ORIGINAL ARTICLE

Exacerbations Among Patients With Asthma Are Largely Dependent on the Presence of Multimorbidity

Domínguez-Ortega J*[1,2,3], Luna-Porta JA*[1,2,3], Olaguibel JM[3,4], Barranco P[1,2,3], Arismendi E[3,5,6,7], Barroso B[3,8], Betancor D[3,8], Bobolea I[3,5,6,7], Caballero ML[1,2,3], Cárdaba B[3,9], Cruz MJ[3,10,11], Curto E[3,12,13,14], González-Barcala FJ[3,15,16,17], Losantos-García I[2,18], Martínez-Rivera C[3,14,19,20], Mendez-Brea P[21], Mullol J[3,5,6,22], Muñoz X[3,11], Picado C[3,5,6,7], Plaza V[3,12,13,14], del Pozo V[3,9], Rial MJ[3,23], Sastre J[3,8], Soto L[3,12,13,14], Valero A[3,5,6,7], Valverde-Monge M[3,8], Quirce S[1,2,3]

[1]Department of Allergy, La Paz University Hospital, Madrid, Spain
[2]Institute for Health Research IdiPAZ, Madrid, Spain
[3]CIBER de Enfermedades Respiratorias (CIBERES), Instituto de Salud Carlos III, Madrid, Spain
[4]Severe Asthma Unit, Department of Allergy, Complejo Hospitalario de Navarra, Pamplona, Navarra, Spain
[5]Clinical and Experimental Respiratory Immunoallergy (IDIBAPS), Barcelona, Spain
[6]Universitat de Barcelona, Barcelona, Spain
[7]Allergy Unit and Severe Asthma Unit, Pneumonology and Allergy Department, Hospital Clínic, Barcelona, Spain
[8]Department of Allergy, Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain
[9]Department of Immunology, Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain
[10]Departamento de Biología Celular, Fisiología e Inmunología, Universitat Autónoma de Barcelona, Barcelona, Spain
[11]Pneumology Department, Hospital Vall d'Hebron, Barcelona, Spain
[12]Respiratory Medicine Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
[13]Instituto de Investigación Biomédica Sant Pau (IIB Sant Pau), Barcelona, Spain
[14]Universidad Autónoma de Barcelona, Departamento de Medicina, Barcelona, Spain
[15]Pneumology Department, Complejo Hospitalario Universitario de Santiago, La Coruña, Spain
[16]Instituto de Investigación Sanitaria de Santiago de Compostela (FIDIS), La Coruña, Spain
[17]Universidad de Santiago de Compostela, La Coruña, Spain
[18]Biostatistics Department, La Paz University Hospital, Madrid, Spain
[19]Pneumology Department, Hospital Germans Trias i Pujol, Barcelona, Spain
[20]Institut d'Investigacio Germans Trias I Pujol (IGTP), Badalona, Barcelona, Spain
[21]Department of Allergy, Complejo Hospitalario Universitario de Santiago, Santiago de Compostela, La Coruña, Spain
[22]Rhinology Unit and Smell Clinic, ENT Department, Hospital Clínic, Barcelona, Spain
[23]Department of Allergy, Complexo Hospitalario Universitario A Coruña, A Coruña, Spain
*Both authors contributed as equal authors

J Investig Allergol Clin Immunol 2023; Vol. 33(4): 281-288
doi: 10.18176/jiaci.0816

Abstract

Introduction: Comorbidities can influence asthma control and promote asthma exacerbations (AEs). However, the impact of multimorbidity in AEs, assessed based on long-term follow-up of patients with asthma of different degrees of severity, has received little attention in real-life conditions.

Objective: To describe the epidemiological and clinical characteristics and predictors of AEs in patients who had presented at least 1 AE in the previous year in the MEchanism of Genesis and Evolution of Asthma (MEGA) cohort.

Methods: The work-up included a detailed clinical examination, pulmonary function testing, fractional exhaled nitric oxide (FeNO), blood counts, induced sputum, skin prick-tests, asthma questionnaires, and assessment of multimorbidity. The number of moderate-severe AEs in the preceding year was registered for each patient.

Results: The study population comprised 486 patients with asthma (23.7% mild, 35% moderate, 41.3% severe). Disease remained uncontrolled in 41.9%, and 47.3% presented ≥1 moderate-severe AE, with a mean (SD) annual exacerbation rate of 0.47 (0.91) vs 2.11 (2.82) in mild and severe asthma, respectively. Comorbidity was detected in 56.4% (66.6% among those with severe asthma). Bronchiectasis, chronic rhinosinusitis with nasal polyps, atopy, psychiatric illnesses, hyperlipidemia, and hypertension were significantly associated with AEs. No associations were found for FeNO, blood eosinophils, or total serum IgE. Sputum eosinophilia and a high-T2 inflammatory pattern were significantly associated with AEs. Multivariable regression analysis showed a significant association with asthma severity, uncontrolled disease, and low prebronchodilator FEV_1/FVC.

Conclusions: Our study revealed a high frequency of AE in the MEGA cohort. This was strongly associated with multimorbidity, asthma severity, poor asthma control, airflow obstruction, higher sputum eosinophils, and a very high-T2 inflammatory pattern.

Key words: Asthma. Exacerbations. MEGA cohort. Asthma control. Multimorbidity.

