Prevalence of asthma in Catalonia (Spain): a retrospective, large-scale population-based study

Short title: Prevalence of asthma in Catalonia (Spain)

Mora T[1]*, Sánchez-Collado I[1]*, Mullol J[2,3,4], Ribó P[3,4,5], Muñoz-Cano R[3,5,6] **, Valero A[3,4,5]**

[1]Research Institute for Evaluation and Public Policies. Universitat Internacional de Catalunya (UIC), Barcelona, Catalonia, Spain.
[2]Rhinology Unit and Smell Clinic, ENT Department, Hospital Clinic, Universitat de Barcelona, Barcelona, Catalonia, Spain.
[3]IRCE - Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS). Barcelona. Spain.
[4]CIBER of Respiratory Diseases (CIBERES), Instituto de Salud Carlos III, 28029 Madrid, Spain.
[5]Allergy Department, Hospital Clinic, Barcelona, Catalonia, Spain
[6]RICORS - Instituto de Salud Carlos III. Madrid. Spain.
*Toni Mora and Irene Sánchez-Collado shared main authorship responsibilities
**Rosa Muñoz-Cano and Antonio Valero authors shared senior responsibilities

Corresponding author:
Rosa Maria Muñoz-Cano
Allergy Department, Hospital Clinic, Barcelona.
c/ Villarroel 170, 08036 Barcelona
Catalonia, Spain
E-mail: rmunoz@clinic.cat

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.18176/jiaci.0903

doi: 10.18176/jiaci.0903

ABSTRACT

Introduction: Asthma epidemiology reports an estimated global prevalence of about 4.3-8.6% in adults, with vast differences among geographical regions. This study analyses a more significant population of asthma patients (473,737 individuals).

Objectives: To study the prevalence of medical diagnosis of asthma, overall and by age, gender, and disease severity, as well as comorbidities and type 2 biomarkers, and undergo medical treatments of a retrospective population-based asthma cohort from Catalonia (Spain).

Methodology: Individuals with a diagnosis of asthma established by medical records at different healthcare levels (primary, hospital, and emergency) from the Catalan Health System (CHS) were included. Socio-demographic characteristics, prevalence, overall and by age and gender, disease severity, comorbidities, and biomarkers of type-2 inflammation were evaluated, together with appropriate medical treatment.

Results: The overall diagnosed asthma prevalence in the population of Catalonia was 6.3%, where patients mainly had mild asthma (5.3%) and were significantly higher in females (6.8%) than males (5.7%). By age groups, asthma was more prevalent in boys and young men adults; however, being more prevalent in females above the age of 30y. The prevalence of severe asthma was 0.4%, 42.6% had uncontrolled asthma, and a high proportion (84.2%) were under systemic corticosteroid prescription. As expected, SABAs were the most prescribed drug (62.6%), followed by systemic corticosteroids (43.3%). More than half (53.8%) of patients showed type 2 inflammation.

Conclusions: Asthma prevalence in Catalonia is similar to other areas studied in Spain, with a high prevalence in women and of T2 asthma.

Key words: Asthma. Epidemiological study. Population-based. Prevalence. Severity. Comorbidities. Type 2 biomarkers.

doi: 10.18176/jiaci.0903

RESUMEN

Introducción: La prevalencia estimada global del asma se estima entre el 4.3-8.6% en adultos, aunque existen grandes diferencias geográficas. Este estudio analiza una población grande de pacientes con asma (473,737 individuos).

Objetivo: Estudiar la prevalencia de los pacientes con diagnóstico médico de asma, en general y en función de la edad, el género, la gravedad de la enfermedad, así como las comorbilidades, los biomarcadores tipo 2, y el tratamiento recibido, en una cohorte de paciente con asma de Cataluña (España).

Metodología: Se incluyeron individuos con diagnóstico médico de asma en base a los informes médicos obtenidos de los diferentes niveles asistenciales (atención primaria, hospital y servicios de urgencias) del Sistema Catalán de Salud. Se evaluaron las características socio-demográficas, la prevalencia global y en función de la edad, género, la gravedad del asma, las comorbilidades, las biomarcadores de inflamación tipo 2, y el tratamiento recibido.

Resultados: La prevalencia global de asma en la población de Cataluña fue del 6.3%, los pacientes presentaron principalmente asma leve (5.3%) con una mayor proporción de mujeres (6.8%) que de hombres (5.7%). Por grupos de edad, el asma fue más prevalente en niños y hombres adultos jóvenes. Sin embargo, fue más prevalente en mujeres mayores de 30 años. La prevalencia de asma grave fue del 0.4%, y el 42.6% estaba no controlada, y una alta proporción (84.2%) recibían tratamiento con corticoides sistémicos. Como era de esperar, los SABA fueron los medicamentos más frecuentemente prescritos (62.6%), seguido de los corticoides sistémicos (43.3%). Más de la mitad (53.8%) de los pacientes presentaban biomarcadores de inflamación tipo 2.

Conclusiones: La prevalencia de asma en Cataluña es similar a la de otras áreas estudiadas en España, con una alta prevalencia entre las mujeres y con un perfil inflamatorio T2.

Palabras clave: Asma. Estudio epidemiológico. Estudio poblacional. Prevalencia. Gravedad, comorbilidades. Biomarcadores tipo 2.

doi: 10.18176/jiaci.0903

INTRODUCTION

Asthma is a chronic airway inflammatory disease clinically diagnosed by assessing a characteristic pattern of respiratory symptoms and a variable expiratory airflow limitation [1,2]. Variations in symptoms and airflow limitations are influenced by external factors such as exercise, allergens or irritant exposure, weather changes, viral respiratory infections, smoking behaviour, and stress. These factors may increase the risk of exacerbations in all patients [3-6]. However, it is particularly evident in patients with uncontrolled asthma [7,8]. Asthma patients usually present with comorbidities that may impact their lung symptoms, including rhinitis, chronic rhinosinusitis, gastroesophageal reflux (GERD), obesity, obstructive sleep apnoea, atopic dermatitis, food allergy, depression, and anxiety, among others [2].

The epidemiology of asthma reports estimated global prevalence of about 4.3-8.6% in adults [9], 11.6% in children (aged 6-7 years) and 13.7% in adolescents (aged 13-14 years) [10]. Evidence of the estimated prevalence for Spanish adults is scarce, and results vary between 4.9%-6.8% for adults [9,11] and between 8.5-14.3% for the children and adolescent population [10,12,13], with vast differences among geographical regions [14]. Prevalence estimates for severe asthma are around 0.3% [15].

Our epidemiological study, using a retrospective large-scale population-based database over the period 2013-2017, aims to investigate the diagnosed prevalence, overall and by age and gender, as well as disease severity, comorbidities, type 2 biomarkers, and undergo medical treatments of an asthma cohort from Catalonia (Spain). To our knowledge, this is the first population-based epidemiological study analysed in a more significant population of asthma patients and with richer patient information than the samples used by previous literature. Hence, providing more robust prevalence results for the overall population and by age groups, as well as data on disease severity, comorbidities, and type 2 inflammation for Spain.

doi: 10.18176/jiaci.0903

MATERIALS AND METHODS

Study population

All residents in Catalonia - the second largest populated region in Spain - with coverage in the statutory National Health Service (NHS) and included in the Agency for Health Quality and Assessment of Catalonia (AQuAS) database with the following criteria were analysed. Inclusion criteria: a) Patients of all ages, and b) with a diagnosis of asthma established by medical records at any care level covered by the NHS (primary, hospital, ambulance, and emergency care) at any point in time from January 2013 until December 2017 (follow-up period different for everyone in the dataset). Exclusion criteria: referred to subjects transferred to other regions in Spain.

