Factors Associated with Frequent Exacerbations in the UK Severe Asthma Registry

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TITLE

Factors associated with frequent exacerbations in the UK Severe Asthma Registry

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COMPETING INTERESTS

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ABBREVIATIONS

ACQ: Asthma Control Questionnaire

ATS: American Thoracic Society

BMI: Body mass index

CPRD: Clinical Practice Research Datalink

ERS: European Respiratory Society

FE: frequent exacerbator

FeNO: fractional exhaled nitric oxide

FEV_1: forced expiratory volume in one second

FVC: forced vital capacity

IQR: inter-quartile range

OCS: oral corticosteroids

OPCRD: Optimum Patient Care Research Database

RCT: randomized controlled trial

SABA: short-acting beta-agonist

UKSAR: United Kingdom Severe Asthma Registry

ABSTRACT

Background: Frequent exacerbations are an important cause of morbidity in patients with severe asthma.

Objective: Our aim was to identify factors associated with frequent exacerbations in a large well-characterized severe asthma population and determine whether factors differed in patients treated with and without maintenance oral corticosteroids (OCS).

Methods: Adults with severe asthma from specialized asthma centers across the UK were recruited to the UK Severe Asthma Registry (UKSAR). Demography, co-morbidities and physiological measurements were collected. We conducted univariable and multivariable logistic regression analyses to identify factors associated with frequent exacerbations, defined as ≥3 exacerbations treated with high-dose systemic corticosteroids in the past year.

Results: Of 1592 patients with severe asthma from the UKSAR, 1137 (71%) were frequent exacerbators (FE) and 833 (52%) were on maintenance OCS. FE were more likely to be ex-smokers, have gastroesophageal reflux disease (GERD), higher Asthma Control Questionnaire-6 (ACQ-6) score and blood eosinophilia. Multivariable regression analyses showed ACQ-6 score >1.5 (OR 4.25, p<0.001), past smoking history (OR 1.55, p=0.024) and FeNO >50ppb (OR 1.54, p=0.044) were independently associated with frequent exacerbations. Past smoking history correlated with frequent exacerbations only in patients on maintenance OCS (OR 2.25, p=0.004), whereas ACQ-6 score >1.5 was independently associated with frequent exacerbations in those treated with and without maintenance OCS (OR 2.74, p=0.017 and OR 6.42, p<0.001, respectively).

Conclusion: Several factors were associated with frequent exacerbations in a large UK severe asthma registry population. High ACQ-6 score had the strongest association with frequent exacerbations irrespective of maintenance OCS status.

HIGHLIGHT BOX

1. What is already known about this topic?

- Risk factors for frequent asthma exacerbations include high T2 biomarkers (FeNO and blood eosinophil count) and asthma associated conditions (obesity and rhinitis) in clinical trial patients or asthma populations with mixed disease severity.

2. What does this article add to our knowledge?

- Poor symptom control has the strongest correlation with frequent exacerbations in patients with severe asthma, good adherence, and treated comorbidities.
- The relationship between T2-high biomarkers and frequent exacerbations is less apparent in patients on maintenance OCS.

3. How does this study impact current management guidelines?

- Tools to aid identification of poor symptom control in severe asthma are key to identifying patients with higher risk of frequent exacerbations.

KEY WORDS

Severe asthma, exacerbations, frequent exacerbations, asthma control, ACQ.

BACKGROUND

Severe exacerbations are an important cause of morbidity and mortality in asthma. Frequent exacerbations are common in patients with severe asthma and are associated with poorer quality of life and higher health care costs.(1-3) Risk factors for exacerbations reported from studies of severe asthma include past history of severe exacerbations, high body mass index (BMI), chronic sinusitis, gastroesophageal reflux disease (GERD), psychological stress, a history of cigarette smoking, reduced lung function, blood or sputum eosinophilia and raised fractional exhaled nitric oxide (FeNO).(2, 4-10) It is uncertain whether risk factors identified from observational studies of participants recruited to clinical trials or cohorts of severe asthma, which have strict inclusion criteria, are generalizable to a population of adults with severe asthma managed in clinical practice. Secondly, elevated FeNO and peripheral eosinophilia are markers of local and systemic inflammation in asthma, which are partially or completely suppressed by inhaled and oral corticosteroid (OCS) treatment. The predictive value of these type 2 inflammatory markers for exacerbations in severe asthma patients, of whom a substantial proportion is taking continuous daily OCS, is unknown.

Prevention of frequent exacerbations and of persistent asthma symptoms are key goals for establishing asthma control. The Asthma Control Questionnaire (ACQ) is a validated tool for assessing asthma control based on patient self-reported symptoms; a higher score indicates poorer control.(11) Post-hoc analysis of clinical trial data showed a positive correlation between ACQ score and exacerbation rates.(12, 13) The correlation between persistent symptoms and frequent exacerbations in patients with severe asthma is not well established. Replication of these findings in a well-characterized severe asthma population not recruited into clinical trials would support the use of ACQ in clinical practice to determine the risk of frequent exacerbations. This would, in turn, offer useful guidance for management planning.

The UK Severe Asthma Registry (UKSAR) was developed in 2015 to collect standardized data on patients referred to specialist asthma services across England, Scotland and Northern Ireland. Specialist centers identified patients with well-characterized severe refractory asthma for inclusion in the registry from subjects with difficult-to-control asthma referred by primary and secondary care centers. The registry provides observational data on the

clinical characteristics, lung function and inflammatory variables in patients with severe asthma of whom half are taking continuous daily OCS. We hypothesized, in a UK severe asthma registry population, asthma symptom control is independently associated with frequent exacerbations and maintenance OCS use will affect factors which correlate with frequent exacerbations.

METHODS

Study population

All subjects on the UK Severe Asthma Registry (UKSAR) who were between the age of 18 and 80 years at first assessment during 2015 or later were included in the study. No other exclusion criteria were applied. UKSAR is a web-based database collecting data from severe asthma patients attending specialist asthma centers across the UK.(14) Severe asthma is defined as asthma which requires high-dose inhaled corticosteroids plus at least one other preventor therapy and/or maintenance OCS.(15) Maintenance OCS is defined as daily use of OCS to maintain asthma control. All subjects provided written informed consent prior to data collection in the registry. Data from 13 specialist centers were included in the analysis. Approval from the UKSAR Steering Committee was obtained prior to data analysis.