Resumen

Antecedentes: Las comorbilidades pueden influir en el control del asma y promover las exacerbaciones del asma (EA). Sin embargo, el impacto de la multimorbilidad en las EA ha sido escasamente estudiado, en condiciones de vida real, a través del seguimiento a largo plazo, en pacientes con asma de diferente gravedad.
Objetivo: Describir las características epidemiológicas, clínicas y los factores predictivos de EA en los pacientes reclutados en el proyecto MEchanism of Genesis and Evolution of Asthma (MEGA) que habían presentado al menos una EA en el último año.
Métodos: Realizamos un examen clínico detallado, pruebas de función pulmonar, fracción de óxido nítrico exhalado (FeNO), hemograma, esputo inducido, pruebas cutáneas, cuestionarios de asma y evaluación de multimorbilidad. Para cada sujeto se registró el número de EA moderadas-graves en el año anterior.
Resultados: Se incluyeron 486 pacientes con asma (23,7% leve, 35% moderada, 41,3% grave). El 41,9% presentaban asma no controlada. El 47,3% presentó ≥1 EA moderada-grave, con una tasa media anual de exacerbaciones de 0,47±0,91 vs 2,11±2,82 en asma leve y grave, respectivamente. El 56,4% (66,6% entre los asmáticos graves) presentó alguna comorbilidad. Las bronquiectasias, la rinosinusitis crónica con pólipos nasales, la atopia, las enfermedades psiquiátricas, la hiperlipidemia y la hipertensión se relacionaron significativamente con las EA. No se encontró esta relación para FeNO, eosinófilos en sangre e IgE sérica total. La eosinofilia en el esputo y un patrón inflamatorio T2 alto se asociaron significativamente con las EA. El análisis de regresión multivariable mostró una asociación significativa con la gravedad del asma, la enfermedad no controlada y el FEV_1/FVC bajo antes del broncodilatador.
Conclusiones: La cohorte MEGA encontró una alta tasa de EA, que se asoció fuertemente con multimorbilidad, gravedad del asma, control deficiente del asma, obstrucción al flujo aéreo, eosinófilos en esputo más altos y un patrón inflamatorio T2 muy alto.

Palabras clave: Asma. Exacerbaciones. Cohorte MEGA. Control de asma. Multimorbilidades.

Summary box

- **What do we know about this topic?**

  Although poor asthma control and previous exacerbations are associated with a higher frequency of asthma exacerbations, the impact of multimorbidity on AE in patients with asthma of different degrees of severity has received little attention in prospective observational real-life studies.

- **How does this study impact our current understanding and/or clinical management of this topic?**

  The MEGA cohort, through long-term prospective follow-up in correctly diagnosed patients with asthma, shows a high rate of AE, which was strongly associated with multimorbidity, airflow obstruction, higher sputum eosinophil count, and a very high-T2-inflammatory pattern.

Introduction

Most patients with asthma remain symptomatic despite adequate maintenance treatment and experience exacerbations. An asthma exacerbation (AE) is defined as a worsening of asthma symptoms and lung function that requires an increase in medication [1]. Exacerbations are the main cause of morbidity and mortality in patients with asthma. In addition, AEs can be life threatening, have a significant economic impact on the health system, and lead to loss of work productivity and reduced quality of life [2].

While a relationship exists between asthma control and decreased risk of exacerbations, the terms are not synonymous [3]. For instance, while AEs are frequent events in severe asthma [4], they can also occur in patients with mild asthma, even in those with well-controlled disease [5]. Efforts to characterize patients with frequent exacerbations indicate that the etiology is multifactorial. The best predictor of future AEs is a history of previous exacerbations. In fact, the number of AEs in the previous 2 years points to the probability of exacerbations in the following year [6]. Other core clinical outcomes and biomarkers have also been associated with a higher risk for AE (viral infection, environmental exposures, poor adherence to treatment, presence of multimorbidity, and eosinophilia in peripheral blood or sputum) [7].

Little research has been carried out on the impact of AEs in real-life conditions through long-term prospective follow-up in correctly diagnosed patients with asthma of different degrees of severity. The MEchanism of Genesis and Evolution of Asthma (MEGA) project is an ongoing multicenter study in Spain aimed at establishing the characteristics that make up this population of patients with asthma [8]. The project has studied the long-term stability of different parameters to determine changes in the patient's condition, exacerbations, and control, as well as biomarkers and their influence on disease progression [9-10]. The current study describes the epidemiological and clinical characteristics and predictors of AEs in patients who had presented at least 1 AE in the previous year.

Methods

We analyzed data from patients with varying degrees of asthma severity in the observational MEGA prospective cohort [8]. The main methodological characteristics are described in the online repository (supplementary E1). All patients signed an informed consent document in line with the Declaration of Helsinki, and the protocol was approved by all local ethics committees.

Our work-up comprised a detailed clinical examination, pulmonary function testing, measurement of fractional exhaled nitric oxide (FeNO), blood counts, induced sputum, skin prick tests, asthma questionnaires, and assessment of multimorbidity. Asthma-related comorbidities were collected, as follows: atopy, allergic rhinitis, atopic dermatitis, bronchiectasis, diabetes, food allergies, heart disease, gastroesophageal reflux disease (GERD), hyperlipidemia, hypertension, nonsteroidal anti-inflammatory drugs–exacerbated respiratory disease,

Table 1. Demographic and Clinical Data of the MEGA Cohort.

