry – ATS/ERS definition for severe asthma
Canada	• GINA confirmed asthma diagnosis.[1]	• Uncontrolled asthma despite a combination of high dose ICS and an additional controller, review of inhaler technique and adherence and appropriate treatment of comorbidities
Colombia	• GINA confirmed asthma diagnosis.[1]	• Aged ≥18 years • On GINA Step 5 or asthma uncontrolled on GINA Step 4. Uncontrolled defined as: (a) Poor symptom control: ACQ consistently>1.5, ACT<20 (or ‘‘not well controlled’’ by NAEPP/GINA guidelines) (b) Severe exacerbations: at least one hospitalisation, ICU stay or mechanical ventilation due to asthma exacerbation in the previous year (c) Frequent exacerbations: two or more bursts of systemic CS (>3days each) in the previous year
Denmark	• GINA confirmed asthma diagnosis.[1]	• Severe asthma, defined as asthma requiring either at least 1600 micrograms of budesonide equivalent ICS plus a second controller (LABA, LAMA, or LTRA) or use of OCS at least 50% of the year
Greece	• GINA confirmed asthma diagnosis.[1]	• Aged >12years • Diagnosis of severe asthma according to ERS/ATS criteria • Patients not controlled on GINA 4 treatment with the combination of high dose of ICS and LABA • Patients experiencing ≥2 asthma exacerbations (requiring systemic corticosteroids) • Patients requiring Continuous or frequent treatment with OCS to achieve asthma control and reduce symptoms and exacerbations
India	• GINA confirmed asthma diagnosis.[1]	• Patients 18 years or older • Patients in receiving treatment according to GINA Step 5 or uncontrolled in Step 4 Uncontrolled defined as: (a) Having Severe asthma symptoms AND/OR (b) Frequent severe asthma exacerbations requiring systemic corticosteroids **Severe asthma symptoms (ERS/ATS Guidelines):** (a) Poor symptom control where Asthma Control Questionnaire consistently >1.5, Asthma Control Test <20

		(b) Airflow limitation: FEV1 < 80% predicted (in the face of reduced FEV1/FVC following a withhold of short and long-acting bronchodilators, i.e. Pre-bronchodilator) (c) Serious exacerbations: at least one hospitalisation, ICU stay or mechanical ventilation in the in the previous year **Frequent severe asthma exacerbations requiring systemic corticosteroids (ERS/ATS Guidelines):** Two or more bursts of systemic Corticosteroids (>3 days course each) in the previous year
Ireland	• GINA confirmed asthma diagnosis.[1]	• Aged ≥18 years • On GINA Step 5 or asthma uncontrolled on GINA Step 4. Uncontrolled defined as: (a).Poor symptom control: ACQ consistently>1.5, ACT<20 (or ‘‘not well controlled’’ by NAEPP/GINA guidelines) (b).Airflow limitation: after appropriate bronchodilator withhold FEV1<80% predicted (in the face of reduced FEV1/FVC defined as less than the lower limit of normal) (c).Serious exacerbations: at least one hospitalisation, ICU stay or mechanical ventilation in the previous year (d) Frequent exacerbation : two or more bursts of systemic CS (>3days each) in the previous year
Italy	• GINA confirmed asthma diagnosis.[1]	• Aged >12 years • Diagnosis of severe asthma according to ERS/ATS criteria (as for UK registry above)[4] • Lack of asthma control despite regular treatment with the combination of high dose ICS and LABA
Japan	• GINA confirmed asthma diagnosis.[1]	• Aged ≥18 years • On GINA Step 5 or asthma uncontrolled on GINA Step 4. • Uncontrolled defined as remaining severe asthma symptoms, frequent severe exacerbations required, systemic corticosteroids
Kuwait	• GINA confirmed asthma diagnosis[1]	• Patients not controlled on GINA step 4-5 treatment in the previous year • Uncontrolled defined as ACT score <20 or prebronchodilator FEV_1 <80% predicted • With the following criteria: ○ ≥2 exacerbations requiring course of systemic corticosteroids ○ ≥2 exacerbations requiring A&E visit or 1 hospital admission, or ICU admission • Airflow limitation: Post bronchodilator FEV_1 <80% predicted (in the face of reduced FEV1/FVC defined as less than the lower limit of normal)