Study design

A retrospective analysis of cross-sectional pseudoanonymized data from UKSAR was used to identify factors associated with frequent exacerbations. Variables used in the analysis were recorded at the initial systematic assessment and included demography, medical history, spirometry and inflammatory biomarkers. Initial systematic assessments were undertaken at specialist centers and defined as baseline in this study. The number of severe exacerbations during the 12 months previous to baseline assessment was recorded and used to stratify patients into frequent exacerbators (FE) and non-FE, defined as those who had ≥3 and <3 severe exacerbations, respectively.(7, 9) Severe exacerbation was defined as a worsening of asthma symptoms which led to at least three consecutive days of OCS treatment or hospital admission. OCS courses within seven days of each other were counted as one exacerbation.

Study assessments

Twenty-eight potential risk factors for frequent exacerbations were evaluated in the severe asthma cohort. Several co-morbidities were assessed, including nasal polyps, GERD, eczema, cardiac disease, depression and anxiety. GERD was diagnosed by physicians based on clinical symptoms or previous eosophagogastroduodenoscopy findings. Obesity was defined as BMI ≥30 Kg/m^2. Continuous variables were categorized to enable detection of non-linear effects. ACQ, a 7-component questionnaire, was used to evaluate asthma symptoms control. The

score is based on patient self-assessment of asthma symptoms, short-acting beta-agonist (SABA) use over the past week and pre-bronchodilator FEV_1 percentage of predicted. The latter is not required in a shortened version of the questionnaire (ACQ-6). In both versions, a score of 0 to 0.75, 0.75 to 1.5 and >1.5 indicates well, intermediate and poorly controlled asthma symptoms, respectively. We used ACQ-6 score as a measure of symptom control given spirometry results were not strictly pre-bronchodilation. Spirometry was performed in a clinical setting therefore treatment restrictions were not applied prior to testing. Baseline blood eosinophil count was recorded at the initial assessment. Highest ever blood eosinophil count was collected retrospectively. Serum total IgE concentrations and FeNO were also measured.

Assessment of treatment adherence

Data on treatment adherence were collected for patients added to the UKSAR. Treatment adherence was assessed using clinical judgement in conjunction with FeNO suppression testing, prescription refill records, serum prednisolone and cortisol measurements where appropriate. In general, the criteria for treatment adherence at the participating centers is over 70-80% use of preventer therapy. FeNO suppression testing is a novel and effective way of identifying non-adherence to inhaled corticosteroids using remote monitoring technology (Vitalograph INCA^{TM} device and Aerocrine NIOX Vero). A positive FeNO suppression test suggests previous suboptimal treatment adherence, however a small proportion of patients are recognized as having severe asthma despite positive FeNO suppression testing. (16)

Statistical analyses

Descriptive statistics were calculated using means (with standard deviations), medians (with interquartile ranges) and counts (with percentages) as appropriate. Initial multivariable logistic regression models were built including variables which have been previously associated with increased exacerbations, and those with strong univariate associations. Variables were removed from the initial multivariable model using modified backwards stepwise selection. All models included year of presentation at the clinic and hospital site as fixed effects. Variables examined for association with frequent exacerbations and included in multivariable logistic regression analysis are listed in the online repository file (Table E9 and E10). Model discrimination was assessed using the receiver operating characteristic

(ROC) curve, and goodness-of-fit was quantified using the area under the curve. We assessed bias using 10-fold internal cross validation.(17)

Our primary analysis was based on complete cases however we used multiple imputation with chained equations, which assumes that the data was missing at random, to assess the impact of missing data.(18) We conducted additional sensitivity analysis using a cut-off of ≥2 or ≥4 exacerbations to define a frequent exacerbator. All analyses were conducted using the STATA 16 software package (StataCorp, Texas, USA).

RESULTS

Patient characteristics

Of 1,592 patients in the UKSAR included in the study, 1,137 (71.4%) were frequent exacerbators and 455 (28.6%) were non-frequent exacerbators. Over the previous year, most patients (60.0%) had four or more severe exacerbation and only 11.6% of patients had no exacerbations. 1005 (63.1%) patients were female and 1214 (76.3%) were Caucasian. Fifty-two percent of patients were taking maintenance OCS. Sixty-four percent of all patients included in the study went on to receive biologic therapy [Table 1].

Key patient characteristics for FE and non-FE are shown in Table 1. The two groups were similar in gender and ethnicity distribution. FE were more likely to be ex-smokers (29.2% vs 21.7%, p=0.028), have GERD (21.3% vs 14.4%, p=0.006), higher ACQ-6 score (mean [SD] 3.1[1.3] vs 2.4[1.4], p<0.001) and baseline blood eosinophil count (median $0.37x10^9$ cells/L vs $0.30x10^9$ cells/L, p=0.006). Highest ever median blood eosinophil count was $0.6 x10^9$ cells/L for both FE and non-FE (p=0.434). Non-FE were more likely to be taking maintenance OCS or have allergic rhinitis. There were no differences between the two groups for BMI, depression or anxiety, FeNO and total IgE level. The difference in percentage of predicted FEV_1 between the two groups was not clinically significant (66.0% vs 68.6%, p=0.045).

Factors associated with frequent exacerbations

An association between frequent exacerbations and several factors were identified using univariate regression analyses. Factors which correlated with frequent exacerbations included ACQ-6 score >1.5 (OR 3.16, p<0.001), past smoking history (OR 1.49, p=0.003) and GERD (OR 1.61, p=0.002). High blood eosinophil count (>$0.45x10^9$ cells/L) was associated with frequent exacerbations (OR 1.49, p=0.006), but elevated FeNO (>50ppb) was not associated with increased exacerbations (OR 1.24, p=0.144). Obesity, history of nasal polyps, depression or anxiety and low FEV_1 percentage of predicted did not correlate with frequent exacerbations. Unsurprisingly, treatment with maintenance OCS was associated with reduced likelihood of frequent exacerbations (OR 0.69, p=0.001) [Table 2].