		P value[a]			*P* value[a]
Mean (SD) age, y	47.5 (12.83)	*P*=.012	Mean (SD) previous admissions to ICU ever	0.09 (0.36)	NA
Female sex, %	66.3	*P*=.210	≥3% eosinophils in sputum, %	59.3	*P*=.002
Mean (SD) asthma duration, y	24.3 (15.70)	*P*=.781	Mild asthma, %	23.2	
Severity (GINA step)		*P*<.001	Moderate asthma, %	32.6	
Mild: Step 1-2, %	23.7		Severe asthma, %	44.2	
Moderate: Step 3, %	35		≥61% neutrophils in sputum, %	20.5	*P*=.401
Severe: Step 4-5, %	41.4		Mild asthma, %	32	
Current asthma control (GINA)		*P*<.001	Moderate asthma, %	18.1	
Not controlled, %	20.2		Severe asthma, %	20.8	
Partially controlled, %	21.7		Eosinophils in blood/mm^3 (mean (SD)	339.68 (329.31)	*P*=.865
Controlled, %	58.1		≥150/mm^3, %	77.2	*P*=.511
Mean (SD) Asthma Control Test (ACT) score	20.29 (4.86)	*P*<.001	≥300/mm^3, %	49.2	*P*=1.000
<20, %	32.6		Total serum IgE (kU/L)	421.61 (830.74)	*P*=.898
20-24, %	43.5		FeNO, ppb (mean (SD)	42.77 (37.05)	*P*=.650
25, %	23.9		≥ 20 ppb, %	72.3	*P*=.803
Mean (SD) moderate-severe exacerbations previous year	1.20 (2.14)		High T2 profile[c], %	27.5	*P*=.019
None, %	52.7		FEV_1 Pre-BD, %	85.45 (21.13)	*P*<.001
Moderate, %	31.5		FVC Pre-BD, %	100.06 (46.31)	*P*<.001
Severe, %	15.8		FEV_1/FVC Pre-BD, %	78.88 (18.82)	*P*=.002
Mild asthma, mean (SD)	0.47 (0.91)		FEV_1 Post-BD, %	85.96 (33.01)	*P*<.012
Moderate asthma, mean (SD)	0.61 (1.206)		FVC Post-BD, %	92.82 (34.90)	*P*=.004
Severe asthma, mean (SD)	2.11 (2.82)		FEV_1/FVC Post-BD, %	79.10 (22.02)	*P*=.002
Mean (SD) corticosteroids bursts in the previous year[b]	1.47 (4.76)		Good adherence to treatment[d], %	64.8	*P*=.848
Mean (SD) emergency department visits last year	0.85 (1.68)		Maintenance systemic corticosteroids, %	8.6	*P*<.001
Mild asthma	0.19 (0.63)		Biological therapy, %	17.7	*P*<.001
Moderate asthma	0.35 (0.99)				
Severe asthma	1.20 (2.04)				

Abbreviations: ACT, Asthma Control Test; BD, bronchodilator; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GINA, Global Initiative for Asthma; ICU, intensive care unit; NA, not analyzed.
[a]*P* value <.05 expresses significant association with having at least 1 moderate-severe exacerbation in the previous year.
[b]Systemic corticosteroids for at least 3 consecutive days.
[c]High T2 inflammatory pattern: FeNO ≥20 ppb AND eosinophils in blood ≥300/mm^3 AND atopy.
[d]Adherence was assessed using a validated Spanish version of the Morisky-Green test.

obesity (body mass index ≥30 kg/m^2), psychiatric illnesses (anxiety and depression), chronic rhinosinusitis with nasal polyps (CRSwNP) or without polyps, obstructive sleep apnea-hypopnea syndrome (OSAHS), thyroid disease, and vocal cord dysfunction.

Moderate exacerbations were defined as deterioration in symptoms or lung function requiring increased use of rescue bronchodilator use for ≥2 days, even if it was not severe enough to warrant treatment with systemic/oral corticosteroids (OCS) [1]. Severe asthma exacerbations (SAEs) were defined as the occurrence of any of asthma-related hospital admission or visits to the emergency department or receiving a course of OCS for at least 3 days [1]. The number of moderate-severe exacerbations in the preceding year was registered for each patient.

Statistical Analysis

Qualitative data were presented as absolute frequencies and percentages and quantitative data as mean (SD), minimum, and maximum if they were normally distributed and as median (IQR) if they were not. The associations between qualitative variables were analyzed using the χ^2 test or Fisher exact test. Qualitative and quantitative data were compared using the Mann-Whitney or Kruskal-Wallis test for independent data. A multivariate logistic regression analysis was performed to evaluate the association between the presence of exacerbations and the variables found to be significant in the previous analysis. In addition, a backward elimination method was applied to create the best predictive model of the risk of exacerbations based on the probability of the Wald statistic. A complete model including all variables statistically associated with the presence of exacerbations was created. Then, at each step, the analysis gradually removed variables from the regression model to construct a reduced model that best explained the data. All statistical tests were considered bilateral. Statistical significance was set at $P<.05$. Data were analyzed using SAS 9.3 (SAS Institute).