Mexico	• GINA confirmed asthma diagnosis, or when not fully reaching the spirometric cut-offs for reversibility: clinical symptoms and elevated FeNO.	• Aged ≥18 years • On GINA Step 5 or asthma uncontrolled on GINA Step 4. Uncontrolled defined as <u>any of the below</u>: o Poor symptom control: ACQ consistently>1.5, ACT<20 (or ''not well controlled'' by NAEPP/GINA guidelines) o Severe exacerbations: at least one hospitalisation, ICU stay or mechanical ventilation due to asthma exacerbation in the previous year • Frequent exacerbations: two or more bursts of systemic CS (>3days each) in the previous year
Poland	• GINA confirmed asthma diagnosis [1]	• The need to use high doses of inhaled glucocorticosteroids (> 1000 mcg of beclometasone dipropionate daily in adults and children aged 12 years and over, in children aged 6-11 years> 400mcg or other inhaled glucocorticosteroid in a dose equivalent according to current guidelines The Global Initiative for Asthma (GINA)) in combination with another asthma control drug (long-acting β-2 adrenergic agonist, leukotriene modifier, long-acting muscarinic receptor blocker). • Two or more episodes of exacerbation per year requiring the use of systemic corticosteroids or increasing their dose in adults and children aged 12 years and above who use them chronically; in children 6-11 years of age - two or more episodes of exacerbation a year despite the use of inhaled glucocorticosteroids. And meeting at least 2 of the following criteria: • Symptoms of uncontrolled asthma (lack of asthma control in the asthma control questionnaire ACQ> 1.5 points), • Hospitalisation within the last 12 months due to exacerbation of asthma, • An asthma attack that may have been life-threatening in the past, • Persistent airway obstruction (forced expiratory volume in one second FEV1 <80% predicted or daily variation in peak expiratory flow PEF> 30%), • Deterioration of quality of life due to asthma (mean score on the miniAQLQ quality of life control test in patients with asthma <5.0 points in adults and children aged 12 and over or PAQLQ <5.0 points in children 6-11 years of age.
Portugal	• GINA confirmed asthma diagnosis.[1]	• Lack of asthma control despite maintenance treatment with GINA step 4-5 treatment in the previous year • Uncontrolled asthma defined as: o poor symptom control (considering cutoff values for ACT and CARAT), or o ≥2 severe exacerbations (need for ≥3 days course of systemic corticosteroids) in the previous year, or o ≥1 hospitalisation, ICU stay or mechanical ventilation in the previous year, or