Data obtained was confidential, anonymous, and dissociated according to the Spanish Organic Law on Data Protection (Law 15/1999 of December 13). The Spanish Agency classified the study for Medicines and Health Products as a No-EPA *(i.e., no drug post-authorization*) study as this is a retrospective observational study of the epidemiological characteristics of asthma. It was approved by the Clinical Research Ethics Committee, International University of Catalonia (Barcelona) and the Ethics Committee from *Hospital Clínic de Barcelona*.

Study design

The database was provided by AQuAS and contains details of all administrative medical registers on available admissions to primary care, hospital care, and ambulance and emergency (A&E) attendances at the individual-patient level of residents in Catalonia with coverage in the NHS.

The asthma diagnostic was given in the database using records grounded on medically certified diagnoses coded with the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM).

The prescribed asthma therapies (active ingredients) available in the database for the period under study can be found in the supplementary material.

doi: 10.18176/jiaci.0903

Given the lack of data on actual drug doses, the Define Daily Dosage (DDD) for each drug prescribed was used to approximate the precise doses of prescribed therapy for everyone under study.

See supplementary material for further description of the database, a complete list of ICD-9-CM diagnostic codes, prescribed treatment codes, drug dosage (suppl. **Table 1** and **Table 2**) and more information on DDD.

Outcomes

Demographic characteristics

Information on socioeconomic and demographic characteristics was obtained from the database: 1) gender, 2) age and 3) annual income levels were constructed and adjusted by household size.

Epidemiology

The overall asthma prevalence in the general population was calculated based on all individuals from the study population who received a diagnosis of asthma over the total population in Catalonia (7,555,830 residents in 2017). Since the database encompasses the entire population of Catalonia, prevalence results do not represent estimated values. Instead, data should be interpreted as the diagnosed prevalence in Catalonia over 2013-2017.

Disease severity

Following treatment recommendation from GEMA 5.0 (REF), individuals were classified as presenting severe asthma (step 5 and step 6 treatment in GEMA 5.0) disease when: 1) ICS high dose intake (consecutive or not) for at least six months over the last year or for at least 12 months over the last two years; or 2) consumption of biologics over the last two years or 3) OCS intake for more than six months over the last year or more than 12 months over the last two years.

Patients were classified as presenting moderate asthma (Step 3 and 4 GEMA 5.0) if the last year individuals were prescribed any of the treatments below for at least six months or at least 12 months in the previous two years: 1) ICS low doses + LABA

doi: 10.18176/jiaci.0903

(Formoterol/Salmeterol/Vilanterol); or 2) ICS low doses + LTRAs (Montelukast / Zafirlukast); or 3) ICS medium doses; or 4) drug combinations: Fluticasone propionate with Salmeterol, Budesonide with Formoterol, Beclomethasone with Formoterol, Fluticasone furoate with Vilanterol, fluticasone propionate with Formoterol, Salbutamol with Sodium cromoglicate, Salbutamol with Beclomethasone, Salbutamol and Ipratropium bromide.

Patients were considered to present mild asthma (Steps 1 and 2 in GEMA 5.0) in all other situations: 1) ICS low doses; or ICS low doses + SABA; or LTRAs; or LTRAs + SABA.

High, medium and low doses of ICS were used according to GEMA 5.0 for adults and adolescents. Some doses were adapted according to the information in the dataset (**Table 1 Supplementary**) and children (**Table 2 Supplementary**).

The prescribed dose of ICS was needed to classify individuals into the severe asthma criteria. Since this information was not directly available from the database, information on the number of DDDs consumed by each ICS by each patient was used. To approximate the actual "ICS dosing (mcg)" prescribed to everyone, we multiplied the average drug consumption in DDDs by the micrograms of ICS in one DDD established by the ATC/DDD index available at the World Health Organization (see https://www.whocc.no/atc_ddd_index/). Each ICS and its corresponding ATC code was associated with one DDD per route of administration. Hence, the ATC/DDD index establishes the equivalence between 1 DDD and the amount of ICS used. If a drug is administered using several routes, the DDDs provided by inhalation administration were preferred.

Using the information available in our dataset, the proportion of severe asthma individuals with severe uncontrolled asthma over the 2016/2017 period is approximated using exacerbations and systemic corticosteroids prescription, which were defined as follows:

1. Frequent exacerbations: patients that visit the emergency care level at least once within a year (we impose a minimum of a fortnight between one emergency and

doi: 10.18176/jiaci.0903

another).

2. Severe exacerbations: patients who are required to be hospitalised due to asthma at least once within a year.
3. The prescription of systemic corticosteroids was at least three treatment rounds over 2016/2017.

Biomarkers of type 2 inflammation

The AQUAS dataset also provided two relevant type 2 inflammation biomarkers to assess the asthma phenotype [2,16,17]: blood eosinophils and total immunoglobulin E (IgE). FeNO was not available in the dataset. Eosinophilia was defined as eosinophil counts ≥300 cells/µL [18-20]. For total serum IgE, values ≥100 KU/L were considered high levels and a biomarker of type 2 inflammation [2], assuming this value correlates with clinical manifestations of allergy. A high type 2 inflammation was considered when one of the two parameters, eosinophils or IgE, was increased.

The maximum value reported for everyone between the 2016-2017 study period was taken. The median (confidence interval) and the number of individuals above and below the cut-point values were also calculated for each biomarker.

Comorbidities

Asthma comorbidities, including respiratory/allergy, systemic and neurologic/psychiatric, were also analysed and found in the supplementary material.

Statistical analysis

An observational, multi-centre, longitudinal retrospective study was performed based on a review of all available medical records related to asthma in Catalonia— from 2013 to 2017 using computerised databases with dissociated data.

Statistical analyses were conducted using the statistical package Stata 17. Descriptive exploratory analysis was performed by reporting frequencies and proportions of individuals in the overall population and by disease severity for confounders, comorbidities, treatment characteristics, and biomarkers. Pearson's chi-square test of

doi: 10.18176/jiaci.0903

independence between categorical variables was reported, as well as mean differences by disease severity. Odds Ratio (OR) with a 95% Confidence Interval (CI) and p-values were reported for the multivariate logistic regression on the probability of having severe asthma against comorbidities and confounders. The overall prevalence of medical diagnosis of asthma was reported, and the prevalence by disease severity (mild, moderate, severe), all analysed by gender and age groups. A p-value < 0.05 was considered statistically significant.

