**Identifying risk of future asthma attacks using UK medical record data: a Respiratory Effectiveness Group initiative**

*Running head: Future asthma attack risk*

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**Abstract**

**Background:** Asthma attacks are common, serious, and costly. Individual factors associated with attacks, such as poor symptom control, are not robust predictors.

**Objective:** We investigated whether the rich data available in UK electronic medical records could identify patients at risk of recurrent attacks.

**Methods:** We analyzed anonymized, longitudinal medical records of 118,981 patients with actively treated asthma (ages 12–80 years) and ≥3 years of data. Potential risk factors during 1 baseline year were evaluated using univariable (simple) logistic regression for outcomes of ≥2 and ≥4 attacks during the following 2-year period. Predictors with significant univariable association (*P*<.05) were entered into multiple logistic regression analysis with backwards stepwise selection of the model including all significant independent predictors. The predictive accuracy of the multivariable models was assessed.

**Results:** Independent predictors associated with future attacks included baseline-year markers of attacks (acute oral corticosteroid [OCS] courses, emergency visits), more frequent reliever use and healthcare utilization, worse lung function, current smoking, blood eosinophilia, rhinitis, nasal polyps, eczema, gastroesophageal reflux disease, obesity, older age, and being female. The number of OCS courses had the strongest association. The final cross-validated models incorporated 19 and 16 risk factors for ≥2 and ≥4 attacks over 2 years, respectively, with areas under the curve of 0.785 (95% CI 0.780–0.789) and 0.867 (0.860–0.873), respectively.

**Conclusions:** Routinely collected data could be used proactively via automated searches to identify individuals at risk of recurrent asthma attacks. Further research is needed to assess the impact of such knowledge on clinical prognosis.

**Study Registration:** ENCePP 4869

**Highlights Box**

*1. What is already known about this topic?*

Asthma attacks are common, serious, and costly. Individual factors associated with attacks, such as poor symptom control, are not robust predictors. Adequately powered studies are required to progress toward a multivariable predictor.

*2. What does this article add to our knowledge?*

This large study shows a combination of risk factors from routine medical record data can identify individuals at high risk of subsequent recurrent asthma attacks.

*3. How does this study impact current management guidelines?*

Routine data from electronic medical records could be used to assess individuals' risks of recurrent asthma attacks, and to guide targeted management of modifiable risk factors.

***Key words:*** asthma, attack, control, medical record, observational, risk factor

***Abbreviations used***

AIC: Akaike Information Criterion

BMI: body mass index

CI: confidence interval

COPD: chronic obstructive pulmonary disease

ED: emergency department

ICS: inhaled corticosteroid

LABA: long-acting β2 agonist

LTRA: leukotriene receptor antagonist

OCS: oral corticosteroids

PEF: peak expiratory flow

QOF: Quality and Outcomes Framework

ROC: receiver operating characteristic

SABA: short-acting β2 agonist

UK: United Kingdom

**Introduction**

Asthma is a common and heterogeneous disease with a wide variety of presentations and clinical courses.1 However, in all subtypes there is the potential for abrupt clinical and lung function deteriorations termed asthma attacks (or severe exacerbations).2 A common cause of unscheduled healthcare utilization,3 asthma attacks are associated with substantial physical4 and psychological morbidity,5 and major direct and indirect healthcare costs.6

Asthma management strategies and action plans have focused largely on symptom control, with less attention to risk stratification schemes and prevention. This focus on symptom management may have contributed to the incidence of asthma attacks and deaths remaining relatively constant, whereas there have been substantial improvements in other disease areas (e.g. cardiovascular disease) for which risk-centered strategies using objective measures have been developed.3,7

Although poor control of asthma symptoms is associated with risk of future attacks, it is not a robust predictor in isolation.8,9 Moreover, there may be a pronounced discordance between daily symptoms and the risk of attack in a substantial proportion of individuals.1,10 Asthma treatments may be selected by some clinicians for their effect on symptoms but not on future risk of exacerbations (e.g. theophylline), whereas other treatments may be chosen for the opposite profile (e.g. mepolizumab).11 Assessing risk could therefore reduce the potential for inappropriate under- or over-treatment, as well as have the positive effect of facilitating shared decision-making.12

Available guidelines do discuss future risk,13,14 and there are a large number of publications that report single or grouped risk factors for asthma attacks.13–15 A simple risk questionnaire based on such published risk factors16 has generated substantial public interest. This risk assessment tool has been intended primarily as a conduit to health promotion opportunities but also highlights a range of risk factors—from smoking status and extent of reliever use to hospitalization history—that need to be evaluated in a single study alongside biomarkers. The relative effect size of these risk factors and their interaction is currently not well characterized, but establishing these elements is an essential step toward the production of a validated risk assessment tool for use in routine practice.