In multivariable regression analyses, the correlation between ACQ-6 score and frequent exacerbations remained significant (p<0.001). In comparison to patients who had well controlled symptoms, an ACQ-6 score >1.5 increased the odds for frequent exacerbations by

over 4-fold. The association between frequent exacerbations and past smoking history also remained significant (OR 1.55, p=0.024). Interestingly, when adjusted for other factors, peripheral eosinophilia was no longer associated with frequent exacerbations (OR 1.09, p=0.683), whereas the relationship between elevated FeNO (>50ppb) and frequent exacerbations became stronger (OR 1.54, p=0.044). The odds for having three or more exacerbations in a year reduced by 42% in patients treated with maintenance OCS compared to those without maintenance OCS [Table 2, Figure 1].

Factors associated with frequent exacerbations in patients treated with and without maintenance oral corticosteroids

Factors associated with frequent exacerbations differed in patients treated with and without maintenance OCS. In patients not on maintenance OCS, univariate regression analyses showed ACQ-6 score of >1.5 (OR 4.70, p<0.001), GERD (OR 1.64, p=0.028), FeNO >50ppb (OR 1.63, p=0.022) and blood eosinophil count >0.45x10^9 cells/L (OR 1.66, p=0.035) correlated with increased exacerbations. Multivariable regression analyses showed ACQ-6 score of >0.75 was the only independent factor associated with frequent exacerbations in patients not on maintenance OCS [Table 3 and Figure 2a]. In patients treated with maintenance OCS, ACQ-6 score >1.5 (OR 2.74, p=0.017) and past smoking history (OR 2.25, p=0.004) correlated with frequent exacerbations after adjustment for other factors [Table 4 and Figure 2b]. High FeNO and blood eosinophil count did not correlate with frequent exacerbations in patients on maintenance OCS. ACQ-6 score >1.5 was independently associated with increased exacerbations irrespective of maintenance OCS status. However, the odds of having frequent exacerbations was much higher in patients not treated with maintenance OCS versus those who were [OR 4.70 vs OR 2.74].

Asthma Control Questionnaire

The majority of UKSAR patients completed an ACQ-6 at initial assessment (n=1,381, 87%), 1341 (97%) of whom performed baseline spirometry on the same day whilst on usual asthma treatments. ACQ-7 was calculated using FEV_1 percentage of predicted from baseline spirometry and ACQ-6 score. The majority of FE (85.6%) and non-FE (69.2%) had an ACQ-6 score of >1.5 [Table E1]. Therefore, exploratory analysis was performed using a higher ACQ-6 score cut-off point of 2.5. This showed the odds of having frequent exacerbations is much greater in those with very high ACQ-6 scores (ACQ-6 score >2.5, OR 5.10, p<0.001) compared to those with

scores just above the validated threshold for poorly controlled symptoms (ACQ-6 score 1.51-2.50, OR 3.10, p<0.001) [Table E2]. We also compared the predictive properties of ACQ-6 and ACQ-7 for frequent exacerbations using AUROC analysis. ACQ-6 was as good a predictor for frequent exacerbation as ACQ-7 (AUC 0.710 vs 0.715) [Figures E1 and E2].

Sensitivity analysis and specialist centers

The internally cross-validated AUC was 0.70 suggesting little test error. Our conclusions were broadly unchanged when using multiple imputation to account for missing, or when using a threshold of ≥2 or ≥4 exacerbations as the threshold to define a frequent exacerbator [Table E3]. The distribution of FE and non-FE across all specialist centers is shown in Table E4.

Treatment adherence

Ten percent of the UKSAR population were deemed to have severe asthma with suboptimal treatment adherence. To confirm the correlation between frequent exacerbations and high ACQ-6 score for patients with severe asthma, we repeated our analyses in a more selective cohort within the UKSAR who had severe asthma and no adherence issues or missing data on treatment adherence. Of 1,592 patients included in our total study population, 1,202 patients (75.5%) fulfilled the ERS/ATS criteria for severe asthma. Results from univariable and multivariable regression analyses are shown in tables E5 to E8. Compared to the whole study population, the relationship between past smoking history and FE was weaker (OR 1.52, p=0.058) in patients with ERS/ATS defined severe asthma. However, the correlation between ACQ-6 score of >1.5 and frequent exacerbations remained significant (ACQ-6 score 1.5-2.5, OR 2.88, p=0.002; ACQ-6 score >2.5, OR 5.54, p<0.001).

DISCUSSION

We showed, in a large well-characterized severe asthma population, poor symptom control correlated significantly with frequent exacerbations. The odds of having three of more exacerbations over a 12-month period increased by 4-fold in patients with an ACQ-6 score >1.5 compared to those who had a score <0.75. The association between high ACQ-6 score and frequent exacerbations remained significant after adjustment for other factors. In particular, high ACQ-6 score correlated with frequent exacerbations regardless of maintenance OCS status. Our findings support the predictive value of symptom control for frequent exacerbations previously demonstrated in clinical trial patients.(13, 19, 20) Type 2 inflammatory markers such as FeNO and blood eosinophil count were associated with frequent exacerbations, but this association was most prominent in severe asthma patients not taking maintenance OCS and in isolation prior to adjustment for other factors. Past smoking history correlated with frequent exacerbations, particularly in patients receiving maintenance OCS. GERD is an important co-morbidity which contributes to frequent exacerbations but was not independent of other variables. To our knowledge, this is the largest study of factors associated with frequent exacerbations in a well-characterized severe adult asthma population not recruited into clinical trials.