RESULTS

Asthma prevalence

473,737 individuals out of 7,555,830 residents in Catalonia in 2017 had a diagnosis of asthma. The overall diagnosed prevalence of medical diagnosis of asthma was 6.3%. Women had significantly higher asthma prevalence than men (Figure 2). The prevalence of medical diagnosis of asthma for the overall population increased until the age of 12-15 for males (11.2%) and until the age of 16-17 for females (7.9%). After that, it decreased to 4.5% for males ≥60 years old. For females, it decreased along the older age cohort but increased to 8.8% for those ≥60 years old (Figure 3A). Moreover, the prevalence was higher for males until approximately the age of 30 than for females; however, this tendency reverses after that age, with women having a higher prevalence than men for the overall (Figure 3A), mild, and severe cohorts (Figure 3B). The differences in overall asthma prevalence between males and females grew from 16 to 17 years old, and again in the ≥40 years old group; the most significant difference was in the ≥ 60-year group. This pattern was also true for mild asthma, but no gender differences were observed in moderate patients. The prevalence of severe asthma increased with age, with maximum gender differences in the ≥ 60-year group (Figure 3B). More than half of the asthma cohort had annual incomes <18,000€.

Overall, 6.3% of the asthma population (29,431 individuals) was classified as having severe asthma, 8.7% as having moderate asthma (41,329 individuals), and 85.1% as presenting mild asthma (402,977 individuals) (**Figure 1**). Then, this prevalence was

doi: 10.18176/jiaci.0903

distributed in mild (5.3%), moderate (0.6%) and severe (0.4%). More women than men had a diagnosis of asthma (1.25:1), in all severity phenotypes, especially in severe (1.82:1) disease.

Prescribed treatments

In the overall cohort, short-acting beta-agonists (SABAs) were the most prescribed drug (62.6%), followed by systemic corticosteroids (43.3%), drug combinations (inhaled corticosteroids and bronchodilators B2) (41.9%), *other medications* (ipratropium, tiotropium, theophylline, azithromycin) (41.8%), and inhaled corticosteroids (36.5%); biologics' prescription was of 0.2%. All medications, except drug combinations, were more prescribed in severe than moderate or mild asthma patients; as expected, this difference in drug prescriptions among severe, moderate, and mild was more relevant for systemic corticosteroids (84.2% vs 58.3% and 38.8% respectively), and *other medications* (94% of the severe cohort). The percentage of individuals consuming ipratropium and tiotropium during the last two years was: 11.2% of mild patients, 22.0% of moderate patients and 77.4% of severe ones. Then, we computed the percentage of individuals using: (i) ICS + LABA + Other; (ii) Combinations + Other. These percentages were 0.95% and 14,54%, respectively. According to mild, moderate, and severe: (i) 0%, 0.02% and 0.05%; and for (ii) were 0.09%, 0.31% and 0.63%. 18% of individuals had no prescription for asthma treatment and were considered mild, although asthma could have also subsided in some of these patients (**Table 1**).

The proportion of individuals with severe uncontrolled asthma to those with severe asthma was 42.6% (12,537 out of 29,431 with severe asthma). This result means that 2,7% of the asthma population is diagnosed with severe uncontrolled asthma (12,537 out of 473,737 individuals). By age range, this proportion was 94.7% (373 individuals) for those among 0-5 years old, 57.6% (160 individuals) among the 6-11y, 31.1% (71 individuals) among 12-17y, 46.8% (2,885 individuals) among the adult population (18-59y), and of 40.5% (9,078 individuals) of 60y and above.

doi: 10.18176/jiaci.0903

Type 2 biomarkers

During the last 2-year period (2016-2017), there were 220,736 individuals with available information on blood eosinophils, both absolute and relative counts, while only 23,107 individuals with data on serum total IgE (tIgE) (**Table 2**). From those with available information, 119,095 (53.8%) patients had a blood absolute eosinophil count ≥300 cell/µL or reported serum total IgE values ≥100 KU/L. Thus, 69% of patients achieved the criteria of type 2 inflammation. This proportion was higher in the moderate (58.2%), followed by mild (53.4%) and severe (50.8%, p<0.0001) asthma patients. Moreover, those patients with comorbidities showed more frequent type 2 biomarkers (atopic dermatitis (AD): 83.9%; nasal polyps (NP): 83.2%; both AD and NP: 91.7%) than those without (58.8%, p<0.0001).

All biomarkers' values were significantly higher (p<0.05) in moderate and mild asthma than in severe asthma. Concerning comorbidities, patients with NP, AD, or both, showed higher levels of type 2 biomarkers (both absolute and relative eosinophil counts) and total IgE than those without comorbidities (**Table 2**).

Exacerbations

Among patients suffering at least 1 exacerbation, 22.8% were mild, 35.4% moderate and 65.4% severe. Regarding the average number of exacerbations based on severity, we observed statistically significant differences. Mild patients showed 0.41 exacerbations during the last two years, whereas moderate and severe patients had 0.60 and 3.28 exacerbations, respectively. Indeed, patients with at least one type 2 inflammation biomarker presented 0.82 exacerbations, compared to the 0.70 exacerbations on average in patients with no biomarkers. According to the considered age boundaries the average number of exacerbations were: 1.97% (Up to 5), 0.95% ([6-11]), 0.32% ([12-15]), 0.17% ([16-17]), 0.18% ([18-29]), 0.26% ([30-39]), 0.37% ([40-49]), 0.58% ([50-59]) and 0.98% (>=60). These differences were statistically significant.

Comorbidities

Allergic rhinitis (20.5%), atopic dermatitis (17.4%), were the most frequent respiratory/allergic comorbidities. NP was only present in 2.5% of the asthma cohort.

doi: 10.18176/jiaci.0903

Hypertension (22.4%), overweight (19.7%), and anxiety (17.7%) were the most frequent non-respiratory comorbidities (**Table 3**).

A higher proportion of patients with severe disease had obstructive sleep apnoea than mild or moderate patients. Moreover, although the frequency of patients with severe asthma and NP (4.6%) was lower than other respiratory comorbidities, it had one of the strongest associations with severe asthma (OR 2.18). All systemic and neurological comorbidities were found in higher proportions in severe individuals than in mild and moderate patients (**Table 3**).

DISCUSSION

This is the first retrospective population-based epidemiological study analysed in a more significant population of asthma patients and with more affluent patient information for Spain. The main findings were 1st) the overall diagnosed prevalence of medical diagnosis of asthma in the general population of Catalonia was 6.3%, where 0.4% presented severe asthma. 2nd) Asthma was more prevalent among females irrespectively of the disease severity; 3rd) the overall prevalence of medical diagnosis of asthma was higher for males until approximately the age of 30 when it reverses, and women have a higher prevalence for the overall, mild and severe populations. 4th) 42.6% had uncontrolled asthma, a high proportion (84.2%). 5th) Most patients (69.0%) can be considered to have type 2 asthma. 6th) Type 2 biomarkers were higher in mild and moderate patients and individuals presenting type 2 asthma-associated comorbidities.