One study suggested that the implementation of practice-based asthma risk registries is feasible in routine clinical care, but a validated risk assessment tool was not used.17 More recently, a risk score for asthma attacks has been developed from a large clinical trial dataset.18 However, enrolled patients were preselected to have uncontrolled asthma symptoms and at least one attack the prior year; thus, the external validity of the risk score is uncertain when applied to the wider population of patients treated for asthma in routine clinical practice, both because most of these patients would not meet typical trial eligibility criteria19 and because the ecology of care in clinical trials is difficult to replicate in general practice.

All individuals in the UK have their electronic medical records centralized at their primary care practice, where information from secondary care and hospitalizations is also aggregated. Our objective was to identify routinely collected characteristics from electronic medical records to develop a multivariable prediction model for multiple asthma attacks over a 2-year outcome period. We hypothesized that the rich data available in longitudinal medical records of UK patients (including previously identified risk factors) could reliably identify patients who subsequently experienced recurrent attacks. We aimed to produce estimates of effect size for risk factors when considered in combination.

**METHODS**

**Data source and study population**

The Optimum Patient Care Research Database (OPCRD) is a quality-controlled, respiratory-focused database containing anonymous data from general practices throughout the UK and approved for clinical research by the Health Research Authority of the UK NHS (REC reference: 15/EM/0150).20 At the time of the study, the OPCRD contained longitudinal medical record data of over 1.7 million patients from more than 400 UK general practices. The anonymized point-of-care records for each patient include demographic information, disease diagnoses as Read codes, prescriptions issued during consultations or as renewals, test results, and information transcribed from secondary care visits and hospitalizations.

This study was an initiative of the Respiratory Effectiveness Group, an investigator-led, not-for-profit, real-life respiratory research and advocacy initiative.21 The study was conducted in line with recommendations for observational research, including an *a priori* research plan, study registration, commitment to publish, and an independent steering committee not remunerated for their participation (please see Online Repository). Written informed consent was not necessary because data were anonymous; however, patients had been given the option to prohibit use of their anonymized data for research use.

Patients 12–80 years old with an asthma diagnostic Read code recorded before study start, active asthma, and at least 3 years of continuous data were included in the study population. Active asthma was defined as two or more prescriptions for asthma drugs during study year 1 (short-acting β2 agonist [SABA], inhaled corticosteroids [ICS], long-acting β2 agonist [LABA], fixed-dose ICS/LABA combination, leukotriene receptor antagonist [LTRA], and/or theophylline), as well as no Read code for resolved asthma during the 3-year study period. Those with a concurrent diagnosis of chronic obstructive pulmonary disease (COPD Read code) recorded at any time in the database (ever-recorded) were excluded from the analyses.

**Study design**

This was a historical, follow-up cohort study of patients with asthma, using longitudinal OPCRD data from February 2005 through September 2014. The study period thus began after the 2004 institution of the UK Quality and Outcomes Framework (QOF),22 an initiative that provides financial incentives for annual review of patients with asthma in primary care and promotes regular coding of symptoms, peak flow, and smoking status.

We examined the most recent 3 years of continuous data for each patient, including 1 year of data for baseline characterization and 2 years of outcome data. Anonymized individual patient data, including patient demographic characteristics, comorbidities, attack history, and current therapy were extracted from routine electronic clinical patient records in primary care practice management systems.

Candidate predictors were selected based on literature review and expert opinion (Table I).23,24

**Model building**

The primary endpoint was the occurrence of an asthma attack (severe exacerbation), as defined by the European Respiratory Society/American Thoracic Society,25 namely, an asthma-related hospitalization, emergency department (ED) attendance, or an acute respiratory presentation resulting in a course of oral corticosteroids (OCS). Multiple events occurring within a 2-week window were considered as a single attack.