Results

The demographic, functional, clinical, and inflammatory characteristics of the MEGA cohort are summarized in Table 1. We analyzed data from 486 patients (66% women), for whom all information in the electronic registry was complete. Slightly more than half (52.7%) were nonsmokers. By degree of severity 23.7% of the patients had mild asthma, 35% moderate asthma, and 41.3% severe asthma. Overall, disease remained uncontrolled in 41.9% of patients according to the GINA criteria and in 32.6% according to the ACT score. Regarding exacerbations, 47.3% presented at least 1 moderate-severe AE in the previous year, although only 15.8% presented a severe one. Three or more AEs were recorded in 15.5%. Of the total number of patients who presented exacerbations, 18.6% required admission to hospital in the previous year, and 9.8% required at least 1 admission to the intensive care unit. Severity of asthma influenced the number of AEs. Patients with SA experienced a mean of 2.11 (2.82) AEs in the previous year, while patients with mild asthma presented 0.47 (0.91). In total, 8.6% of the patients included received OCS in a daily treatment regimen, with significantly more visits to the emergency department than patients with no daily OCS treatment (1.60 [2.26] vs 0.49 [1.29]; $P<.001$]).

Comorbid conditions were detected in 56.4% of patients (66.6% among those with severe asthma), and this issue was significantly associated with experiencing an AE. Table 2 shows the prevalence of different comorbidities in the MEGA population and their association with experiencing an AE in

Table 2. Comorbidities in the MEGA Cohort. A P Value <.05 Expresses a Significant Association With Having at Least 1 Moderate-Severe Exacerbation in the Previous Year.

		***P* value**
Comorbidities, %	56.4	*P*<.001
Smoking habit		*P*=.210
Nonsmoker, %	52.7	
Smoker, %	8.5	
Passive, %	7.6	
Exsmoker, %	31.2	
Bronchiectasis, %	7.2	*P*<.001
Diabetes, %	4.7	*P*=.086
Heart disease, %	2.9	*P*=.848
Hyperlipidemia, %	15	*P*=.021
Hypertension, %	12.6	*P*=.001
Mean (SD) BMI, kg/m^2	27.08 (5.32	*P*=.684
BMI ≥30, %	19.8	*P*=.110
Psychiatric illness, %	12.2	*P*<.001
OSAHS, %	4.3	*P*=.670
Thyroid disease, %	10.3	*P*=.655
Atopy[a], %	74.3	*P*<.001
Skin prick tests		
Animal dander, %	13.1	NA
Molds, %	2.7	NA
House dust mites, %	62.4	NA
Pollen, %	18.5	NA
Other, %	2.2	NA
Allergic rhinitis, %	52.9	*P*=.855
Atopic dermatitis, %	10.7	*P*=.304
Chronic rhinosinusitis		
with nasal polyps, %	30	*P*<.001
without nasal polyps, %	8.8	*P*=.527
NSAID-exacerbated respiratory disease, %	15	*P*=.161
Food allergy, %	4.9	*P*=.835

Abbreviations: BMI, body mass index; NA, not analyzed; NSAID, nonsteroidal anti-inflammatory drug; OSAHS, obstructive sleep apnea–hypopnea syndrome.
[a]Prick test and/or specific IgE positive to a common allergen.

the previous year. In summary, obesity (BMI >30) was found in 19.8% of patients. Bronchiectasis was present in 7% of patients (n=36), of whom 67% (n=24) had severe asthma. CRSwNP affected 30% of patients overall and 43.3% of those with SA (*P*<.001). Among patients with SA and a comorbid condition, 77.1% had presented an exacerbation in the previous year, compared with 53.7% of those who did not present any relevant comorbidity (*P*=.001). The presence of bronchiectasis was significantly associated with experiencing an AE in the previous year. In fact, in patients with severe asthma, this risk increased: 91.7% of patients with severe asthma and bronchiectasis experienced an AE, while this only affected 66.7% in those with severe asthma and no bronchiectasis (*P*=0.016). Other comorbidities associated with AE were atopy (present in 74.3% of the population), psychiatric diseases [9], hyperlipidemia, and hypertension. Interestingly, we did not find associations with these last 2 comorbidities when we analyzed the severe asthma subgroup separately.

Of the 148 patients in whom induced sputum was obtained, 59% presented eosinophilia in sputum (mean count, 10.78% [19.08%]). In this group, 44.2% presented SA. During the previous year, 11.4% of patients with eosinophilic asthma experienced an SAE. Sputum eosinophilia clearly correlated with the risk of experiencing an AE, whereas no associations were found for FeNO, blood eosinophils, or total serum IgE. However, a tendency toward increased eosinophil counts was seen in severe asthma compared to intermittent disease. Similarly, the IgE level also tended to increase at greater degrees of severity [10]. Regarding lung function, significant differences were recorded for pre- and postbronchodilator FEV_1 (%), pre- and post-FVC, and pre- and post-FEV_1/FVC ratio.

Finally, the multivariable regression analysis demonstrated a significant association between experiencing an AE in the previous year and the severity of asthma, uncontrolled disease, and increased obstruction of airflow expressed as the prebronchodilator FEV_1/FVC (Table 3).

Table 3. Results of Multivariable Logistic Regression Analysis (A).[a] Results in the Severe Asthma Population (B).[b]

A	Variable	OR	95%CI	*P* value
	Severity (GINA therapeutic step)	2.193	(1.209-3.979)	.010
	Current asthma control (GINA)	0.300	(0.162-0.556)	<.001
	Pre-BD FEV_1/ FVC, %	0.964	(0.933-0.997)	.031
B	**Variable**	**OR**	**95%CI**	***P* value**
	Current asthma control (GINA)	0.330	(0.202-0.541)	<.001
	Maintenance systemic corticosteroids	4.001	(1.082-14.795)	.038
	Presence of comorbidities	2.427	(1.079-5.461)	.032

Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GINA, Global Initiative for Asthma.
[a]Dependent variable: exacerbations in the last year (yes).
[b]*P*<.05 expresses a significant association.