Previous literature reported risk factors in populations which included patients with severe asthma. (4-10) Severe asthma is often included within a wider group known as difficult-to-control asthma. Distinguishing severe asthma from difficult-to-control or mild/moderate asthma is important because management options differ between these groups. In a difficult-to-control asthma population, Ten Brinke and colleagues reported psychological dysfunction and nasal sinus disease as independent risk factors for frequent exacerbations.(9) This is unsurprising given comorbidities are a significant cause of difficult-to-control asthma. A combined search of the UK OPCRD and CPRD registries for patients with mild to severe asthma showed blood eosinophil count was the best predictor of frequent exacerbations. Other risk factors in this primary care population included older age, female gender, obesity, reflux, rhinitis, anxiety/depression.(21) Results were similar in the SARP-3 cohort, which included children and adults on various levels of asthma treatment.(7) These risk factors were identified in populations which included those with mild asthma and were not specific to severe asthma. A smaller prospective study of

mild/moderate and severe asthma patients showed ACQ score >1.36, FeNO >45ppb and a history of smoking were significantly associated with increased risk of two or more exacerbations during the follow-up year.(10) Only those who had at least one exacerbation in the preceding year were included and the majority of patients had severe asthma. These findings were confirmed in the present study, which further elucidated the relationship between FeNO and frequent exacerbations. The difference between our findings and those from previous studies is likely due to disparity in asthma cohorts. Our study suggests in an asthma population with severe disease, good adherence to high dose inhaled corticosteroids and adequately managed comorbidities, symptom control then becomes the main indicator for frequent exacerbations.

Type 2 inflammatory biomarkers were associated with frequent exacerbations in the present study, but the strength of this association was subject to influence by other factors such as asthma treatments. Previous studies identified elevated FeNO and blood eosinophilia as independent risk factors for frequent exacerbations, however results were inconsistent.(7, 10, 21) Similarly, we showed in a large severe asthma registry cohort, blood eosinophilia correlated with frequent exacerbations prior to adjustment for other variables, but the association between high FeNO and frequent exacerbations only became significant when other variables were taken into account. The relationship between type 2 biomarkers and exacerbation risk became clearer when we performed subgroup analyses based on maintenance OCS use. Individually, FeNO and blood eosinophils were associated with increased exacerbations in those not on maintenance OCS. In patients on maintenance OCS, type 2 biomarkers added little value for exacerbation prediction. Even in those not exposed to maintenance OCS, type 2 biomarkers were not superior to symptoms control when adjusted for confounding factors. The dissociation between exacerbation rates and T2 biomarkers, particularly in patients on maintenance OCS, may reflect the prevalence of infective non-T2 events which are known to occur in severe asthma.(22-24)

Interpretation of the present study findings need to take several factors into account. This is a registry study which collected spirometry results obtained in a clinical setting. Lung function was generally measured whilst on treatment because patients were not routinely asked to withhold asthma treatments prior to testing. Interpretation of the relationship between lung function and frequent exacerbations should take this into consideration.

Secondly, the UKSAR population is enriched with patients who later received biologic therapy. Patients not on maintenance OCS need ≥4 exacerbations over the past year to qualify for biologic treatment in the UK. The present study cohort will as a result represent the most severe cohort of asthma patients of whom many will have an eosinophilic and/or atopic phenotype. Thirdly, the number of current smokers recruited into the UKSAR was very small, therefore should have limited effect on suppressing FeNO levels. The majority of patients went on to receive biologic therapy after specialist assessment. However, 7.3% of patients were on omalizumab at baseline and biologic treatment was not included in our multivariable model. Finally, and perhaps most importantly, this is a retrospective analysis which used historical exacerbations for stratification of FE and non-FE groups. The correlations identified between frequent exacerbations and other factors in our study does not therefore directly translate to causation. There may also be a dissociation between baseline type-2 biomarkers and exacerbation frequency given treatment changes made during the exacerbation year can affect type-2 inflammatory marker measurements.(25) Nevertheless, we identified a clear association between uncontrolled asthma symptoms and frequent exacerbations. A real-world prospective study is required to confirm the causative effect of uncontrolled asthma symptoms on future exacerbation risk.

A major strength of this study is our findings are applicable to patients with severe asthma in clinical practice, given the lack of entry criteria. ACQ-6 is an accessible questionnaire which has been so far limited to use in specialist clinics and research for evaluation of current asthma control and benefits of therapeutic interventions. In contrast to other biomarkers, ACQ-6 can also be measured remotely.(26) ACQ-6 can be utilized in clinical practice to help identify patients most at risk of frequent exacerbations alongside other clinical assessments. Focus had previously been given to the co-morbidities as the key risk factors for frequent exacerbations. However, we have demonstrated in patients with severe asthma, on or off maintenance oral steroids, poor control of asthma had the strongest correlation with frequent exacerbations. Successful management of poorly controlled symptoms with biologic therapy, macrolides or other novel treatments can prevent future exacerbations, thus reducing morbidity and mortality.

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491 **TABLES**

492

493 **Manuscript title:**

494 Factors associated with frequent exacerbations in the UK Severe Asthma Registry

495

496

497 **Table 1.** Baseline characteristics for all severe asthma patients and comparison of baseline
498 characteristics in frequent exacerbators and non-frequent exacerbators.
499