Univariable logistic regression analysis was used to identify individual characteristics that were predictive of two different binary outcomes (1) two or more (yes/no) asthma attacks during the 2-year outcome period; and (2) four or more (yes/no) asthma attacks during the 2-year outcome period. Collinear associations between potentially related predictors were assessed using Spearman rank-order correlation coefficients. The values of variables were rank-ordered for calculating these correlation coefficients, and relationships with rank correlation coefficients greater than 0.30 were defined as being collinear.

All predictors with a significant univariable association (*P*<.05) were entered into a multiple logistic regression analysis with backwards selection of the model, performed manually based on significant *P* values*.* For the variables that were found to be collinear, we repeated the multiple regression analyses, substituting the second variable of the pair for the first (e.g., number of acute OCS courses for number of asthma attacks) and selected the variable leading to the lowest Akaike Information Criterion (AIC) of the model.

Since not all patients had recorded values for all predictors, we categorized predictors and included a separate category to indicate absence of available data for the following variables: body mass index (BMI), smoking status, percent predicted peak expiratory flow (PEF), and blood eosinophil count.

**Model performance and internal validation**

The ability of the model to distinguish patients with multiple asthma attacks from other patients with asthma was assessed by its discrimination performance calculating the *C* statistic (area under the receiver operating characteristic [ROC] curve). The *C* statistic confidence intervals (CIs) were generated by bootstrapping with 1000 resamples. Other performance measures, including sensitivity, specificity, and positive and negative predictive values, were plotted for different cutoff points of the estimated risk of multiple asthma attacks as calculated by the models in plots generated using R package ROCR version 1.0-5.

Potential optimism in estimated discrimination performance and overfitting of the models was evaluated using bootstrapping with 100 resamples and by cross-validation with a random split of the data as 70% for model development (sample set) and 30% for performance testing (test set).

Calibration analysis was performed and results were presented by plots showing the correlation of the mean observed risk with mean predicted risk among 500 groups encompassing all patients in the study (n=118,981).

**RESULTS**

Of 338,482 patients in the OPCRD with an asthma diagnosis and 3 consecutive years of data, 132,717 (39%) patients aged 12–80 years had active asthma (Figure E1 in the Online Repository). We excluded patients with an ever-recorded COPD diagnosis (n=13,736; 10%), leaving 118,981 patients in the total study population.

Key patient characteristics are summarized in Table II. The mean (SD) age at start of the study was 45 (18) years, 67,534 (57%) patients were female, 35,544 (30%) were obese, and 19,022 (16%) were current smokers. Most patients (n=104,345; 88%) were prescribed ICS, either as monotherapy (n=61,358; 52%) or in combination with a LABA (n=42,987; 36%); 40% (n=47,652) were prescribed high-dose ICS at their last prescription (≥400 μg/day fluticasone-equivalent). Seventeen percent of patients (n=20,711) had at least one OCS course prescribed in the baseline year. (Online Repository Table E1 depicts distributions of all other candidate predictors at baseline.)

During the subsequent 2-year outcome period, one quarter of patients (n=30,234; 25%) experienced one or more, 12,736 (11%) experienced two or more, and 3198 (3%) experienced four or more asthma attacks (Table III).

**Model building**

All candidate predictors recorded in the baseline period, with the exception of beta-blocker prescriptions, were significantly associated with the risk of frequent asthma attacks (two or more or four or more) during the outcome period (Online Repository Table E2). Descriptions of collinear associations among risk factors are in the Online Repository.

The final multivariable (multifactor) models contained 19 independent predictors for two or more attacks (Table IV) and 16 predictors for four or more attacks (Table V), of which the number of acute OCS courses in the baseline year had the strongest association.

Older age, female sex, current smoking, and obesity were significant risk predictors for both outcomes, as were blood eosinophilia, higher mean daily SABA dose, and LTRA or LABA prescriptions in the baseline year. Comorbidities significantly contributing to risk prediction of both outcomes were active rhinitis and a history of nasal polyps or anaphylaxis. The odds of frequent attacks were increased for patients with more frequent primary care consultations and for those with baseline year markers of asthma attacks, such as acute OCS courses or ED attendance (Tables IV and V). The odds of two or more or four or more attacks were significantly lower for patients with lower medication possession ratio.