Discussion

Most AEs are preventable, and a risk-based approach has been shown to be more effective than focusing solely on daily symptom control [11]. Furthermore, the incidence of AEs in real-life surveys is much higher than in clinical trial settings [12]. In this context, the identification of individuals with a higher risk of AEs and the recognition of indicators of potential severity provide an opportunity for targeted management, making it possible to establish the most appropriate treatment to improve asthma control and the most effective preventive measures for AEs.

The current analysis offers data from the largest cohort of confirmed asthma patients treated under real-world conditions in Spain. The strengths of the study include its longitudinal design and well-characterized, objectively diagnosed asthma patients. The large size of the cohort strengthens the robustness of the results for the study of the clinical and biological variables that are associated with exacerbation-prone asthma and construction of a biomarker-based, clinical prediction model for exacerbation rates.

Of note, 47.3% of the cohort had an exacerbation in the previous year (average annualized SAE rate of 1.20). Risk factors for frequent AEs span social, clinical, comorbid, biological, and environmental domains [13]. We found a clearly significant association between exacerbation rates and current poor asthma control, more severe asthma, and having used OCS. In general, our findings are consistent with those found in other large asthma cohorts throughout the world and recognized in guidelines as risk factors for exacerbations [3-14]. AEs can arise regardless of the severity of asthma. Although AEs are a common feature of patients with severe asthma (2.11 [2.81] in this study), our results showed that even patients on GINA steps 1-2 had experienced a mean of 0.47 (0.91) AEs in the previous year. This finding is remarkable, because we did not observe many singular differences between patients with different grades of severity.

Comorbidities can influence asthma control, both acutely (promoting exacerbations) and during stable periods [15]. Furthermore, more frequent susceptibility to exacerbations has been associated with more comorbid conditions (eg, obesity, psychiatric disorders, smoking, CRSwNP, allergy, GERD, recurrent respiratory infections, and OSAHS) [3-14]. Interestingly, in the MEGA population, 56.4% of the patients had comorbid conditions, although only some of these were associated with AEs. We observed a significant impact of CRSwNP on exacerbations. CRSwNP is frequently associated with more severe asthma and a greater propensity to exacerbations [16]. It should be noted that the prevalence of CRSwNP reached 30% in our population, ie, similar to or even greater than the data published in other cohorts [17-18], considering that only 41.4% of the patients in the MEGA trial had severe asthma. Patients with moderate-severe asthma with CRSwNP usually have higher levels of peripheral blood eosinophils and FeNO [19], although in our study we did not find either marker to be associated with an increased risk of exacerbations. It should also be noted that CRSwNP often requires bursts of OCS to shrink polyps and improve symptoms, leading to increased use of

corticosteroids, which has been identified as one of the main risk factors for AEs.

Metabolic syndrome is another relevant chronic comorbid condition associated with asthma [20-21]. The association between increased cardiovascular risk and asthma is well known [22]. In their cohort study of patients with exacerbation-prone asthma, Peters et al [6] suggested that metabolic syndrome is the key factor in AE. In our study, as in a comparable Italian cohort [23], BMI did not seem to play a key role in the increased occurrence of asthma attacks, whereas dyslipidemia was clearly associated. Dyslipidemia can be the cause of this association but also the consequence of a more intense chronic inflammatory status [24]. Controversial results from different studies show how metabolic syndrome might affect AEs, particularly in the elderly and in late-onset asthma. In addition, in our cohort, diabetes did not seem to have a significant role in the risk of exacerbations, although we consider that the low prevalence of diabetes in the sample (less than 14.8% in the adult population in Spain [25]) could have influenced our results. In contrast, a recent Japanese retrospective study showed dyslipidemia to be associated with a reduced risk of exacerbations [26]. Statins have been reported to reduce asthma-related emergency care, hospitalizations, and systemic corticosteroid use in asthma patients in several retrospective studies, suggesting anti-inflammatory effects [27-28]. Similarly, a recent meta-analysis suggested that metformin decreased the risk of asthma-related emergency department visits for patients with concurrent asthma and diabetes [29]. Unfortunately, we did not analyze the use of metformin or whether statins could play a role in the number of exacerbations, since we did not separately evaluate the different statins, the doses taken, or adherence to treatment.

Uncontrolled rhinitis in asthma patients is a predictor of asthma symptoms and poor asthma control [30]. Remarkably, allergic rhinitis (AR) did not appear to play a role in increasing the risk of exacerbations in our cohort. Asthma and allergic rhinitis are heterogeneous chronic respiratory conditions that often coexist and share similar triggers and pathophysiology. Furthermore, asthma patients with mild allergic rhinitis have better asthma control than those with severe rhinitis, and it has been shown that in Spain, asthma patients with allergic rhinitis are usually younger and have less severe disease in both primary care and specialized settings [31]. However, we did not record data on the severity or level of control of allergic rhinitis.

As for adherence, surprisingly, there was no significant association with exacerbations, even in patients with severe asthma. Adherence to medication regimens is a key element of successful asthma management, while poor adherence to asthma treatment has detrimental consequences, leading to poor control and increased asthma attacks [3,32]. However, adherence was measured in this study using the Morisky-Green questionnaire, which is not specific and less sensitive for inhalation therapy.