	n	All severe asthma patients (n=1592)	Non-frequent Exacerbator (n=455)	Frequent Exacerbator (n=1,137)	p-value[†]
Age at first assessment (years) [Mean (SD)]	1592	49.4 (14.4)	51.0 (14.2)	48.8 (14.5)	**0.008**
Age at onset of symptoms (years) [Mean (SD)]	1393	23.9 (19.0)	25.5 (19.6)	23.3 (18.7)	0.059
Female (%)	1005	1005 (63.1%)	279 (61.3%)	726 (63.9%)	0.344
Ethnicity (%)	1579				0.685
Caucasian		1214 (76.9%)	343 (76.1%)	871 (77.2%)	
South East Asian		92 (5.8%)	24 (5.3%)	68 (6.0%)	
North East Asian		61 (3.9%)	18 (4.0%)	43 (3.8%)	
African		79 (5.0%)	22 (4.9%)	57 (5.1%)	
Mixed		14 (0.9%)	7 (1.6%)	7 (0.6%)	
Other		119 (7.5%)	37 (8.2%)	82 (7.3%)	
BMI Kg/m^2 [Mean (SD)]	1559	30.6 (7.0)	30.1 (6.6)	30.8 (7.1)	0.065
Smoking status (%)	1564				**0.028**
Never smoked		1084 (69.3%)	333 (74.5%)	751 (67.2%)	
Ex-smoker		423 (27.0%)	97 (21.7%)	326 (29.2%)	
Current smoker		57 (3.6%)	17 (3.8%)	40 (3.6%)	
Pack years smoked* (years)	391	0 (0,1)	0 (0,0)	0 (0,3)	**0.007**
Atopic disease (%)	1581	976 (61.7%)	282 (62.4%)	694 (61.5%)	0.940
Eczema (%)	1559	59 (3.8%)	21 (4.7%)	38 (3.4%)	0.315
Rhinitis (%)	1563	136 (8.7%)	46 (10.3%)	90 (8.1%)	0.345
Allergic rhinitis (%)	1558	97 (6.2%)	41 (9.2%)	56 (5.0%)	**0.009**
Chronic rhinitis (%)	1555	3 (0.2%)	1 (0.2%)	2 (0.2%)	0.962
Nasal polyps (%)	1560	291 (18.7%)	94 (21.1%)	197 (17.7%)	0.298
Gastroesophageal reflux (%)	1563	302 (19.3%)	64 (14.4%)	238 (21.3%)	**0.006**
Depression or anxiety (%)	1562	125 (8.0%)	33 (7.4%)	92 (8.2%)	0.730
Hospital admissions for asthma in last 12 months*	1572	0 (0,1)	0 (0,1)	0 (0,2)	**<0.001**
Number of invasive ventilation events ever*	1398	0 (0,0)	0 (0,0)	0 (0,0)	0.267
Blood eosinophil count* (x10^9 cells/L)	1571	0.34 (0.17,0.60)	0.30 (0.11,0.55)	0.37 (0.20,0.60)	**0.006**
Highest ever blood eosinophil count* (x10^9 cells/L)	1530	0.60 (0.37,0.94)	0.60 (0.37,1.00)	0.60 (0.37,0.90)	0.434

FeNO* (ppb)	1302	39.0 (20.0,74.0)	39.0 (20.0,70.0)	40.0 (21.0,77.0)	0.230
Total IgE* (IU/mL)	1515	166 (56,475)	180 (64,528)	158 (53,456)	0.192
FEV_1 (Litres) [Mean (SD)]	1409	1.98 (0.80)	2.06 (0.82)	1.95 (0.79)	**0.015**
FEV_1 % Predicted (%) [Mean (SD)]	1308	66.8 (21.3)	68.6 (21.4)	66.0 (21.2)	**0.045**
ACQ-6 Score [Mean (SD)]	1380	2.9 (1.4)	2.4 (1.4)	3.1 (1.3)	**<0.001**
ACQ-7 Score [Mean (SD)]	1387	3.0 (1.3)	2.6 (1.3)	3.2 (1.2)	**<0.001**
Inhaled corticosteroid dose* beclometasone equivalent (mcg)	1431	2000 (1600,2000)	2000 (1600,2000)	2000 (1600,2000)	0.865
Home nebuliser (%)	1560	310 (19.9%)	56 (12.6%)	254 (22.8%)	**<0.001**
Maintenance oral corticosteroids use (%)	1581	833 (52.7%)	267 (59.2%)	566 (50.1%)	**0.004**
Maintenance oral corticosteroids dose* (mg)	823	10.0 (7.5,17.5)	10.0 (7.0,15.0)	10.0 (10.0,20.0)	**<0.001**
Number of rescue corticosteroids courses in the last 12 months (%)	1590				**<0.001**
0		185 (11.6%)	185 (40.7%)	0 (0.0%)	
1		140 (8.8%)	140 (30.8%)	0 (0.0%)	
2		130 (8.2%)	130 (28.6%)	0 (0.0%)	
3		179 (11.3%)	0 (0.0%)	179 (15.8%)	
≥4		956 (60.1%)	0 (0.0%)	956 (84.2%)	
Met ERS/ATS criteria for severe asthma	1592	1202 (88.7%)	355 (88.8%)	847 (88.7%)	1.000

Results are shown as count (%), mean (SD) or *median [IQR].

† p-values are shown for comparison between frequent exacerbators and non-frequent exacerbators.

Abbreviations: ACQ: Asthma control questionnaire; BMI: Body mass index; FeNO: Fractional exhaled nitric oxide; FEV_1: forced expiratory volume in one second; IgE: Immunoglobulin E.

Definition: Frequent exacerbator: ≥3 exacerbations treated with high-dose systemic corticosteroids in the past year

524 **Table 2.** Factors associated with frequent exacerbations in severe asthma – Univariable and
525 multivariable logistic regression.
526