**Model performance and internal validation**

The overall *C* statistic was 0.785 (95% CI 0.780–0.789) for the ability of the model to distinguish patients who experienced two or more asthma attacks in the 2-year outcome period (Figure E2 in the Online Repository). The model performed better in predicting four or more attacks with a *C* statistic of 0.867 (0.860–0.873) (Online Repository, Figure E3). We found no indication of relevant optimism in estimated model performance or overfitting of the model in this large dataset (data not shown).

Calibration plots showed good correlation between the probabilities of having multiple asthma attacks in the outcome period as estimated by the models and the observed outcome frequencies, although higher predicted risks, observed in relatively small proportions of the population, were slightly overestimated (Figure 1).

As forecasted by the multivariable model, 3% (n=3497) of the population had a ≥50% predicted risk of experiencing two or more asthma attacks in the next 2 years; and 58% (n=2019) of these individuals actually experienced two or more attacks in the outcome period (positive predictive value at the cutoff point). The negative predictive value was 91% at that cutoff point.

Only 246 (0.2%) patients had a ≥50% predicted risk of experiencing four or more asthma attacks; and 54% (n=133) experienced four or more attacks in the outcome period. Only 3% (n=3065) of the patients with a lower predicted risk experienced four or more attacks (negative predictive value 97%).

Table VI illustrates the predicted risk calculation for four hypothetical patients with asthma.

**DISCUSSION**

A combination of risk factors from longitudinal medical records of UK patients was effective in predicting which individuals subsequently experienced recurrent attacks, and in particular in predicting the high-risk patients who experienced four or more attacks over a 2-year period. This large database study has confirmed that asthma attacks are common in an unselected UK population, with 25% of patients experiencing one or more attacks during the 2-year outcome period. The risk factors we identified are largely consistent with previous findings.

This study has strengths in its large sample size and the range of factors considered concurrently (see Online Repository for post-hoc power calculations). Asthma is a common and important disease with a variety of presentations and underlying mechanisms; therefore, multiple factors should be included in any risk prediction model. Prior studies have evaluated individual risk factors or limited numbers of risk factors to predict asthma attacks, for example, those representing subacute lack of asthma control.26 Questionnaire-based methods of predicting risk have been studied as well.27 Instead, the risk factors we identified are all collected from routine electronic patient data, suggesting that an informatics-based approach to risk stratification is possible, with lists of high-risk patients being automatically generated for the attention of the clinical team, e.g. by alerts placed on the clinical records. Moreover, the current study also formally describes the potential predictive ability of the risk model developed and lends itself to the development of an individualized web-based assessment tool as employed in other disease areas, such as for cardiovascular risk assessment.28

The risk factors included in our model have been identified in prior studies including the recent UK National Review of Asthma Deaths29; these include previous asthma attacks, asthma severity as described by level of treatment, current symptom control, nasal disease, and generally hazardous comorbidities (smoking, obesity).13,30 Obesity may predispose to asthma attacks through the effect of extrathoracic restriction from adipose tissue and from the effect of adipokines on overall immune function and airway inflammation.31 Additionally, there may be a common genetic predisposition to both asthma and obesity.32,33

For those individuals with available blood counts, blood eosinophil counts (>0.4 x 109/L) were also associated with frequent asthma attacks. This finding is consistent with a recent large database study investigating the dose-response relationship between blood eosinophils and exacerbation risk.34 Furthermore, this work expands on and complements a study published earlier this year.35 Although of a similar design, that study investigated a narrower range of risk factors over a shorter follow-up period (1 year) for the subpopulation of patients who had a blood eosinophil count; the findings therefore may not be representative of the wider population of individuals with asthma.

In this general population of people treated for asthma, 51% filled <60% of their prescription refills during the baseline year, and the odds of multiple attacks were lower amongst those with lower medication possession ratios than amongst patients with medication possession ratios of 80–100%. We can speculate that perhaps individuals with milder asthma took their treatment less regularly (e.g. over a pollen season) and this was an effective strategy for them.36 In their systematic review of medication adherence and risk of asthma attacks, Engelkes et al37 reported that some studies found an association between low adherence (expressed as medication possession ratio) and low risk of attack, perhaps because of self-titration according to level of control or of heterogeneity in treatment response. Others have reported variations in adherence over time.38 Up to a third of people treated for asthma do not have objective supportive evidence of asthma when tested for airway dysfunction and inflammation.39 Therefore, it may be that some individuals in this study were not regularly collecting medication because they did not have active asthma symptoms, and they were also at very low risk for asthma attacks. Conversely, individuals who have experienced a recent attack and have less stable asthma may be concordant with inhaled therapy but still remain at a higher risk of attack.