Our study is based on medical records from the Catalan health care system at the primary, hospital, or emergency care level, which allowed the identification of a cohort of 473,737 patients with asthma, 6.3% of the studied population in Catalonia. This prevalence is in line with what was reported in previous studies for Spain using different definitions of asthma: 4.9%-6.8% for adults [9,11] and 10% among children [12]. The prevalence of severe asthma (0.4%) is also in line with recent studies (0.3%) by [15] for Spain. In line with earlier studies [10,13], the prevalence of medical diagnosis of asthma

doi: 10.18176/jiaci.0903

is highest among children (0-17 years), where boys have a higher prevalence of medical diagnosis of asthma than girls. Our study further shows that this pattern changes during adulthood, with asthma being more prevalent among women than men after 30 years old.

Among individuals with available information, 69% showed type 2 inflammation. Our results align with the existing literature, where the proportion of type 2 inflammation in asthma patients is estimated between 50% and 84% [21]. A recent study by [15] also found a high proportion (58.6%) of asthma patients with blood eosinophils counts ≥300 cells/µL in a small sample of 268 severe asthmatic patients. In our study, type 2 inflammation is more frequent for those with comorbidities, particularly when associated with nasal polyposis. Regarding blood eosinophil and total IgE values, higher values are found for mild and moderate than for severe, and again, for individuals presenting type 2 asthma-associated comorbidities (AD, NP, or both), similarly found in previous studies [22,23].

This study also finds other results concerning prescribed treatments and comorbidities. As expected, and according to high prescriptions already identified by previous literature [24,25], SABAs were the most prescribed drug (62.6%), with 76.7% of individuals having a mono-dose treatment. Systemic corticosteroids were highly prescribed among the severe (84.2%) but also the moderate (58.3%) and mild (38.6%) patients. This is to the existing literature, as systemic corticosteroids still exist for asthma treatment, especially to treat exacerbations and severe uncontrolled asthma [26]. We may suspect that the high prevalence of systemic corticosteroid use in mild and moderate asthma is related to exacerbations. Similarly, another recent study on the Spanish population using big data showed that 56.6% of asthmatic patients had a prescription for oral corticosteroids during the study period (2015 – 2019) [27]. The use of systemic corticosteroids was more frequent in older individuals with hypertension, dyslipidaemia, diabetes, obesity, depression, and hiatus hernia. No information related to asthma severity was referred by the authors.

doi: 10.18176/jiaci.0903

Finally, we found 42.6% of severe individuals with uncontrolled asthma, which is in line with what was found in previous studies such as [28]. Our research is aligned with the results obtained by [29] that identified that 3.9% of the asthma population had a diagnostic severe uncontrolled asthma. Our results showed that 2.7% of the asthmatic population was classified as having severe uncontrolled asthma. The difference between the [28] results may arise from the populations studied (they only referred to patients from hospital pneumology and allergology units). The high percentage of 0-5 years old individuals classified as severe uncontrolled asthma (94.7%, 373 individuals) may be a result of the definition used for this condition and the high rate of emergency visits and/or hospitalisation at these ages for respiratory infections that frequently are treated with oral corticosteroids. Among the uncontrolled asthma patients (12,537), 427 individuals were already prescribed biologics leaving room for 12,110 individuals, which could also be potentially treated with them. As expected, we observed that severe and moderate patients suffered exacerbations more frequently than mild ones (65 vs 35 vs 23%). The average of exacerbations during the study period was significantly lower in mild than moderate and severe asthma patients. In a previous work [30], it was reported in a cohort of mild asthma patients, that 22.8% of patients suffered at least one exacerbation in the previous 12 months, and half of them required OCS treatment. In our study, the exacerbation rate of mild patients was similar, although only 39% required OCS.

Overall, AD and respiratory comorbidities were the most frequent comorbidities. However, respiratory and systemic comorbidities were found more frequently in severe patients. Moreover, anxiety and depression were observed more in severe asthma. Those findings are from the few existing population-based studies on asthma comorbidities, with higher prevalence for AD, allergic rhinitis, COPD, and depression/mental health conditions [31-33]. Moreover, although the frequency of patients with severe asthma and NP (4.6%) was lower than other respiratory comorbidities, it had one of the strongest associations with severe asthma (OR 2.18).

doi: 10.18176/jiaci.0903

This study also has some limitations. First, the retrospective nature of the research and the fact that the severity of treatment is retrieved from prescribed medication instead of medical diagnosis. Prescribed medication is understood as prescribed and purchased by the individuals. However, information on whether taken or not is not available. Second, we cannot determine whether some drugs, such as OCS, were prescribed to treat asthma or other concomitant diseases. Therefore, using OCS intake as severity criteria might overestimate prevalence results for severe and uncontrolled asthma, particularly in young children when asthma diagnosis is most challenging for the lack of use of objective parameters. However, although the characteristics of the data do not allow us to differentiate between chronic and acute use, several courses of OCS may also be related to severe and uncontrolled asthma.

On the other hand, the prevalence for severe asthma patients could also be underestimated by assuming patients with no drug information present mild asthma, which might or might not always be the case. And third, the lack of inclusion of individuals diagnosed and treated outside of the statutory NHS in private hospitals or medical centres could underestimate the prevalence and disease severity results. This is, however, a minor limitation as, during the considered period, around 18% of individuals had this additional coverage. Notwithstanding, people use primarily public healthcare rather than complementary private coverage for severe clinical procedures.

In summary, this study uses a more significant number of asthma patients than previous studies, including information on most of the patients diagnosed with asthma from the general adult population of Catalonia. Our findings show an overall prevalence of 6.3%, a bit lower than in previous literature. Overall, the disease is more prevalent in females than males; however, in boys and young men and adults and from 30 years old onwards more prevalent in females. A high proportion of patients is found with type 2 inflammation (69%), especially those presenting with comorbidities (AD, NP, or both) than without. Severe uncontrolled asthma is found in 42.6% of severe individuals. The most present comorbidities are acute rhinosinusitis, acute bronchitis, allergic rhinitis, AD, acute respiratory infections, hypertension, and depression. Individuals with allergies

doi: 10.18176/jiaci.0903

(allergic rhinitis, food allergy, and not specific allergy) account for about 27% of the population presenting some allergy pathology. Overall, our results corroborate the results from previous population-based studies for asthma which often used smaller sample sizes than the one used for the present study and used a limited population age range. It also provides comprehensive information on severe asthma patients and type 2 inflammation.

CONFLICT OF INTEREST

All the authors received specific funding for developing this work from the International University of Catalonia (UIC) Real-World Evidence Chair. There are no patents, products in development or marketed products to declare. The authors of this manuscript have no relevant financial or other relationships to disclose.

FUNDING

This study was sponsored by the UIC Real-World Evidence Chair (unrestricted grant from SANOFI).

