Exacerbations among patients with asthma are largely dependent on the presence of multimorbidity

Short Title: Asthma exacerbations in the MEGA Cohort

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ABSTRACT

Introduction: Comorbidities can influence asthma control and promote asthma exacerbations (AE). However, the impact of multimorbidity in AE, through long-term follow-up in patients with asthma of different severity has been scarcely studied in real-life conditions.

Objective: To describe the epidemiological and clinical characteristics and predictive factors of AE in patients who had presented at least one AE in the last year among patients recruited in the MEchanism of Genesis and Evolution of Asthma (MEGA) project.

Methods: We carried out a detailed clinical examination, pulmonary function testing, fractional exhaled nitric oxide (FeNO), blood counts, induced sputum, skin prick-tests, asthma questionnaires, and multimorbidity assessment. For each subject, the number of moderate-severe AE in the preceding year was registered.

Results: 486 patients with asthma were included (23.7% mild, 35% moderate, 41.3% severe). 41.9% remained uncontrolled. 47.3% presented ≥1 moderate-severe AE, with mean annual exacerbation rate of 0.47±0.91 vs 2.11±2.82 in mild and severe asthma, respectively. 56.4% (66.6% among severe asthmatics) presented some comorbidity. Bronchiectasis, chronic rhinosinusitis with nasal polyps, atopy, psychiatric illnesses, hyperlipidaemia and hypertension were significantly related with AE. No associations were found for FeNO, blood eosinophils and total serum IgE. Sputum eosinophilia and a high-T2 inflammatory pattern were significantly associated with AE. Multivariable regression analysis showed significant association with asthma severity, uncontrolled disease and low pre-bronchodilator FEV_1/FVC.

Conclusions: The MEGA cohort found a high AE rate, which 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.

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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.

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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, AE can be life threatening, comprising a significant amount of the economic impact on the health system, loss of work productivity while worsening the patient's quality of life [2].

While a relationship exists between asthma control and risk of exacerbations, both terms are not synonymous [3]. For instance, AE are frequent events in severe asthma (SA) [4], but AE can also occur in patients with mild asthma, even in those with well-controlled disease [5]. Efforts to characterize patients with frequent exacerbations show that the aetiology is likely multifactorial. The best predictor of future AE is a history of previous exacerbations. In fact, the number of AE in the previous two years informs the probability of exacerbations in the next year [6]. Other core clinical outcomes and biomarkers have been also associated to a higher risk for AE (viral infection, environmental exposures, lack of adherence to treatment, presence of some multimorbidities, and eosinophilia in peripheral blood or sputum) [7].

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

METHODS

Data were analyzed from the observational MEGA prospective cohort trial patients with varying degrees of asthma severity [8] and its main methodological characteristics are described in the online repository section (supplementary E1). All patients signed an informed consent adherent to the Declaration of Helsinki and the protocol was approved by the institutional Ethics Committee of each centre.

We carried out a detailed clinical examination, pulmonary function testing, measurement of fractional exhaled nitric oxide (FeNO), blood counts, induced sputum, skin prick tests, asthma questionnaires, and multimorbidity assessment. Asthma-related co-morbidities were collected: atopy, allergic rhinitis, atopic dermatitis, bronchiectasis, diabetes, food allergies, heart disease, gastroesophageal reflux disease (GERD), hyperlipidaemia, hypertension, Non-Steroidal Anti-inflammatory Drugs (NSAID)-Exacerbated Respiratory Disease, obesity (Body Mass Index ≥30 kg/m^2), psychiatric illnesses (anxiety and depression), Chronic rhinosinusitis

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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, and increased rescue bronchodilator use for at least 2 days or more, but not severe enough to warrant treatment with systemic/oral corticosteroids (OCS) [1]. Severe asthma exacerbations (SAE) were defined as the occurrence of any of asthma-related hospital admission or emergency department (ED) attendance, or receiving a course of OCS for at least 3 days [1]. For each subject, the number of moderate-severe exacerbations in the preceding year was registered.

For statistical analysis, qualitative data were presented as absolute frequencies and percentages and quantitative data as means ± standard deviation (SD), minimum and maximum if they follow normality and by means of median and interquartile range if they did not. The association between qualitative variables were analyzed using the chi-square test or Fisher's exact test. For the comparison between qualitative and quantitative data, the Mann-Whitney or Kruskall-Wallis test for independent data, as non-parametric tests, were used. 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 presenting exacerbations, based on the probability of the Wald statistic. A complete model was created that included all variables statistically associated with the presence of exacerbations. Then, at each step, the analysis gradually removed variables from the regression model to find a reduced model that best explained the data. All statistic tests were considered bilateral and those including p-values lower than 0.05 were considered significant. Data were analyzed by the statistics software SAS 9.3 (SAS Institute, Cary, NC, USA).