Given the population we studied and the method of data collection, these real-life findings are directly applicable to patients treated for asthma in the UK. This is in contrast to the limited inclusion criteria of most randomized controlled trials, which often exclude up to 95% of typical patients seen in general practice, such as smokers and those with comorbidities.19 The generalizable nature of these findings has the potential to inform future changes in practice and thus have an early clinical impact.

As with any observational study, these findings do not provide mechanistic insight into how the identified factors increase future risk. Moreover, several other potential risk factors would have been of interest to consider, including allergen exposure, inhaler technique assessment, and socioeconomic status, but these were not readily available from the database. Although the study population is dispersed across the country, it is unclear if the findings would be applicable outside the UK NHS framework and its largely Caucasian population in terms of relative magnitude of effects. In addition, this type of data carries the potential for under-recording of secondary care attendances: asthma attacks that require ED attendance are not invariably recorded in primary care notes because recording requires a manual step. This potential for missing outcomes could result in underestimating the attack rate or biasing the predictors towards those associated with more moderate exacerbations that do not require hospitalization.

Our study period (February 2005 to September 2014) began after the 2004 institution of the UK QOF, which has improved data recording in electronic patient records through financial incentives.22,40,41 Within that period, we analyzed the most recent 3-year interval of data for eligible patients to include their most current available data. The prescription data used in this study were drawn from the electronic record of prescriptions issued at the time of a consultation (e.g. for acute illness or change in regular medication) or as renewals that continued existing chronic prescriptions. While there is currently no UK-wide system that links prescribing and dispensing data for primary care, several sources cite the reliability of prescribing data in another similar UK primary care database, the General Practice Research Database (GPRD, now the Clinical Practice Research Datalink), noting that there is good agreement between GPRD prescribing data and national dispensing data.42,43 Moreover, in the UK, pharmacists must dispense medications as prescribed.

We are developing a simple risk scoring tool as an example of the type of individualized information that could be available to people with asthma and their healthcare providers in the near future, or that could be automatically applied to routine electronic medical records where computer-based clinical record-keeping is used. During the development of the model, the extent of missing data varied from 6% for smoking status to 34% for blood eosinophil count, as recorded in Table II. For those variables with missing data, we were able to include a “missing data” category in the risk model, thereby to enable clinicians to use the risk calculator even when some data are missing, a common situation in real life.

This study provides clinically relevant measures of the relative importance of risk factors for recurrent asthma attacks. Additional work will be required to validate the model in other datasets, and prospectively for patients in different settings, and to develop these findings into questions or data queries to create a reliable tool for clinical practice. Further analyses will be required to explore potential time-to-event measures and also to ascertain which are the most important predictors in the models. Prospective trials will be required to assess the implementation of such models in clinical practice and the effect on asthma-related outcomes of risk-based decision-making, at both individual and group levels.

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**TABLE I.** Candidate predictors assessed for inclusion in the models