REFERENCES

1. GEMA. J Investig Allergol Clin Immunol 2021; Vol 31(Suppl.1 - GEMA 5.0): 1-1. doi: 10.18176/jiaci.0664
2. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2022. [cited 2022 October 20th] Available from: www.ginasthma.org
3. McCoy K, Shade DM, Irvin CG, Mastronarde JG, Hanania NA, Castro M, et al. Predicting episodes of poor asthma control in treated patients with asthma. J Allergy Clin Immunol. 2006;118:1226-33.

doi: 10.18176/jiaci.0903

4. Meltzer EO, Busse WW, Wenzel SE, Belozeroff V, Weng HH, Feng J, et al. Use of the Asthma Control Questionnaire to predict future risk of asthma exacerbation. J Allergy Clin Immunol. 2011;127:167-72.
5. FitzGerald JM, Barnes PJ, Chipps BE, Jenkins CR, O'Byrne PM, Pavord ID, et al. The burden of exacerbations in mild asthma: a systematic review. ERJ Open Res. 2020;6.
6. Moorman JE, Akinbami LJ, Bailey CM, Zahran HS, King ME, Johnson CA, et al. National surveillance of asthma: United States, 2001-2010. Vital Heal Stat 3. 2012;(35)1-58.
7. Peters SP, Ferguson G, Deniz Y, Reisner C. Uncontrolled asthma: a review of the prevalence, disease burden and options for treatment. Respir Med. 2006;100:1139-51.
8. Jain N, Satish K, Abhyankar N, Velayudhan N, Gurunathan J. Repeated exacerbation of asthma: An intrinsic phenotype of uncontrolled asthma. Lung India. 2019;36:131-8.
9. To T, Stanojevic S, Moores G, Gershon AS, Bateman ED, Cruz AA, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. BMC Public Health. 2012;12:204.
10. Asher MI, Montefort S, Björkstén B, Lai CKW, Strachan DP, Weiland SK, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet. 2006;368:733-43.
11. Estudio Europeo del asma. Prevalencia de hiperreactividad bronquial y asma en adultos jóvenes de cinco áreas españolas. Grupo Español del Estudio Europeo del Asma [European study on asthma. Prevalence of bronchial hyperreactivity and asthma in young adults from 5 Spanish areas. Spanish Group of the European Study on Asthma]. Med Clin (Barc). 1996 May 25;106(20):761-7. Spanish. PMID: 8801394.
12. Aguinaga I, Arnedo A, Bellido J, Guillén F, Suárez MM. Prevalencia de síntomas relacionados con el asma en niños de 13-14 años de 9 poblaciones españolas. Grupo Español del Estudio ISAAC (International Study of Asthma and Allergies in Childhood). Med Clin (Barc). 1999; 112:171-5).

doi: 10.18176/jiaci.0903

13. Arnedo-Pena A, García-Marcos L, Fernández-Espinar JF, Bercedo-Sanz A, Aguinaga-Ontoso I, González-Díaz C, et al. Sunny hours and variations in the prevalence of asthma in schoolchildren according to the International Study of Asthma and Allergies (ISAAC) Phase III in Spain. Int J Biometeorol. 2011;55:423-34.
14. Carvajal-Urueña I, García-Marcos L, Busquets-Monge R, Morales Suárez-Varela M, García de Andoin N, Batlles-Garrido J, et al. Geographic variation in the prevalence of asthma symptoms in Spanish children and adolescents. International Study of Asthma and Allergies in Childhood (ISAAC) Phase III, Spain. Arch Bronconeumol. 2005;41:659-66.
15. Sicras-Mainar A, Capel M, Navarro-Artieda R, Nuevo J, Orellana M, Resler G. Real-life retrospective observational study to determine the prevalence and economic burden of severe asthma in Spain. J Med Econ. 2020;23:492-500.
16. Kay AB. The role of eosinophils in the pathogenesis of asthma. Trends Mol Med. 2005;11:148-52.
17. Matucci A, Vultaggio A, Maggi E, Kasujee I. Is IgE or eosinophils the key player in allergic asthma pathogenesis? Are we asking the right question? Respir Res. 2018;19:113.
18. Gotlib J. World Health Organization-defined eosinophilic disorders: 2011 update on diagnosis, risk stratification, and management. Am J Hematol. 2011;86:677-88.
19. Kovalszki A, Weller PF. Eosinophilia. Prim Care. 2016;43:607-17.
20. McBrien CN, Menzies-Gow A. The Biology of Eosinophils and Their Role in Asthma. Front Med. 2017;4:93.
21. Seys SF, Scheers H, Van den Brande P, Marijsse G, Dilissen E, Van Den Bergh A, et al. Cluster analysis of sputum cytokine-high profiles reveals diversity in T(h)2-high asthma patients. Respir Res. 2017;18:39.
22. Lee E, Lee SH, Kwon JW, Kim YH, Cho HJ, Yang SI, et al. Atopic dermatitis phenotype with early onset and high serum IL-13 is linked to the new development of bronchial hyperresponsiveness in school children. Allergy. 2016;71:692-700.
23. Howarth P, Chupp G, Nelsen LM, Bradford ES, Bratton DJ, Smith SG, et al. Severe eosinophilic asthma with nasal polyposis: A phenotype for improved sinonasal and

doi: 10.18176/jiaci.0903

asthma outcomes with mepolizumab therapy. J Allergy Clin Immunol. 2020;145:1713-5.

24. McKibben S, Bush A, Thomas M, Griffiths C. “Tossing a coin:” defining the excessive use of short-acting beta(2)-agonists in asthma-the views of general practitioners and asthma experts in primary and secondary care. NPJ Prim care Respir Med. 2018;28:26.
25. Nwaru BI, Ekström M, Hasvold P, Wiklund F, Telg G, Janson C. Overuse of short-acting β(2)-agonists in asthma is associated with increased risk of exacerbation and mortality: a nationwide cohort study of the global SABINA programme. Eur Respir J. 2020;55:1901872.
26. 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;201:276-93.
27. Izquierdo JL, Almonacid C, Campos C, Morena D, Benavent M, González-de-Olano D, Rodríguez JM. Systemic Corticosteroids in Patients with Bronchial Asthma: A Real-Life Study. J Investig Allergol Clin Immunol 2023; Vol. 33(1).
28. Ribas CD, Sagardia AS, Prina E, Mainar AS, Navarro AS, Teijero CE. Late Breaking Abstract-Prevalence, characterization and costs of severe asthma in Spain (BRAVO 1). European Respiratory Journal. 2020; 56: Suppl. 64, 4639.
29. Quirce S, Plaza V, Picado C, Vennera M, Casafont J. Prevalence of uncontrolled severe persistent asthma in pneumology and allergy hospital units in Spain. J Investig Allergol Clin Immunol. 2011;21:466-71.
30. Golam, S. M., C. Janson, R. Beasley, J. M. FitzGerald, T. Harrison, B. Chipps, R. Hughes, H. Mullerova, J. M. Olaguibel, E. Rapsomaniki, H. K. Reddel, M. Sadatsafavi, and Novelty investigators. 2022. 'The burden of mild asthma: Clinical burden and healthcare resource utilisation in the NOVELTY study', Respir Med, 2022: 106863.
31. Mirabelli MC, Hsu J, Gower WA. Comorbidities of asthma in U.S. children. Respir Med. 2016;116:34-40.