Considering bronchial inflammation and its influence on risk of exacerbation, total sputum and blood eosinophil counts and FeNO level are surrogate biomarkers for type 2 airway inflammation and have been associated with an increased risk of AE [33]. Eosinophilic airway inflammation is more closely associated with AE and response to OCS than with asthma symptoms and variable airflow limitation [34]. In fact, T2-high asthma tends to have several features of increased asthma severity, including increased rates of AE [35]. Blood and airway eosinophils in humans with asthma have been shown to correlate with asthma severity [36], and treatment directed at normalizing sputum eosinophil counts was shown to markedly reduce SAEs [37]. We found that sputum eosinophilia clearly correlates with the risk of AEs, while blood eosinophils were not associated with exacerbations in this population. Variability in eosinophil count values was recently shown to be more closely associated with emergency department visits and hospitalizations than count values, particularly in patients with higher variability [38]. Our results probably reinforce the need to measure eosinophils in sputum, a more sensitive method for appropriately defining the characteristics of mucosal inflammation in asthma [39]. Moreover, while FeNO levels correlated well with blood eosinophils, they had no significant influence on risk of AE. We consider that our data reflect the situation at inclusion, with many possible factors influencing the pattern of both biomarkers. Interestingly, we confirmed that patients with the most pronounced T2 inflammatory pattern (FeNO ≥20 ppb and blood eosinophilia and sensitization to allergens) experienced significantly more exacerbations and that 25% experienced at least 1 severe AE (P=.019).

Our study has several limitations, such as the lack of a control group and the fact that patients were recruited in specialized centers with a higher number of severe asthma patients than mild cases. Moreover, it is important to remark that the MEGA project is a prospective cohort, and further evaluation of these results is needed at different time points.

To conclude, we found AE to be very frequent in patients with different degrees of severity. This frequency was strongly associated with multiple comorbid conditions (eg, bronchiectasis, metabolic syndrome, CRSwNP, asthma severity, and poor asthma control). Other important risk factors for exacerbations were a higher sputum eosinophil count, the presence of a very high T2 inflammatory pattern, and corticosteroid use among severe asthma patients.

Funding

The MEGA project was supported by Sanofi (02/055), Fondo de Investigación Sanitaria–FIS (PI15/00803 and PI15/01900), the Merck Health Foundation, CIBER de Enfermedades Respiratorias (CIBERES), a Carlos III Institute of Health initiative, and FEDER funds.

Conflicts of Interest

Javier Domínguez-Ortega declares having received payment or honoraria for having served as a consultant and participating in lectures from AstraZeneca, Sanofi, MSD, GSK, ALK, Novartis, Teva, Chiesi, and LETI Pharma.

Juan Alberto Luna-Porta reports personal fees from AstraZeneca outside the submitted work.

José María Olaguibel declares consulting fees from ALK and AstraZeneca, honoraria for lectures from Mundipharma and GSK, and payment for expert testimony from ALK.

Pilar Barranco declares honoraria for lectures from AstraZeneca, GSK, and Novartis.

Diana Betancor is supported by a Rio Hortega Research Contract from Instituto Carlos III, Ministry of Science.

Elena Curto declares grants or contracts from the Spanish Society of Respiratory Medicine (SEPAR) and GSK.

Francisco-Javier González-Barcala declares the following: grants or contracts from GSK; consulting fees or honoraria for lectures from ALK, AstraZeneca, Bial, Chiesi, Gebro Pharma, GSK, Menarini, Novartis, Rovi, Roxall, Sanofi, Stallergenes-Greer, and Teva; support for attending meetings from ALK, Menarini, and Sanofi; participation on advisory boards for ALK, AstraZeneca, GSK, Menarini, Novartis, Sanofi, and Teva.

Carlos Martínez-Rivera declares the following: payment for lectures from AstraZeneca, GSK, Sanofi, Teva, Novartis, and Chiesi; support for attending meetings from Chiesi, Novartis, and AstraZeneca; participation on advisory boards for AstraZeneca and Sanofi.

Paula Méndez-Brea declares payment for lectures or support for attending meetings from ALK, Stallergens, GSK, Allergy Therapeutics, and Chiesi.

Joaquim Mullol declares the following: support from MSD for this manuscript, consulting fees or honoraria for lectures or participation on advisory boards from AstraZeneca, Genentech, GSK, Glenmark, Menarini, Mitsubishi-Tanabe Pharma, MSD, Viatris (Mylan-Meda Pharma), Novartis, Proctor & Gamble, Regeneron, Pharmaceuticals Inc, Sanofi-Genzyme, UCB Pharma, and Uriach Group; participation on the Executive Committee of ARIA, GALEN, and ECARF and on the Scientific Committee of EUFOREA.

Xavier Muñoz declares grants or consulting fees or honoraria for lectures or support for attending meetings from AstraZeneca, Boehringer, Chiesi, Faes, GSK, Menarini, Novartis, and Sanofi.

Vicente Plaza declares the following: support from GSK for this manuscript; consulting fees from Sanofi; honoraria for lectures from AstraZeneca, Chiesi, MSD, and Boehringer Ingelheim; support for attending meetings from AstraZeneca; institutional grants for research from Chiesi and Menarini.