		• FEV_1 <80% predicted after bronchodilation (coupled with FEV_1/FVC <70%)
Saudi Arabia	• GINA confirmed asthma diagnosis.[1]	• Aged ≥18 years • On GINA Step 5 or asthma uncontrolled on GINA Step 4. • Uncontrolled asthma defined as remaining severe asthma symptoms ACT<20, frequent severe exacerbations requiring ER visit or short course of steroids, patient on daily systemic corticosteroids
South Korea	• GINA confirmed asthma diagnosis[1]	• Patients NOT controlled continuously on GINA Step 4 treatment • Patients controlled on GINA Step 4 treatment, but who meets the following criteria: ○ ≥1 urgent care visit (emergency room or unscheduled out-patient department visit) ○ ≥3 courses of systemic corticosteroid/year ○ Immediate asthma deterioration after 25% reduction of ICS/OCS • History of near fatal asthma attack
Spain	• GEMA confirmed diagnosis	• Aged ≥18 years • Lack of asthma control despite maintenance treatment with a combination of high dose ICS and LABA • Uncontrolled asthma defined as: ○ poor symptom control (ACQ ≥1.5 or ACT < 20), or ○ ≥2 severe exacerbations (need for ≥3 days course of systemic corticosteroids) in the previous year, or ○ ≥1 hospitalisation, ICU stay or mechanical ventilation in the previous year, or ○ FEV_1 <80% predicted after bronchodilation (coupled with FEV_1/FVC <70%)
Taiwan	•	• Aged ≥20 years • Patients in receiving treatment according to GINA Step 5 or uncontrolled in Step 4 according to GINA 2017 guideline. • Uncontrolled is defined as (a). Poor symptom control: ACQ consistently>1.5, ACT<20 (or ‘‘not well controlled’’ by NAEPP/GINA guidelines) (b). Airflow limitation: after appropriate bronchodilator withhold FEV1<80% predicted (in the face of reduced FEV1/FVC defined as less than the lower limit of normal) (c). Serious exacerbations: at least one hospitalisation, ICU stay or mechanical ventilation in the previous year (d). Frequent exacerbation: two or more bursts of systemic CS (>3 days each) in the previous year

United Arab Emirates	• GINA confirmed asthma diagnosis.[1]	• Aged ≥18 years • On GINA Step 5 or asthma uncontrolled on GINA Step 4. • Uncontrolled asthma defined as: ○ poor symptom control (ACT < 20), or ○ ≥2 severe exacerbations (need for ≥3 days course of systemic corticosteroids) in the previous year, or ○ ≥1 hospitalisation, ICU stay or mechanical ventilation in the previous year, or • FEV_1 <80% predicted after bronchodilation (coupled with FEV_1/FVC <70%) • Uncontrolled asthma despite a combination of high dose ICS and an additional controller, review of inhaler technique and adherence and appropriate treatment of comorbidities.
UK	• NICE or BTS/SIGN Guidelines[2,3]	• Diagnosis of severe asthma according to ERS/ATS criteria[4] ○ Requires treatment with guideline suggested medications for GINA steps 4-5 asthma for the previous year or systemic corticosteroids for ≥50% of the previous year to prevent it from becoming 'uncontrolled' or which remains 'uncontrolled' despite this therapy • Uncontrolled asthma defined as: ○ Poor symptom control: ACQ consistent ≥1.5, ACT< 20 or 'not well controlled' by NAEPP/GINA guidelines ○ Frequent severe exacerbations: ≥2 bursts of systemic corticosteroids (≥3 days each) in the previous year ○ Serious exacerbations: ≥1 hospitalisation, ICU stay or mechanical ventilation in the previous year ○ Airflow limitation: after appropriate bronchodilator withhold FEV_1 <80% predicted (in the face of reduced FEV_1/FVC defined as less than the lower limit of normal) • At least one of the following: ○ An event of acute severe asthma which is life threatening, requiring invasive ventilation within the last 10 years ○ Continuous or frequent treatment with OCS ○ Fixed airflow obstruction, with a post-bronchodilator FEV_1 <70% of predicted normal • Referred as an adolescent transition patient from a paediatric severe asthma service
USA	• ATS confirmed asthma diagnosis[4]	• Aged ≥18 years ○ On GINA Step 5 or asthma uncontrolled on GINA Step 4 ○ Uncontrolled defined as ACT score <20 or prebronchodilator FEV_1 <80% predicted

ACQ: Asthma Control Questionnaire; ACT: Asthma Control Test; A&E: Accident & Emergency; AHR: airway hyper-responsiveness; ATS: American Thoracic Society; BG: Bulgaria; BTS: British Thoracic Society; CN: Canada; DK: Denmark; ERS: European Respiratory Society; ES: Spain; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; GINA: Global Initiative for Asthma; GR: Greece; ICS: inhaled corticosteroid; ICU: Intensive Care Unit; ISAR: International Severe Asthma Registry; IT: Italy; JP: Japan; KW: Kuwait; LABA: long-acting β_2-agonist; LAMA: long-acting muscarinic

antagonist; LTRA: leukotriene receptor antagonist; NAEPP: National Asthma Education and Prevention Programme; NICE: National Institute for Clinical Excellence; OCS: oral corticosteroid; pMDI: pressurised metered dose inhaler; SK: South Korea.