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) with complete information in the electronic registry. 52.7% were non-smokers; 23.7% of the patients had mild asthma, 35% moderate asthma and 41.3% severe asthma. Overall, 41.9% of the patients remained uncontrolled according to GINA criteria, and 32.6% as determined by ACT score. Regarding exacerbations, 47.3% presented at least one moderate-severe AE in the last year, although only 15.8% presented a severe one. 15.5% had developed three or more exacerbations. Of the total number of patients who presented exacerbations, 18.6% required hospital admission in the last year and 9.8% of the patients, required ever in life at least one admission to the intensive care unit. Severity of asthma influenced the number of AE. Patients with SA experienced a mean of 2.11±2.82 AE in the previous year while patients with mild asthma presented 0.47±0.91. In total, 8.6% of the included subjects received OCS on a daily treatment regimen, with significantly more visits to the ED than those patients with no daily OCS treatment [(1.60±2.26) vs (0.49±1.29) ($p<0.001$)].

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56.4% patients (66.6% among severe asthmatics) presented any comorbidity, and this issue was significantly associated with experiencing an AE. Table 2 represents the prevalence of different comorbidities in the MEGA population and their relation with experiencing an AE in the previous year. In summary, obesity (BMI >30), was found in 19.8% of patients. Bronchiectasis were presented in 7% of patients (n = 36), with 67% of them (n = 24) having severe asthma. CRSwNP affected 30% of the patients, and up to 43.3% among those with SA ($p < 0.001$). Among the patients with SA with any comorbidity, 77.1% had presented an exacerbation in the last year, compared to 53.7% of those who did not present any relevant comorbidity ($p= 0.001$). The presence of bronchiectasis was significantly related with suffering an AE in the previous year. In fact, in severe asthmatics this risk increased. 91.7% of patients with severe asthma and bronchiectasis experienced an AE while only 66.7% in those severe asthmatics without them ($p= 0.016$). Other related comorbidities with AE were atopy, present in 74.3% of the population, psychiatric illnesses [9], hyperlipidaemia and hypertension. Interestingly, we did not find associations with these last two comorbidities when we analysed separated the severe asthmatic subgroup.

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

Finally, the multivariable regression analysis demonstrated a significant association between suffering an AE in the previous year and the severity of asthma, uncontrolled disease and increased obstruction to airflow expressed by the FEV_1/FVC pre-bronchodilator (Table 3).

DISCUSSION

Most asthma exacerbations 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 asthma exacerbations 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 asthma exacerbations and the recognition of indicators of potential severity offer the opportunity to perform targeted management, establishing the most appropriate treatment to improve asthma control and the most effective preventive measures for asthma exacerbations.

The current analysis offers data from the largest cohort of confirmed asthmatic patients in real world conditions in Spain. The strengths of the study certainly include the longitudinal design and well-characterized asthmatic patients, with an objective diagnosis of asthma. The large size of the cohort strengthens the robustness of the results to study the clinical and

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biological variables that are associated with exacerbation-prone asthma and to construct a biomarker and clinical prediction model for exacerbation rates.

In this cohort, it stands out that 47.3% of the population included has had an exacerbation in the last year. Moreover, this population presents an average annualized SAE rate of 1.20. Risk factors for frequent asthma exacerbations span social, clinical, comorbid, biological, and environmental domains [13]. We have 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 described throughout the world, and recognized in guidelines as risk factors for exacerbations [3-14]. AE can arise regardless of the severity of asthma. Although exacerbations 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) exacerbations in the past year. It is remarkable because we have not observed 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, a greater number of comorbid conditions have been associated with a more frequent susceptibility to exacerbations, including 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 any comorbidities but only some of them have been associated with AE in this study. We have observed a significant impact of CRSwNP on exacerbations. CRSwNP is frequently associated with more severe asthma and more prone to exacerbations [16]. It should be noted that the prevalence of CRSwNP rises up to 30% in our population, which is similar or even higher than the data published in other cohorts [17-18], considering that only 41.4% of the subjects in the MEGA trial were severe asthmatics. Patients with moderate-severe asthma with CRSwNP usually have higher levels of peripheral blood eosinophils and FeNO [19], although in our study we have not observed that any of both markers could increase the risk for 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 having an exacerbation of asthma.