Victoria del Pozo is Associate Editor of the Journal of Investigational Allergology and Clinical Immunology and declares having received payment or honoraria for having served as a consultant and participating in lectures from AstraZeneca and GSK.

Manuel J. Rial declares having received payment or honoraria for having served as consultant and participating in lectures from AstraZeneca, Novartis, TEVA, GSK, Chiesi, and LETI Pharma outside the submitted work.

Joaquín Sastre declares grants or consulting fees or honoraria for lectures or support for attending meetings from Sanofi, AbbVie, Novartis, Faes Pharma, and GSK and unpaid relationships with AAAIC, EAACI, and SEAIC.

Lorena Soto declares honoraria for lectures from AstraZeneca, GSK, Sanofi, Novartis and Stallergenes-Greer and support for attending meetings from GSK, Hal Allergy, and Allergy Therapeutics.

Marcela Valverde-Monge declares consulting fees from Organon and honoraria for lectures from GSK.

Santiago Quirce has been on advisory boards for and has received speaker's honoraria from AstraZeneca, GlaxoSmithKline, Novartis, Chiesi, Mundipharma, Teva, and Sanofi.

The remaining authors declare that they have no conflicts of interest.

References

1. Reddel HK, Taylor DR, Bateman ED, Boulet lP, Boushey HA, Busse WW, et al. An official American Thoracic Society/ European Respiratory Society statement: Asthma control and exacerbations: Standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med. 2009;180:59-99.
2. Lee TY, Petkau J, Sadatsafavi M. Long-term natural history of severe asthma exacerbations and their impact on the disease course. Ann Am Thorac Soc. 2022;19(6):907-15.
3. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2021. Available from: www.ginasthma.org
4. Czira A, Turner M, Martin A, Hinds D, Birch H, Gardiner F, et al. A systematic literature review of burden of illness in adults with uncontrolled moderate/severe asthma. Respir Med. 2021;191:106670.
5. Mohan A, Ludwig A, Brehm C, Lugogo NL, Sumino K, Hanania NA. Revisiting Mild Asthma: Current Knowledge and Future Needs. Chest. 2022;161:26-39.
6. Peters MC, Mauger D, Ross KR, Phillips B, Gaston B, Cardet JC, et al. Evidence for exacerbation-prone asthma and predictive biomarkers of exacerbation frequency. Am J Respir Crit Care Med. 2020;202:973-82.
7. Federico MJ, Denlinger LC, Corren J, Szefler SJ, Fuhlbrigge AL. Exacerbation-Prone Asthma: A Biological Phenotype or a Social Construct. J Allergy Clin Immunol Pract. 2021;9:2627-34.
8. Muñoz X, Álvarez-Puebla MJ, Arismendi E, Arochena L, Ausín MDP, Barranco P, et al. The MEGA Project: A Study of the Mechanisms Involved in the Genesis and Disease Course of Asthma. Asthma Cohort Creation and Long-Term Follow-Up. Arch Bronconeumol (Engl Ed). 2018 Mar 19:S0300-2896(18)30009-7.
9. Baptista-Serna L, Rodrigo-Muñoz JM, Mínguez P, Valverde-Monge M, Arismendi E, Barranco P, et al. Anxiety and body mass index affect asthma control: data from a prospective Spanish cohort. J Allergy Clin Immunol Pract. 2021:S2213-2198(21)01130-2.
10. Rial MJ, Álvarez-Puebla MJ, Arismendi E, Caballero ML, Cañas JA, Cruz MJ, et al. Clinical and inflammatory characteristics of patients with asthma in the Spanish MEGA project cohort. Clin Transl Allergy. 2021;11:e12001.
11. Blakey JD, Woolnough K, Fellows J, Walker S, Thomas M, Pavord ID. Assessing the risk of attack in the management of asthma: a review and proposal for revision of the current control-centred paradigm. Prim Care Respir J. 2013;22:344-52.
12. Jackson DJ, Sykes A, Mallia P, Johnston SL. Asthma exacerbations: Origin, effect and prevention. J Allergy Clin Immunol. 2011;128:1165-74.