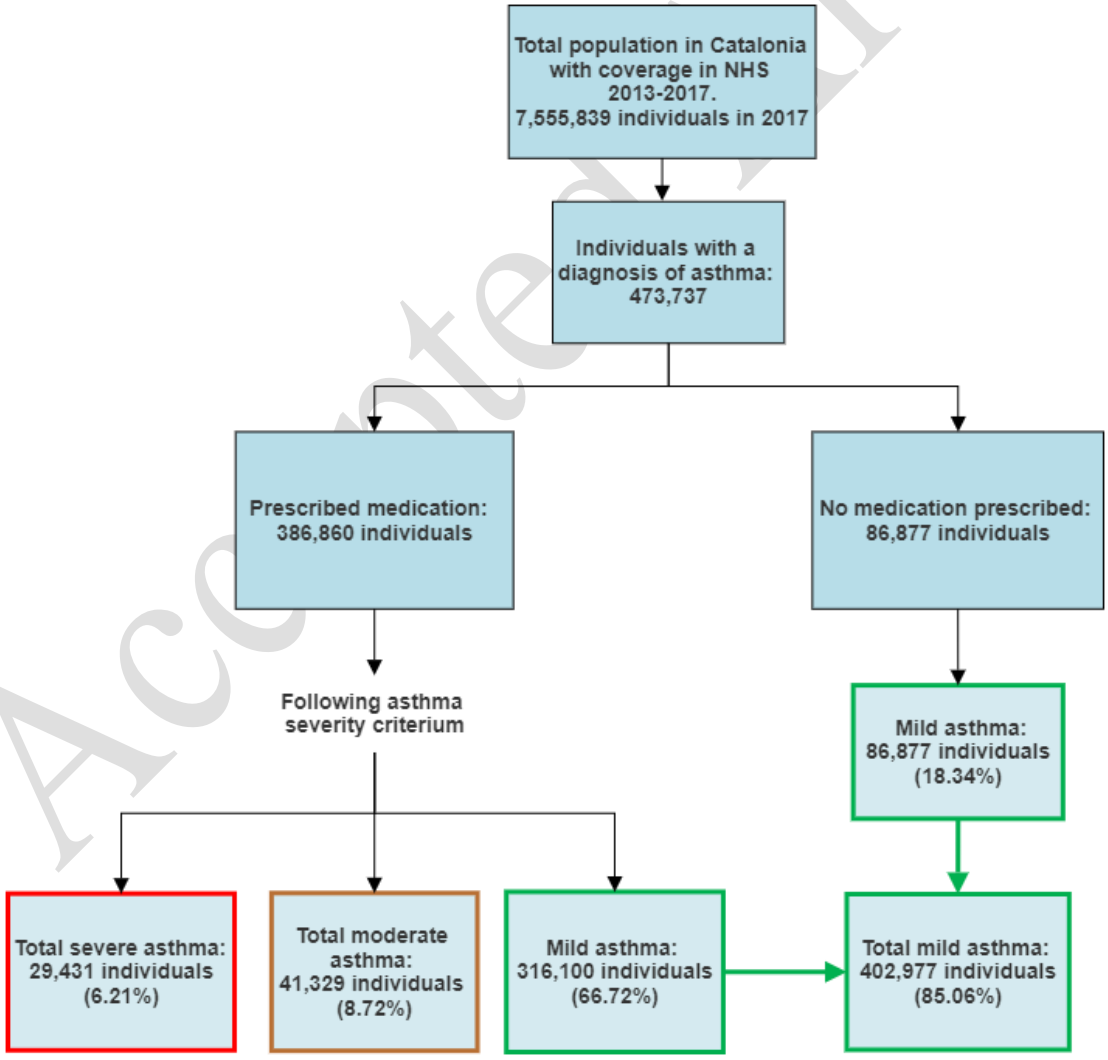
doi: 10.18176/jiaci.0903

32. Fueyo A, Ruiz MA, Ancochea J, Guilera M, Badia X. Asthma control in Spain. Do season and treatment pattern matter? The ESCASE study. Respir Med. 2007;101:919-24.
33. Weatherburn CJ, Guthrie B, Mercer SW, Morales DR. Comorbidities in adults with asthma: Population-based cross-sectional analysis of 1.4 million adults in Scotland. Clin Exp Allergy. 2017;47:1246-52.

doi: 10.18176/jiaci.0903

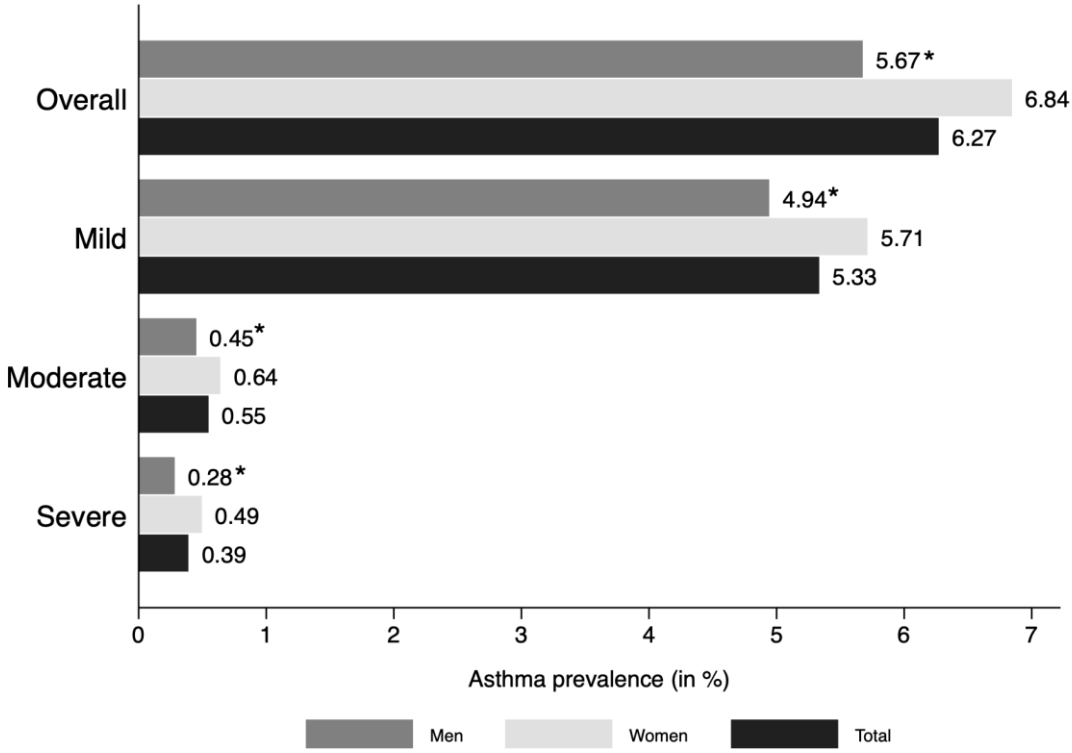
FIGURES LEGENDS

Figure 1. Flowchart classification of the asthma cohort, overall and by disease severity according to prescribed medication. Among all individuals from the study population who received a diagnosis of asthma (473,737 individuals), the type and amount of medication received for the treatment of asthma could be retrieved for 81.7% of the cases (386,860 individuals). Based on this severity criterium, there were 29,431 individuals with severe asthma, 41,329 individuals were classified as moderate asthma, and 316,100 with mild asthma. Individuals with no information on drug consumption over the study period were assumed to be mild asthma (86,877 individuals). This assumption relies on the fact that severe medication for asthma might be expensive, so most likely retrieved from pharmacies. Therefore, those diagnosed at the NHS but without medication might be individuals with mild asthma who might not need treatment or decided not to take the prescribed medication, perhaps because of mild symptoms. NHS – National Health Service.