Metabolic syndrome (MS) is another relevant chronic comorbid condition associated with asthma [20-21]. The association of an increase in cardiovascular risk and asthma is well known [22]. Peters et al, in a cohort study of patients with exacerbation-prone asthma, suggested that MS is the key factor of AE [6]. In our study, as in a comparable Italian cohort [23], BMI does not seem to play a key role in the increased occurrence of asthma attacks, while dyslipidaemia is clearly associated. Dyslipidaemia can be the cause of this association but also the consequence of a more intense chronic inflammatory status [24]. However, there are controversial results from different studies on how MS might affect asthma exacerbations, particularly in the elderly and in late-onset asthma. In addition, in our cohort, diabetes does not seem to have a significant implication in the risk of exacerbations, but we consider that the low prevalence of diabetes in the sample (less than the 14,8% in the adult population in Spain [25]) could have influenced our results. On the contrary, in a recent Japanese

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retrospective study, dyslipidaemia was detected as a factor associated with a reduction in the risk of exacerbations [26]. Statin use has been reported to reduce asthma-related emergency care, hospitalizations, and systemic steroid use in asthma patients in several retrospective studies, suggesting some anti-inflammatory effects of statins [27-28]. Similarly, a recent meta-analysis suggested that metformin decreased the risk of asthma-related ED visits for patients with concurrent asthma and diabetes [29]. Unfortunately, we did not analyse 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 that treatment.

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

Regarding adherence to treatment, there was surprisingly 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, treatment adherence was measured in this study using the Morisky-Green questionnaire that is not specific and less sensitive for inhalation therapy.

Considering bronchial inflammation and its influence on exacerbation risk, total sputum and blood eosinophil count and FeNO level are surrogate biomarkers for type 2 airway inflammation and have been associated with increased risk for developing an AE [33]. Eosinophilic airway inflammation is more closely associated with AE and OCS responsiveness 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 SAE [37]. In our study we found that sputum eosinophilia clearly correlates with the risk of experiencing AE, while blood eosinophils were not associated with exacerbations in this population. Recently, variability in eosinophil count values has showed a better association with ED visits and hospitalizations than the counting values, particularly in those patients with higher variability [38]. Probably, our results reinforce the need to measure eosinophils in sputum, a more sensitive method to properly define the characteristics of the mucosal inflammation in asthma [39]. Moreover, FeNO levels, although showed a good correlation with blood eosinophils, had no significant influence on AE risk. We consider that our data reflect the situation at the study inclusion, with many possible factors influencing the pattern of both biomarkers. Interestingly, it has been confirmed in our cohort that those patients with the highest T2 inflammatory pattern (FeNO ≥20 ppb AND blood

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eosinophilia AND sensitization to allergens), experienced significantly more exacerbations and 25% experienced at least one severe AE (p = 0.019).

The study has a number of 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 a high asthma exacerbation rate in this patient population with different severity levels, which was strongly associated with multimorbidities, such as bronchiectasis, MS and CRSwNP, asthma severity and poor asthma control. Other important risk factors for exacerbations were the presence of higher number of sputum eosinophils, the presence of a very high T2-inflammatory pattern as well as a corticosteroid use among severe asthma patients.

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Conflict of Interest

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

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Table 1. Demographic and clinical data of the MEGA cohort. P value <0.05 expresses significant association with having at least one moderate-severe exacerbation in the previous year.

		p value
Age (Mean ± SD)	47.5 ± 12.83	**p = 0.012**
Female (%)	66.3	P = 0.210
Asthma duration, years (mean ± SD)	24.3 ± 15.70	P = 0.781
Severity (GINA step)		**P < 0.001**
Mild - Step 1-2 (%)	23.7	
Moderate - Step 3 (%)	35	
Severe -Step 4-5 (%)	41.4	
Current asthma control (GINA)		**P < 0.001**
Not controlled (%)	20.2	
Partially controlled (%)	21.7	
Controlled (%)	58.1	
Asthma Control Test (ACT) (mean ± SD)	20.29 ± 4.86	**P < 0.001**
< 20 (%)	32.6	
20-24 (%)	43.5	
25 (%)	23.9	
Moderate-severe exacerbations last year (mean ± SD)	1.20 ± 2.14	
None (%)	52.7	
Moderate (%)	31.5	
Severe (%)	15.8	
Mild asthma (mean ± SD)	0.47 ± 0.91	
Moderate asthma (mean ± SD)	0.61 ± 1.206	
Severe asthma (mean ± SD)	2.11 ± 2.82	
Corticosteroids bursts in the last year [a] (mean ± SD)	1.47 ± 4.76	
Emergency department visits last year (mean ± SD)	0.85 ± 1.68	
Mild asthma (mean ± SD)	0.19 ± 0.63	
Moderate asthma (mean ± SD)	0.35 ± 0.99	
Severe asthma (mean ± SD)	1.20 ±2.04	
Previous admission in ICU ever (mean ± SD)	0.09 ± 0.36	NA
≥ 3 % eosinophils in sputum (%)	59.3	**P = 0.002**
Mild asthma %	23.2	
Moderate asthma %	32.6	
Severe asthma %	44.2	
≥ 61% neutrophils in sputum (%)	20,5	P = 0.401
Mild asthma %	32	
Moderate asthma %	18,1	
Severe asthma %	20,8	
Eosinophils in blood cells/mm^3 (mean ± SD)	339.68 ± 329.31	P = 0.865
≥150 cells/mm^3 (%)	77,2	P = 0.511
≥300 cells/mm^3 (%)	49.2	P = 1.000
Total serum IgE (kU/L)	421.61 ± 830.74	P = 0.898
FeNO, ppb (mean ± SD)	42.77 ± 37.05	P = 0.650
≥ 20 ppb (%)	72.3	P = 0.803
High T2 profile [b] (%)	27.5	**P = 0.019**
FEV_1 Pre-BD (%)	85.45 ± 21.13	**P < 0.001**
FVC Pre-BD (%)	100.06 ± 46.31	**P < 0.001**
FEV_1/FVC Pre-BD (%)	78.88 ± 18.82	**P = 0.002**