13. Pola-Bibian B, Dominguez-Ortega J, Vilà-Nadal G, Entrala A, González-Cavero L, Barranco P, et al. Asthma exacerbations in a tertiary hospital: clinical features, triggers, and risk factors for hospitalization. J Investig Allergol Clin Immunol. 2017;27:238-45.
14. GEMA 5.0. J Investig Allergol Clin Immunol. 2021;31(Suppl.1): 1-130.
15. Delgado J, Martinez-Moragón E, Fernández-Sánchez T. Factors affecting the success of Step-up therapy in patients with moderate-severe asthma: A Real-Life Study. J Investig Allergol Clin Immunol. 2021;31:145-50.
16. Laidlaw TM, Mullol J, Woessner KM, Amin N, Mannent LP. Chronic rhinosinusitis with nasal polyps and asthma. J Allergy Clin Immunol Pract. 2021;9:1133-41.
17. Perez de Llano L, Martínez-Moragón E, Plaza Moral V, Trisan Alonso A, Sánchez CA, Callejas FJ, et al. Unmet therapeutic goals and potential treatable traits in a population of patients with severe uncontrolled asthma in Spain. ENEAS study Respir Med. 2019;151:49-54.
18. Ricciardolo FLM, Levra S, Sprio AE, Bertolini F, Carriero V, Gallo F, et al. A real-world assessment of asthma with chronic rhinosinusitis. Ann Allergy Asthma Immunol. 2020;125:65-71.
19. Chan R, Lipworth B. Impact of nasal polyps on endotype and phenotype in patients with moderate to severe asthma. Ann Allergy Asthma Immunol. 2021;127:548-52.
20. Brumpton BM, Camargo CA Jr, Romundstad PR, Langhammer A, Chen Y, Mai XM. Metabolic syndrome and incidence of asthma in adults: the HUNT study. Eur Respir J. 2013;42:1495-502.
21. Picado C, Pernigotti A, Arismendi E. Asthma: A New Cardiovascular Risk Factor? Arch Bronconeumol (Engl Ed). 2019;55:353-4.
22. Park JW. Asthma Phenotype with Metabolic Dysfunction. Yonsei Med J. 2022;63:1-7.
23. Sprio AE, Carriero V, Levra S, Botto C, Bertolini F, Di Stefano A, et al. Clinical Characterization of the Frequent Exacerbator Phenotype in Asthma. J Clin Med. 2020;9:2226.
24. Pollevick ME, Xu KY, Mhango G, Federmann EG, Vedanthan R, Busse P, et al. The relationship between asthma and cardiovascular disease: An examination of the Framingham Offspring Study. Chest. 2021;159:1338-45.
25. International Diabetes Federation https://www.idf.org/our-network/regions-members/europe/members/159-spain.html Last accessed 2022 Mar 25.
26. Hozawa S, Maeda S, Kikuchi A, Koinuma M. Exploratory research on asthma exacerbation risk factors using the Japanese claims database and machine learning: A retrospective cohort study. J Asthma. 2021 Apr;29:1-19.
27. Kim JH, Wee JH, Choi HG, Park JY, Hwang YI, Jang SH, et al. Association between Statin Medication and Asthma/Asthma Exacerbation in a National Health Screening Cohort. J Allergy Clin Immunol Pract. 2021;9:2783-91.
28. Wang JY, Yao TC, Tsai YT, Wu AC, Tsai HJ. Increased dose and duration of statin use is associated with decreased asthma-related emergency department visits and hospitalizations. J Allergy Clin Immunol Pract. 2018;6:1588-95.
29. Wen L, Zhong W, Chai Y, Zhong Q, Gao J, Guan L, et al. Association of Metformin Use with Asthma Exacerbation in Patients with Concurrent Asthma and Diabetes: A Systematic Review and Meta-Analysis of Observational Studies. Can Respir J. 2020;2020:9705604.
30. Vandenplas O, Dramaix M, Joos G, Louis R, Michils A, Verleden G, et al. The impact of concomitant rhinitis on asthma-related quality of life and asthma control. Allergy. 2010;65:1290-7.
31. Castillo JA, Navarro A, Quirce S, Molina J, García-Marcos L, Juliá B, et al. Prevalence and characteristics of rhinitis in adult asthmatic patients attending allergist, primary care and pulmonologist settings in Spain (AIR study). Med Clin (Barc). 2011;136:284-9.
32. Dima AL, van Ganse E, Stadler G, de Bruin M. Does adherence to inhaled corticosteroids predict asthma-related outcomes over time? A cohort study. Eur Respir J 2019;54:1900901.
33. Busse WW, Wenzel SE, Casale TB, FitzGerald JM, Rice MS, Daizadeh N, el al. Baseline FeNO as a prognostic biomarker for subsequent severe asthma exacerbations in patients with uncontrolled, moderate-to-severe asthma receiving placebo in the LIBERTY ASTHMA QUEST study: a post-hoc analysis. Lancet Respir Med. 2021;9:1165-73.
34. Wenzel SE, Schwartz LB, Langmack EL, Halliday JL, Trudeau JB, Gibbs RL, et al. Evidence that severe asthma can be divided pathologically into two inflammatory subtypes with distinct physiologic and clinical characteristics. Am J Respir Crit Care Med. 1999;160:1001-8.
35. Coverstone AM, Seibold MA, Peters MC. Diagnosis and Management of T2-High Asthma. J Allergy Clin Immunol Pract. 2020;8:442-50.
36. Bousquet J, Chanez P, Lacoste JY, Barnéon G, Ghavanian N, Enander I, et al. Eosinophilic inflammation in asthma. N Engl J Med. 1990;323:1033-9.
37. Green RH, Brightling CE, McKenna S, Hargadon B, Parker D, Bradding P, et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. Lancet. 2002;360:1715-21.
38. Toledo-Pons N, van Boven JFM, Muncunill J, Millán A, Román-Rodríguez M, López-Andrade B, et al. Impact of Blood Eosinophil Variability in Asthma: A Real-Life Population Study. Ann Am Thorac Soc. 2022;19(3):407-14.
39. Caballero ML, Dominguez-Ortega J, Nin-Valencia AR, Sánchez-Ocando H, Barranco P. Eosinophil count could be more sensitive in induced sputum than in peripheral blood for phenotyping of patients with severe eosinophilic asthma. J Investig Allergol Clin Immunol. 2021;31: 360-1.

Manuscript received April 6, 2022; accepted for publication April 13, 2022.

Juan Alberto Luna Porta

Department of Allergy
La Paz University Hospital, IdiPAZ
Paseo de la Castellana, 261
28046 Madrid, Spain
E-mail: juanalberto.luna@salud.madrid.org