	Univariable model (n=1,592)			Multivariable model† (n=877)	
	n	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Male	587	0.90 (0.72,1.12)	0.344	1.01 (0.71,1.43)	0.950
Age at first assessment					
18-34	278	1		1	
35-54	683	0.83 (0.60,1.15)	0.257	0.61 (0.37,0.99)	**0.047**
55-79	631	0.69 (0.50,0.95)	**0.024**	0.55 (0.33,0.91)	**0.020**
Ethnicity					
Caucasian	1214	1		1	
South East Asian	92	1.12 (0.69,1.81)	0.656	0.45 (0.22,0.94)	**0.033**
North East Asian	61	0.94 (0.54,1.65)	0.832	0.84 (0.37,1.93)	0.689
African	79	1.02 (0.61,1.69)	0.938	0.79 (0.41,1.54)	0.493
Mixed	14	0.39 (0.14,1.13)	0.083	0.29 (0.06,1.34)	0.114
Other	119	0.87 (0.58,1.31)	0.513	1.26 (0.71,2.23)	0.436
BMI					
<24.9	329	1		1	
25-29.9	475	0.93 (0.68,1.26)	0.633	1.04 (0.66,1.64)	0.859
≥30	758	1.19 (0.89,1.59)	0.230	1.10 (0.72,1.69)	0.655
Smoking status					
Never smoked	1084	1		1	
Ex-smoker	423	1.49 (1.15,1.93)	**0.003**	1.55 (1.06,2.26)	**0.024**
Current smoker	57	1.04 (0.58,1.87)	0.886	1.12 (0.51,2.43)	0.783
Nasal polyps	291	0.80 (0.61,1.06)	0.121	0.72 (0.48,1.09)	0.119
Gastroesophageal reflux	302	1.61 (1.19,2.18)	**0.002**	1.02 (0.67,1.56)	0.911
Depression or anxiety	125	1.12 (0.74,1.69)	0.590	0.63 (0.33,1.19)	0.156
ACQ-6 Score					
Well Controlled (Score 0.0-0.75)	122	1		1	
Grey Zone (Score 0.75-1.5)	145	1.40 (0.86,2.26)	0.176	2.02 (1.04,3.94)	**0.038**
Poorly Controlled (Score>1.5)	1113	3.16 (2.16,4.62)	**<0.001**	4.25 (2.50,7.22)	**<0.001**
FEV_1 % Predicted (%)					
<50	298	1		1	
50-70	438	1.20 (0.86,1.68)	0.292	1.53 (0.97,2.40)	0.065
70-90	384	0.80 (0.57,1.12)	0.194	0.96 (0.61,1.51)	0.848
>90	188	0.71 (0.48,1.05)	0.084	0.80 (0.47,1.38)	0.421
FeNO (ppb)					
Low (<25)	390	1		1	
Intermediate (25-50)	383	0.99 (0.73,1.33)	0.923	1.25 (0.83,1.90)	0.290
High (>50)	529	1.24 (0.93,1.65)	0.144	1.54 (1.01,2.34)	**0.044**
Blood eosinophil count ($x10^9$ cells/L)					
≤0.15	366	1		1	

0.15-0.30	221	0.94 (0.66,1.34)	0.723	0.85 (0.52,1.38)	0.499
0.30-0.45	369	1.24 (0.91,1.71)	0.175	1.16 (0.72,1.88)	0.542
>0.45	615	1.49 (1.12,1.99)	**0.006**	1.09 (0.71,1.69)	0.683
Maintenance oral corticosteroids	833	0.69 (0.55,0.86)	**0.001**	0.58 (0.41,0.82)	**0.002**

† Hospital and assessment year also achieved statistical significance in our univariable analysis and were included as independent variables in our multivariable regression model.

Abbreviations: ACQ: Asthma control questionnaire; BMI: Body mass index; FeNO: Fractional exhaled nitric oxide; FEV_1: forced expiratory volume in one second

554 **Table 3.** Factors associated with frequent exacerbations in patients not on maintenance oral
555 corticosteroids – Univariable and multivariable logistic regression.
556

	Univariable model (n=740)			Multivariable model† (n=465)	
	n	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Male	255	0.99 (0.70,1.41)	0.961	0.97 (0.57,1.64)	0.910
Age at first assessment					
18-34	156	1		1	
35-54	327	1.05 (0.67, 1.63)	0.841	0.62 (0.32, 1.20)	0.154
55-79	265	1.01 (0.64, 1.59)	0.983	0.59 (0.29, 1.18)	0.135
Ethnicity					
Caucasian	532	1		1	
South East Asian	60	0.97 (0.52,1.80)	0.923	0.24 (0.10,0.61)	**0.003**
North East Asian	37	1.01 (0.46,2.19)	0.988	1.06 (0.33,3.39)	0.925
African	51	1.05 (0.53,2.07)	0.885	0.78 (0.31,1.97)	0.605
Mixed	6	1.62 (0.19,13.97)	0.662	0.57 (0.03,10.55)	0.705
Other	54	0.77 (0.41,1.42)	0.402	0.86 (0.35,2.09)	0.733
BMI					
<24.9	163	1		1	
25-29.9	227	1.12 (0.71,1.76)	0.624	1.64 (0.84,3.21)	0.147
≥30	339	1.41 (0.92,2.16)	0.117	1.41 (0.75,2.68)	0.289
Smoking status					
Never smoked	501	1		1	
Ex-smoker	208	1.33 (0.90,1.97)	0.152	1.12 (0.63,1.98)	0.710
Current smoker	31	0.63 (0.29,1.35)	0.236	0.55 (0.18,1.67)	0.293
Nasal polyps	121	0.86 (0.55,1.33)	0.496	0.53 (0.27,1.04)	0.065
Gastroesophageal reflux	161	1.64 (1.06,2.56)	**0.028**	1.01 (0.54,1.88)	0.980
Depression or anxiety	67	1.05 (0.58,1.89)	0.871	0.62 (0.22,1.74)	0.366
ACQ-6 Score					
Well controlled (Score 0.0-0.75)	59	1		1	
Grey zone (Score 0.75-1.5)	61	1.71 (0.83,3.52)	0.146	2.97 (1.08,8.12)	**0.034**
Poorly controlled (Score>1.5)	522	4.70 (2.70,8.19)	**<0.001**	6.42 (2.99,13.80)	**<0.001**
FEV_1 % predicted (%)					
<50	135	1		1	
50-70	188	1.21 (0.70,2.08)	0.500	1.43 (0.69,2.93)	0.333
70-90	195	0.69 (0.42,1.15)	0.156	0.82 (0.41,1.62)	0.561
>90	98	0.56 (0.31,1.01)	0.053	0.85 (0.38,1.92)	0.694
FeNO (ppb)					
Low (<25)	208	1		1	
Intermediate (25-50)	208	1.30 (0.85,2.00)	0.231	1.36 (0.74,2.49)	0.321
High (>50)	261	1.63 (1.07,2.47)	**0.022**	1.41 (0.75,2.64)	0.286
Blood eosinophil count ($x10^9$ cells/L)					
≤0.15	132	1		1	

0.15-0.30	121	0.76 (0.45,1.30)	0.314	0.64 (0.30,1.36)	0.250
0.30-0.45	166	1.19 (0.71,1.99)	0.516	0.90 (0.43,1.85)	0.767
>0.45	321	1.66 (1.04,2.66)	**0.035**	1.44 (0.72,2.88)	0.307

† Hospital and assessment year also achieved statistical significance in our univariable analysis and were included as independent variables in our multivariable regression model.