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FEV_1 Post-BD (%)	85.96 ± 33.01	**P < 0.012**
FVC Post-BD (%)	92.82 ± 34.90	**P = 0.004**
FEV_1/FVC Post-BD (%)	79.10 ± 22.02	**P = 0.002**
Good adherence to treatment [c] (%)	64.8	P = 0.848
Maintenance systemic corticosteroids (%)	8.6	**P < 0.001**
Biological therapy (%)	17.7	**P < 0.001**

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, non-analyzed.

[a] Systemic corticosteroids treatment for at least 3 consecutive days. [b] High T2 inflammatory pattern: FeNO ≥20 ppb AND eosinophils in blood ≥300 cells/mm^3 AND atopy. [c] Adherence was assessed using a Spanish validated version of the Morisky-Green test.

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Table 2. Comorbidities in the MEGA cohort. P value <0.05 expresses significant association with having at least one moderate-severe exacerbation in the previous year.

		p value
Comorbidities (%)	56.4	**P < 0.001**
Smoking habit		P = 0.210
Non-smoker (%)	52.7	
Smoker (%)	8.5	
Passive (%)	7.6	
Ex-smoker (%)	31.2	
Bronchiectasis (%)	7.2	**P < 0.001**
Diabetes (%)	4.7	P = 0.086
Heart disease (%)	2.9	P = 0.848
Hyperlipidaemia (%)	15	**P = 0.021**
Hypertension (%)	12.6	**P = 0.001**
BMI Kg/m^2**(**mean ± SD)	27.08 ± 5.32	p = 0.684
BMI ≥ 30 (%)	19.8	P = 0.110
Psychiatric illness (%)	12.2	**P < 0.001**
OSAHS (%)	4.3	P = 0.670
Thyroid disease (%)	10.3	P = 0.655
Atopy [a] (%)	74.3	**P < 0.001**
Skin prick tests		
Animal dander (%)	13.1	NA
Molds (%)	2.7	NA
House dust mites (%)	62.4	NA
Pollen (%)	18.5	NA
Others (%)	2.2	NA
Allergic rhinitis (%)	52.9	P = 0.855
Atopic dermatitis (%)	10.7	P = 0.304
Chronic rhinosinusitis		
with nasal polyps (%)	30	**P < 0.001**
without nasal polyps (%)	8.8	P = 0.527
NSAID-Exacerbated Respiratory Disease (%)	15	P = 0.161
Food allergy (%)	4.9	P = 0.835

Abbreviations: BMI, Body Mass Index; NA, non-analyzed; NSAID, Non-Steroidal Anti-Inflammatory Drugs; OSAHS, Obstructive Sleep Apnea–Hypopnea Syndrome.

[a] Prick test and/or specific IgE positive to a common allergen.

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Table 3. A) Results of multivariable logistic regression analysis. Dependent variable: exacerbations in the last year (yes). B) Results in the severe asthma population. P value <0.05 expresses significant association.

A

Variable	OR	OR CI 95%	p value
Severity (GINA therapeutic step)	2.193	(1.209,3.979)	0.010
Current asthma control (GINA)	0.300	(0.162,0.556)	<0.001
Pre-BD FEV_1/ FVC (%)	0.964	(0.933,0.997)	0.031

B

Variable	OR	OR CI 95%	p value
Current asthma control (GINA)	0.330	(0.202, 0.541)	<0.001
Maintenance systemic corticosteroids	4.001	(1.082, 14.795)	0.038
Presence of comorbidities	2.427	(1.079, 5.461)	0.032

Abbreviations: CI, confidence interval; FEV_1, Forced Expiratory Volume in 1 second; FVC, Forced Vital Capacity; GINA, Global Initiative for Asthma; OR, odds ratio.

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