* GINA confirmed asthma diagnosis with confirmed variable airflow obstruction current or historical within 10 years[1]:

- Bronchodilator response > 200 mL or >12% (post-bronchodilator FEV_1 following administration of 400 µg salbutamol, pMDI with spacer after 10 mins AND/OR
- AHR in response to any standard challenge agent (e.g. methacholine, histamine, hypertonic saline, mannitol, adenosine monophosphate, exercise) AND/OR
- Peak flow variability > 12% over at least 1 week AND/OR FEV_1 variability >12% within 2 months

Reference GEMA 4.0: Guía Española para el manejo del asma (Spanish Guideline for Asthma Management). Plaza Moral V; Comité Ejecutivo de GEMA. [GEMA(4.0). Guidelines for Asthma Management. Arch Bronconeumol. 2015 Jan;51 Suppl 1:2-54. doi: 10.1016/S0300-2896(15)32812-X. Diagnostic criteria: Asthma symptoms plus: positive bronchodilator response, or PEF variability, or exhaled nitric oxide > 50 ppb, or bronchial hyperresponsiveness, or complete reversion of bronchial obstruction after an oral corticosteroid test.

2. Patient characteristics and average recommendation scores

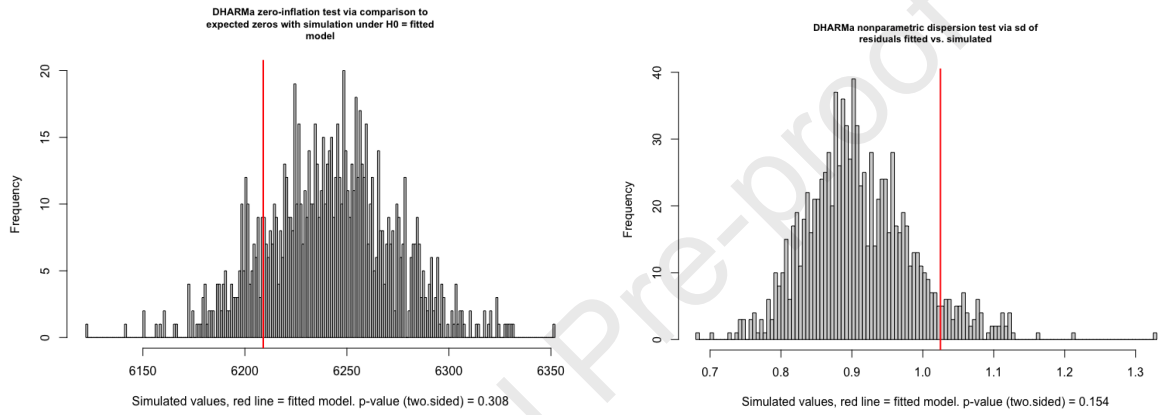
Baseline patient characteristics whose average recommendation scores are 3.9 or higher on a scale from 1 (not recommended) to 5 (highly recommended) based on a survey of 70 leading experts in severe asthma and management. The selected covariates had the average recommendation scores of 3.9 or higher on a scale from 1 (not recommended) to 5 (highly recommended), and <50% missingness.