Abbreviations: ACQ: Asthma control questionnaire; BMI: Body mass index; FeNO: Fractional exhaled nitric oxide; FEV_1: forced expiratory volume in one second

564 **Table 4.** Factors associated with frequent exacerbations in patients on maintenance oral
565 corticosteroids – Univariable and multivariable logistic regression.
566

	Univariable model (n=828)			Multivariable model† (n=412)	
	n	**Odds ratio (95% CI)**	**p-value**	**Odds ratio (95% CI)**	**p-value**
Male	326	0.86 (0.64,1.16)	0.322	1.22 (0.73,2.05)	0.446
Age at first assessment					
18-34	119	1		1	
35-54	352	0.65 (0.40, 1.05)	0.077	0.52 (0.22, 1.24)	0.141
55-79	362	0.52 (0.32, 0.85)	0.008	0.37 (0.16, 0.88)	0.024
Ethnicity					
Caucasian	672	1		1	
South East Asian	31	1.31 (0.58,2.97)	0.523	1.43 (0.33,6.13)	0.633
North East Asian	24	0.76 (0.33,1.76)	0.518	0.63 (0.16,2.51)	0.510
African	28	0.82 (0.37,1.80)	0.619	0.91 (0.30,2.71)	0.860
Mixed	8	0.15 (0.03,0.76)	**0.021**	0.17 (0.01,2.11)	0.170
Other	65	0.95 (0.55,1.64)	0.861	1.57 (0.69,3.56)	0.280
BMI					
<24.9	162	1		1	
25-29.9	242	0.82 (0.54,1.25)	0.354	0.64 (0.32,1.28)	0.206
≥30	418	1.08 (0.73,1.59)	0.711	0.86 (0.45,1.63)	0.643
Smoking status					
Never smoked	578	1		1	
Ex-smoker	211	1.54 (1.08,2.19)	**0.017**	2.25 (1.29,3.91)	**0.004**
Current smoker	24	1.59 (0.62,4.06)	0.335	2.67 (0.76,9.31)	0.124
Nasal polyps	169	0.81 (0.57,1.16)	0.245	0.76 (0.42,1.36)	0.350
Gastroesophageal reflux	140	1.49 (0.98,2.25)	0.061	1.05 (0.56,1.95)	0.878
Depression or anxiety	58	1.13 (0.63,2.03)	0.679	0.57 (0.23,1.41)	0.222
ACQ-6 Score					
Well controlled (Score 0.0-0.75)	62	1		1	
Grey zone (Score 0.75-1.5)	83	1.11 (0.57,2.15)	0.756	1.40 (0.52,3.77)	0.508
Poorly controlled (Score>1.5)	586	2.20 (1.30,3.74)	**0.003**	2.74 (1.20,6.26)	**0.017**
FEV_1 % predicted (%)					
<50	163	1		1	
50-70	246	1.24 (0.80,1.92)	0.329	1.80 (0.96,3.40)	0.068
70-90	185	0.88 (0.56,1.38)	0.583	1.49 (0.76,2.93)	0.244
>90	88	0.80 (0.46,1.38)	0.415	1.11 (0.48,2.54)	0.809
FeNO (ppb)					
Low (<25)	180	1		1	
Intermediate (25-50)	171	0.69 (0.44,1.06)	0.091	0.93 (0.50,1.73)	0.810
High (>50)	265	0.96 (0.64,1.44)	0.859	1.58 (0.86,2.92)	0.140
Blood eosinophil count ($x10^9$ cells/L)					
≤0.15	231	1		1	

0.15-0.30	100	1.03 (0.63,1.69)	0.912	1.07 (0.53,2.16)	0.855
0.30-0.45	200	1.18 (0.79,1.77)	0.424	1.51 (0.75,3.04)	0.251
>0.45	289	1.23 (0.85,1.78)	0.272	0.65 (0.35,1.21)	0.173

† Hospital and assessment year also achieved statistical significance in our univariable analysis and were included as independent variables in our multivariable regression model.

Abbreviations: ACQ: Asthma control questionnaire; BMI: Body mass index; FeNO: Fractional exhaled nitric oxide; FEV_1: forced expiratory volume in one second

575 **FIGURES**

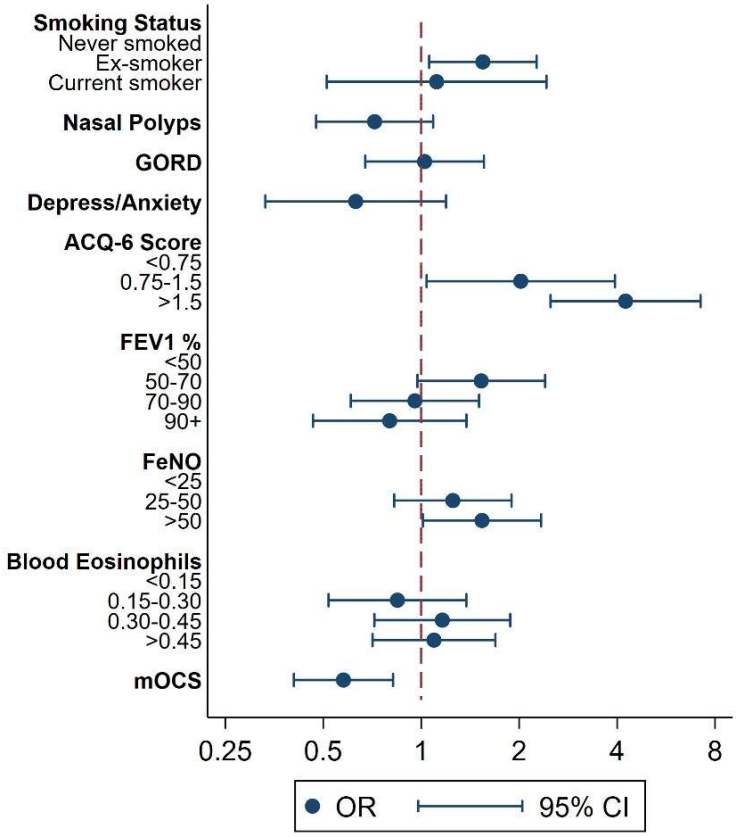
576

577 **Manuscript title:**

578 Factors associated with frequent exacerbations in the UK Severe Asthma Registry

579

580 **Figure 1.** Factors associated with frequent exacerbations in severe asthma – Multivariable
581 logistic regression.
582



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586 **Abbreviations:** ACQ: Asthma control questionnaire; FeNO: Fractional exhaled nitric oxide;

587 FEV_1: forced expiratory volume in one second; GORD: gastro-oesophageal reflux disease;

588 mOCS: maintenance oral corticosteroids.