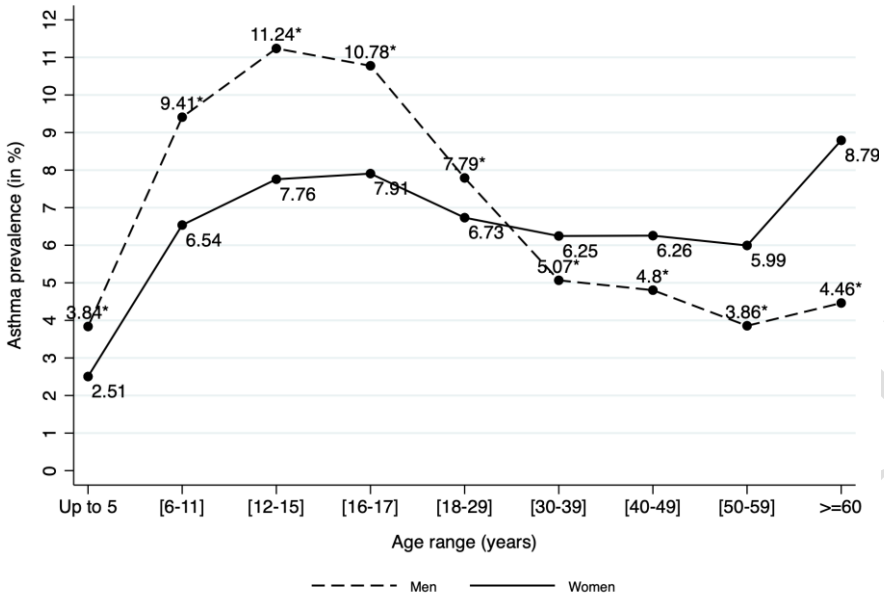
doi: 10.18176/jiaci.0903

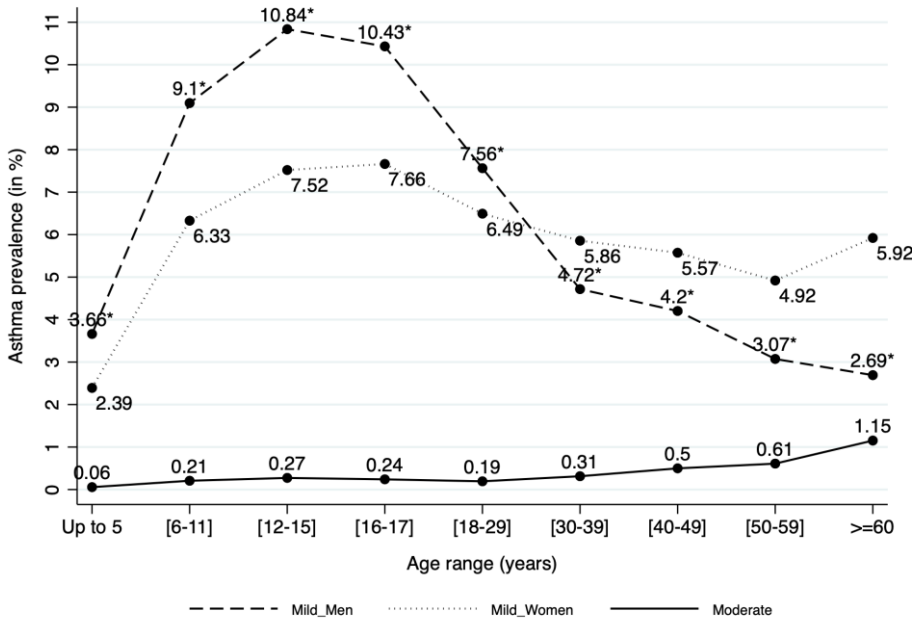
Figure 2. **Prevalence of medical diagnosis of asthma in the Catalan asthma cohort.** Differences in asthma prevalence by gender within each severity group (overall, mild, moderate, and severe). * p<0.01



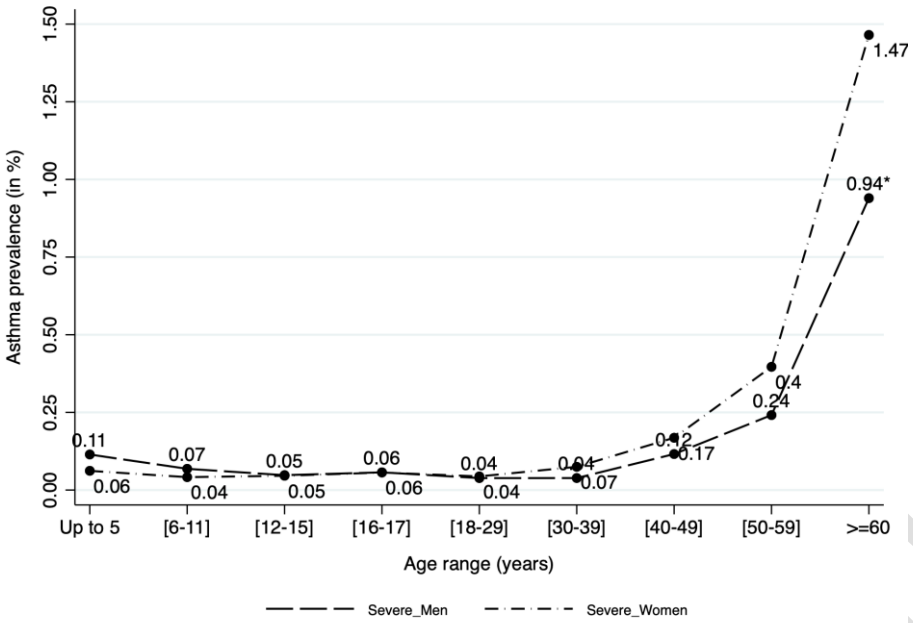
doi: 10.18176/jiaci.0903

Figure 3. **Prevalence of medical diagnosis of asthma by age groups (in % terms).** Distribution by A) gender and B) and C) asthma severity. Differences in asthma prevalence by gender and severity within each age group were evaluated. No gender differences for individuals with moderate asthma were found in B). * p<0.01.





doi: 10.18176/jiaci.0903



doi: 10.18176/jiaci.0903

Tables

Table 1. Prescribed treatment according to disease severity

	Overall Cohort	Cohort by asthma severity		
Performed treatment N (%)	**N = 386,860 (100%)**	**Mild N = 316,100 (66.7%)**	**Moderate N =41,329 (8.7%)**	**Severe N = 29,431 (6.2%)**
Drugs				
Inhaled CS	173,138 (36.5)	143,571 (35.6)	143,571 (35.6)	14,562 (49.5)
SABA	296,711 (62.6)	241,695 (60)	31,766 (76.9)	23,250 (79)
LTRAs	66,496 (14.0)	47,327 (11.7)	11,163 (27)	8,006 (27.2)
LABA	24,084 (5.1)	13,926 (3.5)	5,863 (14.2)	4,295 (14.6)
Systemic CS	204,897 (43.3)	156,030 (38.7)	24,076 (58.3)	24,791 (84.2)
Biologics	1,170 (0.2)	-	-	1,170 (4.0)
Drug combinations	198,612 (41.9)	136,488 (33.9)	38,761 (93.8)	23,363 (79.4)
Other medications	198,012 (41.8)	147,695 (36.7)	22,628 (54.8)	27,689 (94.1)
No drugs	86,877 (18.3)	86,877 (21.6)	-	-