Baseline patient characteristics	**Definition**	**Average score**
Age	Age of the patient.	4
Smoking status	Whether the patient has ever smoked.	4.4
BMI	Basal Metabolic Index (BMI) = Weight (kg)/(Height (m))^2 of the patient.	4.4
Asthma control	Defined and categorised by GINA 2022 assessment of asthma symptom control, Asthma Control Test, or Asthma control questionnaire.	4.9
Pre FEV1	Pre-bronchodilator measure of forced expiratory volume at 1 second (FEV1).	4.3
Fractional exhaled nitric oxide	Fractional Exhaled Nitric Oxide test result at baseline visit.	4.4
Eosinophil counts	Highest blood eosinophils count in last year.	4.7
Severe exacerbations	Total number of exacerbations occurring in the last year.	4.8
ER visits	Total asthma-related Emergency Room (ER) visits in the past year.	4.6
Hospital visits	Total asthma-related cases of hospitalisation within the past year.	4.8
Invasive Ventilation	Total number of invasive ventilations within the past year.	4.3
Long-term OCS	Whether the patient takes long-term/maintenance oral corticosteroids (OCS).	4.5
Steroid sparing	Whether the patient takes steroid sparing drugs	3.9

Allergic rhinitis	Did this patient have a positive diagnosis of allergic rhinitis as of or prior to baseline visit?	3.9
Chronic rhinosinusitis	Did this patient have a positive diagnosis of Chronic rhinosinusitis of or prior to baseline visit?	4.3
Nasal polyps	Did this patient have a positive diagnosis of Nasal polyps of or prior to baseline visit?	4.4
Obesity	Did this patient have a positive diagnosis of Obesity. of or prior to baseline visit?	3.9

3. Diagnostic tests

The zero-inflation component in the naïve model was estimated to be less than 1e-7, indicating the zero-component is not necessary. Further, the simulation-based hypothesis tests for zero-inflation (left) and overdispersion (right) indicate that the adjusted negative binomial model adequately handled anticipated excess zeros and overdispersion with p-values of 0.31 and 0.15, respectively.



4. Average marginal effect framework

We estimated country-specific exacerbation rates using the average marginal effect (AME) framework.[1,2] This framework allows for interpretation of a predictor in a complex model, such as a random-effects zero-inflated model, in terms of the original scale of the response variable. They are obtained by calculating the marginal effects of the predictor at *every* observed value of the other predictors in the dataset and then averaging the marginal effects by the predictor. Put differently, for each country, an identical, hypothetical dataset that emulated the distribution of the original data was used to compute the average rate of exacerbations as a natural summary measure. For the prediction, we set the offset term to one person-year and used the empirical Bayes estimates as the country specific-intercept for the random-effects model.

5. Sensitivity analysis: nested random-effects model

We investigated whether there was substantial difference in severe exacerbation rate between regions, over and beyond country-level differences, using a nested-random effects model, in which each country was nested in a region. In terms of the model syntax, we replaced the random-effects term (1|country) with (1|region) + (1|region:country). We grouped the countries into six regions as follows: Asia [Japan, South Korea, Taiwan], Europe [Bulgaria, Denmark, Greece, Italy, Spain, United Kingdom], Middle East [Kuwait, Saudi Arabia, United Arab Emirates], North America [Canada, Mexico, United States of America], South America [Argentina, Colombia], Oceania [Australia]. We found that the regional effect was not substantial (*P*-value: 0.56), with all the confidence intervals of empirical Bayes estimates of the regions covering 0.

6. Heterogeneity in patient characteristics (average values) and severe exacerbation rates between countries.

Country	Age (years)	Body mass index (kg/m^2)	Pre-forced expiratory volume at 1 second	Hospital visits	Invasive ventilation	Emergency room visit
Argentina	51	30	1.90	0.00	0.00	0.54
Australia	57	30	1.98	0.36	0.00	0.30
Bulgaria	58	28	1.60	0.79	0.01	0.25
Canada	59	30	2.15	0.15	0.12	0.59
Colombia	56	28	1.84	0.20	0.06	0.44
Denmark	54	27	2.30	0.02	0.00	0.01
Greece	53	28	2.09	0.26	0.01	0.50
Italy	56	26	2.12	0.17	0.02	0.20
Japan	62	25	1.74	0.14	0.07	0.29
South Korea	54	25	1.90	0.05	0.00	0.05
Kuwait	48	33	1.93	0.16	0.04	1.71
Saudi Arabia	46	32	1.89	0.51	0.09	4.60
Spain	55	27	2.05	0.12	0.01	0.55
Taiwan	61	26	1.75	0.09	0.01	0.17
United Arab Emirates	46	30	2.04	0.14	0.00	0.79
United Kingdom	50	29	1.92	0.85	0.14	0.95
United States of America	55	29	2.29	0.00	0.00	0.00
Total	**55**	**29**	**2.16**	**0.13**	**0.02**	**0.23**