Figure 2a. Factors associated with frequent exacerbations in patients not on maintenance oral corticosteroids – Multivariable logistic regression.

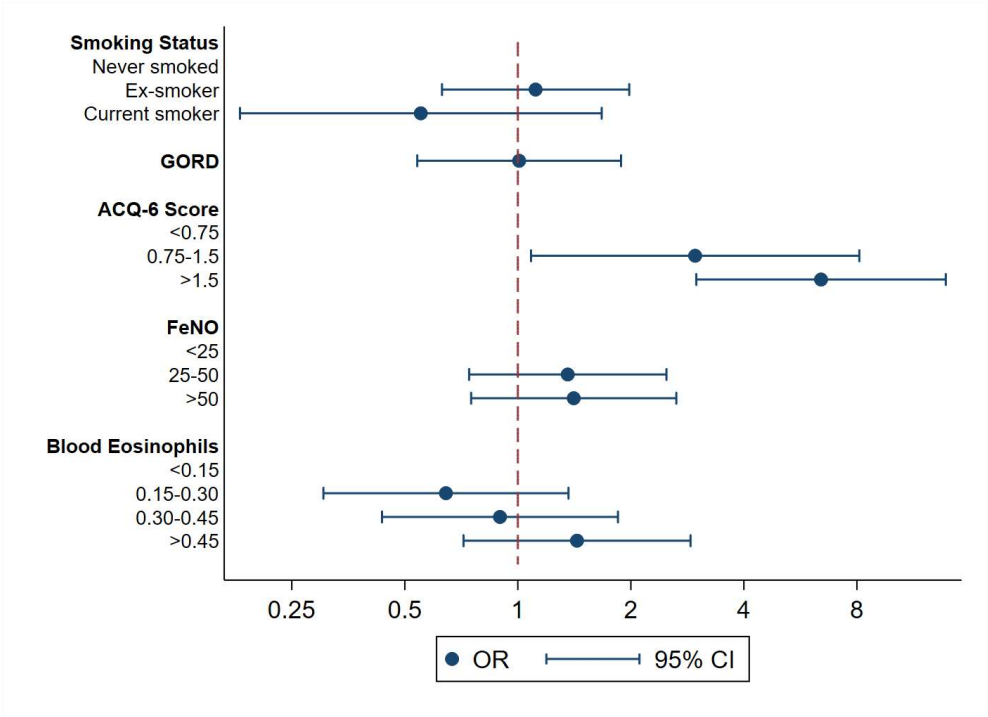
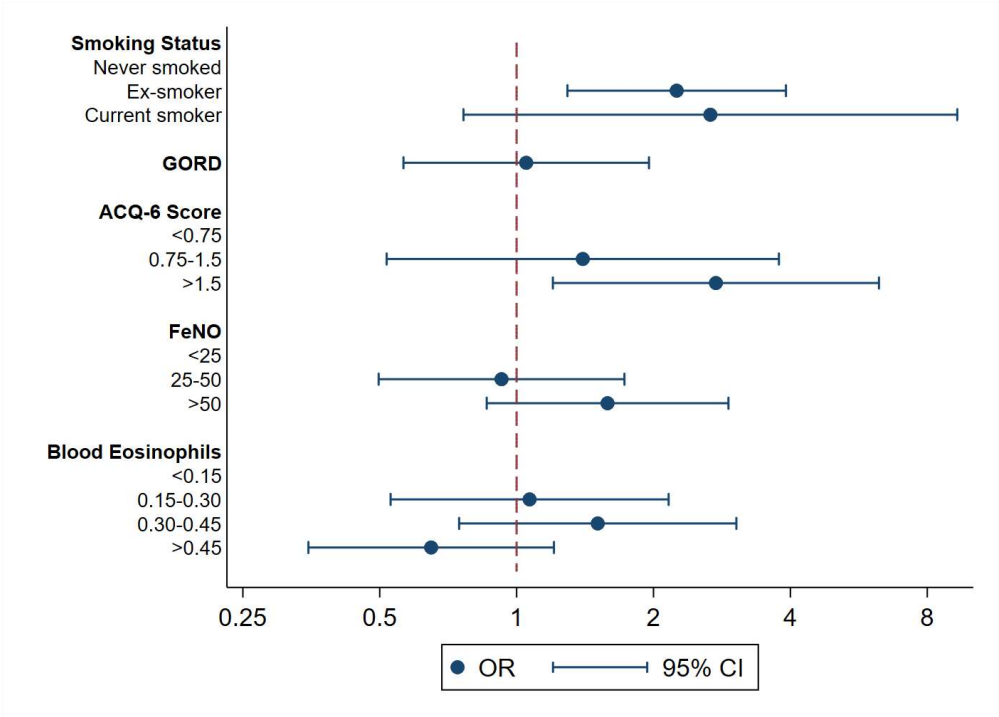


Figure 2b. Factors associated with frequent exacerbations in patients on maintenance oral corticosteroids – Multivariable logistic regression.



Abbreviations: ACQ: Asthma control questionnaire; FeNO: Fractional exhaled nitric oxide; FEV_1: forced expiratory volume in one second; GORD: gastro-oesophageal reflux disease.