P-values are for the test of differences in means between the severity degrees mild and moderate (collapsed categories) against severe for each treatment under study at a 95% confidence level of significance. Other medications category included ipratropium bromide, tiotropium bromide, theophylline, and azithromycin. Drug combinations refer to combined therapy, including inhaled corticosteroids and LABA. 86,877 individuals with asthma diagnoses had no prescription for any asthma treatment and were assumed to have mild asthma. Drugs are not mutually exclusive, as one individual can simultaneously prescribe more than one group of medications.

SABA, short-acting beta-agonists; LTRAs, leukotriene receptor antagonists; LABA, long-acting beta-agonists; CS, corticosteroids.

doi: 10.18176/jiaci.0903

Table 2. Type 2 biomarker values for the asthma cohort over the 2016-2017 period.

Biomarkers - Median values (95% CI)	Total Population	By asthma severity			By comorbidities			
		Mild	Moderate	Severe	Asthma alone	Asthma + NP	Asthma + AD	Asthma + NP +AD
Blood eosinophils	**N = 220,736**	**N = 176,280**	**N = 25,137**	**N = 19,319**	**N = 174,437**	**N = 37,725**	**N = 7,281**	**N = 1,293**
Absolute value, Eos/µl	300 (300 - 300)	300 (300 - 300)	300 (300 - 300)	290* (290 - 300)	290 (290 - 290)	300* (300 - 300)	500* (500 - 500)	500* (470 - 500)
Serum total IgE	**N = 23,107**	**N =19,293**	**N = 2,268**	**N = 1,546**	**N = 14,995**	**N = 6,650**	**N = 1,233**	**N = 229**
KU/L	168.6 (164 - 172)	172 (167.2 – 176)	172* (159 – 184)	120* (109 - 134)	160 (155 - 166)	193.9* (185 - 205)	146* (136 - 159)	132.7* (107.7 - 172)

For each biomarker, median values are calculated and reported across the maximum value reported for everyone with available information on the biomarker between the 2016-2017 period. 95% Confidence Intervals were reported in parenthesis for the median value and the test of statistically significant differences in means across severity degrees and among multimorbidity phenotypes (*, P-value < 0.05). Median values were preferred above average as the Kernel distribution for each biomarker was very asymmetric with extremely high skewness and Kurtosis. For instance, for eosinophils measured in absolute value, skewness was 10.41 and Kurtosis 294.46. Eos, Eosinophils; IgE, Immunoglobulin E; AD, Atopic Dermatitis; NP, Nasal Polyposis.

doi: 10.18176/jiaci.0903

Table 3. Comorbidities of the asthma cohort.

	Total Population	Population by disease severity					
Asthma related Comorbidities,	**N = 473,737** (100)	**Mild N = 402,977 (85.1)**	**Moderate N = 41,329 (8.7)**	**Severe N = 29,431 (6.2)**	**P-value**	**Logit regression Pr (severe) Odds Ratio (95% CI)**	**P-value**
Respiratory & allergy, N (%)							
Allergic rhinitis	97,172 (20.5)	84,358 (20.9)	9,116 (22.1)	3,698 (12.6)	p<0.0001	1.00 (0.98 1.03)	0.713
Atopic dermatitis	82,222 (17.4)	71,583 (17.8)	6,015 (14.6)	4,624 (15.7)	p<0.0001	1.03 (1.01 1.06)	0.010
Nasal Polyposis	11,708 (2.5)	7,472 (1.9)	2,868 (6.9)	1,368 (4.6)	p<0.0001	2.18 (2.09 2.27)	<0.0001
Obstructive sleep apnoea	13,849 (2.9)	8,564 (2.1)	2,150 (5.2)	3,135 (10.7)	p<0.0001	1.36 (1.30 1.42)	<0.0001
Not specify allergy	27,514 (5.8)	24,109 (6.0)	2,209 (5.3)	1,196 (4.1)	p<0.0001	1.01 (0.97 1.06)	0.507
Systemic & general, N (%)							
Hypertension	105,898 (22.4)	69,830 (17.3)	17,147 (41.5)	18,921 (64.3)	p<0.0001	1.32 (1.29 1.36)	<0.0001
Overweight	93,403 (19.7)	69,639 (17.3)	12,296 (29.8)	11,468 (39.0)	p<0.0001	1.10 (1.07 1.12)	<0.0001
Dyslipidaemia	40,334 (8.5)	25,828 (6.4)	5,889 (14.2)	8,617 (29.3)	p<0.0001	1.14 (1.11 1.17)	<0.0001
Diabetes	40,490 (8.5)	26,325 (6.5)	5,965 (14.4)	8,200 (27.9)	p<0.0001	1.04 (1.01 1.07)	0.004
Ischemic heart disease	15,395 (3.2)	8,942 (2.2)	2,273 (5.5)	4,180 (14.2)	p<0.0001	1.17 (1.12 1.22)	<0.0001
Gastroesophageal reflux	19,357 (4.1)	13,909 (3.5)	2,843 (6.9)	2,605 (8.9)	p<0.0001	1.09 (1.05 1.13)	<0.0001
Psychiatric & neurologic, N (%)							
Anxiety	83,625 (17.7)	68,916 (17.1)	8,290 (20.1)	6,419 (21.8)	p<0.0001	0.96 (0.93 0.98)	<0.0001
Depression	22,464 (4.7)	15,563 (3.9)	2,966 (7.2)	3,935 (13.4)	p<0.0001	1.05 (1.02 1.09)	0.003

Data on the proportion of individuals over the total adult population in each phenotype are in parenthesis.

P-values are for the test of differences in means between severity degrees (mild-to-moderate vs severe) for each multimorbidity under study at a 95% confidence level of significance—logistical regression analysis for the probability of severe asthma. The model includes sociodemographic characteristics as control variables.

NP – Nasal Polyposis; COPD – Chronic Obstructive Pulmonary Disease. Alcohol-related diseases include alcohol induced-mental disorders, alcohol dependence and abuse, alcoholic polyneuropathy, alcoholic cardiomyopathy, alcoholic fatty liver, acute alcoholic hepatitis, alcoholic cirrhosis of the liver, the excessive blood level of alcohol, toxic (acute) effect of alcohol, alcoholic gastritis with or without mention of haemorrhage, fetal alcohol syndrome. Tobacco-related diseases include Chronic pharyngitis, uncomplicated chronic bronchitis, and leucoplakia of the oral mucosa, including the tongue.

doi: 10.18176/jiaci.0903