Country	Nasal polyps (%)	Allergic rhinitis (%)	Chronic rhinosinusitis (%)	Obesity (%)	Eosinophil count	Fractional exhaled nitric oxide
Argentina	12	69	12	42	394	46
Australia	36	74	0	41	411	36
Bulgaria	25	81	60	32	500	31
Canada	33	64	70	39	536	43
Colombia	23	57	41	32	578	39

Denmark	38	50	51	24	844	58
Greece	24	83	34	30	870	43
Italy	43	65	33	19	761	52
Japan	32	82	52	16	1045	62
South Korea	21	71	34	5	857	47
Kuwait	32	79	42	64	693	34
Saudi Arabia	62	82	69	56	654	41
Spain	36	56	29	27	889	57
Taiwan	11	76	21	16	612	51
United Arab Emirates	14	68	19	51	636	30
United Kingdom	31	73	34	40	514	65
United States of America	41	79	38	38	462	44
Total	**37**	**74**	**36**	**35**	**551**	**46**

Country	**Long-term oral corticosteroid (%)**	**Long-acting beta-agonists / long-acting muscarinic antagonists (%)**	**Long-acting muscarinic antagonists (%)**	**Macrolide (%)**	**Steroid sparing (%)**
Argentina	4	0	0	0	0
Australia	5	0	0	0	0
Bulgaria	1	0	1	12	0
Canada	8	0	11	5	0
Colombia	7	0	2	0	0
Denmark	28	0	3	0	0
Greece	6	0	9	0	0
Italy	17	0	1	1	0
Japan	9	0	4	21	0
South Korea	13	0	0	0	0
Kuwait	2	0	1	0	0
Saudi Arabia	9	0	11	0	0
Spain	8	0	0	0	0

Taiwan	14	0	32	2	0
United Arab Emirates	1	0	0	0	0
United Kingdom	13	0	0	0	0
United States of America	7	0	12	20	3
Total	**9**	**0**	**8**	**12**	**2**

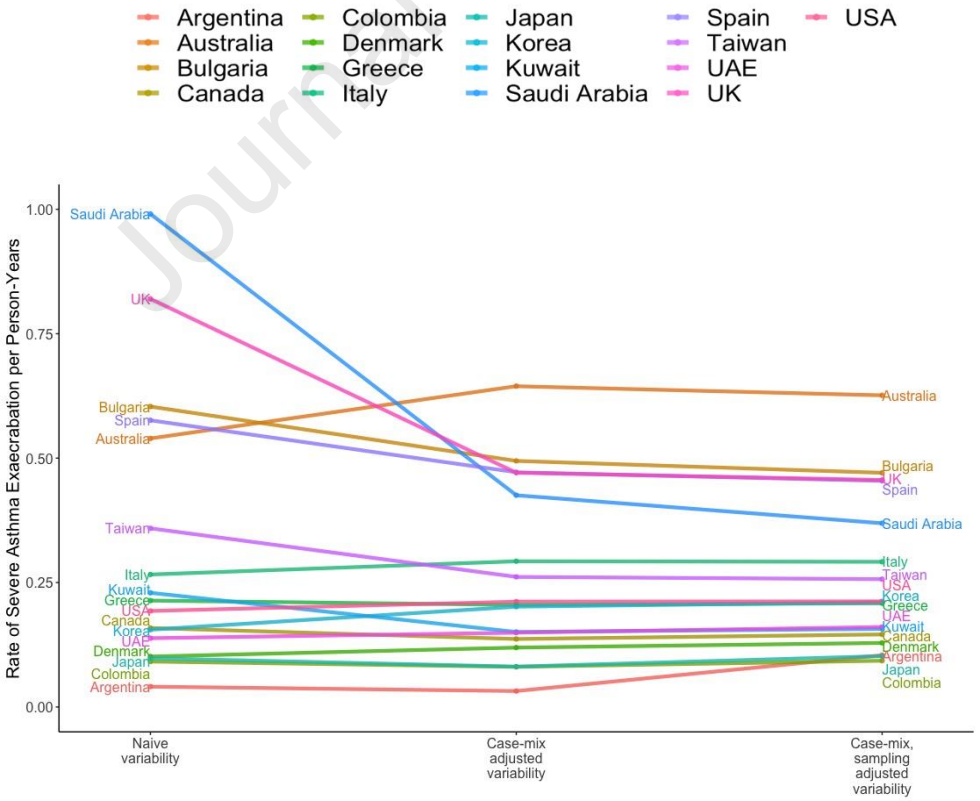
	Asthma control (%)			**Smoking status (%)**		
Country	**Uncontrolled**	**Partially controlled**	**Well controlled**	**Current**	**Never**	**Past**
Argentina	73	12	15	0	81	19
Australia	59	27	24	10	49	41
Bulgaria	61	24	14	20	67	13
Canada	79	13	9	3	60	37
Colombia	79	15	5	0	78	22
Denmark	78	12	10	3	58	39
Greece	91	4	4	4	68	28
Italy	61	26	13	3	72	25
Japan	36	52	12	7	63	31
South Korea	79	18	3	8	68	24
Kuwait	48	34	18	6	87	7
Saudi Arabia	49	42	9	4	91	4
Spain	58	29	13	6	66	28
Taiwan	89	10	1	9	67	25
Taiwan	94	5	1	10	83	7
United Arab Emirates	56	21	22	9	65	26
United Kingdom	52	30	18	15	53	32
Total	**58**	**27**	**15**	**11**	**59**	**29**

7. Country-specific estimates of severe asthma exacerbation rates using the average marginal effect framework

Country	Naïve variability	Adjusted fixed-effect	Adjusted random-effects
Argentina	0.04 (0.00,0.12)	0.03 (0.00,0.10)	0.11 (0.01,0.21)
Australia	0.54 (0.43,0.65)	0.66 (0.51,0.80)	0.64 (0.50,0.77)
Bulgaria	0.61 (0.41,0.81)	0.51 (0.34,0.68)	0.48 (0.32,0.64)
Canada	0.17 (0.09,0.25)	0.15 (0.08,0.22)	0.16 (0.09,0.22)
Colombia	0.08 (0.04,0.13)	0.08 (0.04,0.12)	0.09 (0.05,0.13)
Denmark	0.11 (0.06,0.16)	0.12 (0.07,0.18)	0.13 (0.08,0.19)
Greece	0.21 (0.09,0.32)	0.20 (0.09,0.32)	0.21 (0.10,0.32)
Italy	0.25 (0.20,0.29)	0.28 (0.22,0.33)	0.28 (0.22,0.33)
Japan	0.13 (0.05,0.21)	0.11 (0.04,0.17)	0.12 (0.06,0.19)
South Korea	0.29 (0.06,0.52)	0.34 (0.08,0.61)	0.31 (0.10,0.52)
Kuwait	0.25 (0.15,0.35)	0.18 (0.10,0.25)	0.18 (0.11,0.25)
Saudi Arabia	0.88 (0.36,1.40)	0.45 (0.15,0.74)	0.39 (0.16,0.62)
Spain	0.55 (0.39,0.71)	0.47 (0.34,0.61)	0.46 (0.33,0.59)
Taiwan	0.38 (0.23,0.52)	0.28 (0.16,0.39)	0.27 (0.17,0.38)
United Arab Emirates	0.13 (0.05,0.21)	0.15 (0.06,0.23)	0.16 (0.08,0.25)
United Kingdom	0.76 (0.62,0.90)	0.43 (0.32,0.54)	0.42 (0.32,0.53)
United States of America	0.20 (0.18,0.21)	0.22 (0.20,0.24)	0.22 (0.20,0.24)

8. Sensitivity analysis: exclusion of patients with use of biologics during follow-up

After excluding 8.2% of the patients that received biologics during follow-up period, we repeated the whole analysis. The main results are summarised below. We found that the interpretation of the original results was largely unchanged. There was substantial heterogeneity in severe exacerbation rate between countries without any adjustment (IQR: 0.14–54). After adjustment for differences in case-mix, between-country variability in severe exacerbation rate reduced but remained significant (IQR: 0.14–0.43). Adjustment for sampling variability led to a further decrease in the heterogeneity in severe exacerbation rate across countries, which was still considerable (IQR: 0.15–0.37). Excluding the patients who received biologics during follow-up did not always increase severe exacerbation rate. For instance, South Korea had a higher severe exacerbation rate when those patients were included.



Country	Naïve variability	Adjusted fixed-effect	Adjusted random-effects
Argentina	0.04 (0.00,0.12)	0.03 (0.00,0.10)	0.11 (0.01,0.21)
Australia	0.54 (0.43,0.65)	0.66 (0.51,0.80)	0.64 (0.50,0.77)
Bulgaria	0.61 (0.41,0.81)	0.51 (0.34,0.68)	0.48 (0.32,0.64)
Canada	0.17 (0.09,0.25)	0.15 (0.08,0.22)	0.16 (0.09,0.22)
Colombia	0.08 (0.04,0.13)	0.08 (0.04,0.12)	0.09 (0.05,0.13)
Denmark	0.11 (0.06,0.16)	0.12 (0.07,0.18)	0.13 (0.08,0.19)
Greece	0.21 (0.09,0.32)	0.20 (0.09,0.32)	0.21 (0.10,0.32)
Italy	0.25 (0.20,0.29)	0.28 (0.22,0.33)	0.28 (0.22,0.33)
Japan	0.13 (0.05,0.21)	0.11 (0.04,0.17)	0.12 (0.06,0.19)
South Korea	0.29 (0.06,0.52)	0.34 (0.08,0.61)	0.31 (0.10,0.52)
Kuwait	0.25 (0.15,0.35)	0.18 (0.10,0.25)	0.18 (0.11,0.25)
Saudi Arabia	0.88 (0.36,1.40)	0.45 (0.15,0.74)	0.39 (0.16,0.62)
Spain	0.55 (0.39,0.71)	0.47 (0.34,0.61)	0.46 (0.33,0.59)
Taiwan	0.38 (0.23,0.52)	0.28 (0.16,0.39)	0.27 (0.17,0.38)
United Arab Emirates	0.13 (0.05,0.21)	0.15 (0.06,0.23)	0.16 (0.08,0.25)
United Kingdom	0.76 (0.62,0.90)	0.43 (0.32,0.54)	0.42 (0.32,0.53)
United States of America	0.20 (0.18,0.21)	0.22 (0.20,0.24)	0.22 (0.20,0.24)
Interquartile range	**0.13–0.54**	**0.15–0.43**	**0.15–0.39**

9. Power calculations

We used the power size calculation proposed by Zhu and Lakkis (Approach 3 – maximum likelihood estimation) under the following assumptions 1) a reduction of 20% in the severe exacerbation rate from the comparator group compared to the control group, 2) equal sample sizes in each arm, and 3) rates coming from a negative binomial model with the dispersion parameter of 0.46 (which was the estimate in the adjusted random-effects model).[3]

References

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3. Zhu H, Lakkis H. Sample size calculation for comparing two negative binomial rates. *Statistics in Medicine* 2014;33(3):376–387.