|  |  |
| --- | --- |
| **Variable** | **Description** |
| **Sex** | male or female |
| **Age** | in years at the start of the 3-year study period |
| **Body mass index (BMI)** | last recorded, in kg/m2; categorized as underweight (<18.5), normal (18.5–24.9), overweight (25–29.9), or obese (≥30) |
| **Smoking status** | last recorded, categorized as never smoker, current smoker, or ex-smoker |
| **Charlson comorbidity index** | score in the baseline year, categorized as 0, 1-4, 5-9, ≥10 (comorbidity weights taken from Hospital Standardised Mortality Ratios, version 9)22,23 |
| **Comorbidities\*** | recorded ever or active: eczema, allergic and non-allergic rhinitis, nasal polyps, anaphylaxis diagnosis, anxiety/depression diagnosis, diabetes (type 1 or 2), GERD, cardiovascular disease, ischemic heart disease, heart failure, psoriasis |
| **Comedications** | in baseline year, prescription (yes/no) for paracetamol, NSAIDs, beta-blockers, statins |
| **% predicted PEF** | recorded ever, expressed as percentage of predicted normal, categorized as unknown, <60%, 61–79% and ≥80% |
| **Blood eosinophil count** | last recorded, in 109cell/L, categorized as ≤0.4 or >0.4 |
| **BTS step†** |  |
| step 1 | inhaled SABA as needed |
| step 2 | ICS or LTRA |
| step 3 | add LABA to ICS or use high-dose ICS (≥400 μg/day FP equivalent) |
| step 4 | add LTRA/Theo to [ICS+LABA] or add LABA/LTRA/Theo to high-dose ICS |
| step 5 | add OCS |
| **Average daily dose of SABA / ICS** | Cumulative dose of SABA / ICS prescribed in baseline year, expressed in μg/day albuterol or FP equivalent and divided by 365.25 |
| **Prescribed daily ICS dose** | Dose of ICS prescribed at last prescription of baseline year in μg/day, FP equivalents |
| **ICS medication possession ratio** | ICS refill rate during the baseline year: sum of number of days per pack (number of actuations per pack / number of actuations per day) / 365.25 |
| **ICS device type** | in baseline year. categorized as no ICS, MDI, BAI or DPI |
| **Spacer use with ICS pMDI** | recorded In baseline year (yes/no) |
| **Oral corticosteroid use** | any maintenance prescription for corticosteroids in baseline year (yes/no) |
| **Prior asthma education** | recorded ever (yes/no) |
| **Primary care consults** | number of primary care consultations, categorized as 0, 1-5, 6-12, ≥13 |
| **Primary care consults for asthma** | number of primary care consultations with an asthma-related Read code |
| **Antibiotics with lower respiratory consult** | number of consultations that resulted in antibiotic prescription (included to capture asthma events that may have been misclassified as LRTI) |
| **Acute respiratory events** | number of events in the baseline year, defined as asthma-related hospitalization or ED attendance or an acute course of OCS or antibiotics prescription with lower respiratory consultation |
| **Acute OCS courses** | number of acute courses of OCS in baseline year, categorized as 0,1, ≥2 |
| **Acute OCS courses with lower respiratory consult** | number of OCS courses with Read code for lower respiratory consultation in baseline year, categorized as 0,1, ≥2 |
| **Antibiotics courses** | number of antibiotics prescriptions with Read code for lower respiratory consultation in baseline year, categorized as 0,1, ≥2 |
| **Hospital attendance/admission** | number of asthma-related‡ ED, inpatient, and outpatient attendance/admission in baseline year |
| **Asthma attacks** | number of asthma-related‡ hospital ED attendance, inpatient admission, or acute OCS course |

BAI, breath-actuated inhaler; BMI, body mass index; BTS, British Thoracic Society; DPI, dry powder inhaler; ED, emergency department; FP, fluticasone propionate; GERD, gastroesophageal reflux disease; ICS, inhaled corticosteroid; LABA, long-acting β2 agonist; LRTI, lower respiratory tract infection; LTRA, leukotriene receptor antagonist; MDI, metered-dose inhaler; NSAIDs, nonsteroidal anti-inflammatory drugs; OCS, oral corticosteroid; PEF, peak expiratory flow; SABA, short-acting β2 agonist; Theo, theophylline.

\*Comorbidity recorded ‘ever’ was defined as a diagnostic Read code during the baseline year or at any time before baseline. ‘Active’ refers to those for which a diagnosis was recorded within the baseline year and/or a prior diagnosis was accompanied by a prescription for the comorbidity within the baseline year. ‘Rhinitis’ included allergic and nonallergic rhinitis.

†Based on the British guideline on the management of asthma (October 2014) for adults and children ≥12 years.14

‡Any with a lower respiratory Read code (asthma or LRTI code).

**TABLE II.** Patient demographic and clinical characteristics during the baseline year

|  |  |
| --- | --- |
| **Variable** | **All patients**  **(n=118,981)** |
| Male sex\* | 51,447 (43) |
| Age at study start, mean (SD)\* | 45 (18) |
| 12–18 years | 13,452 (11) |
| 19–34 years | 21,381 (18) |
| 35–54 years | 44,375 (37) |
| 55–80 years | 39,773 (33) |
| Body mass index\* |  |
| Underweight | 3480 (3) |
| Normal | 35,400 (30) |
| Overweight | 36,608 (31) |
| Obese | 35,544 (30) |
| Unknown | 7949 (7) |
| Smoking status\* |  |
| Current smokers | 19,022 (16) |
| Ex-smokers | 26,758 (22) |
| Non-smokers | 65,489 (55) |
| Unknown smoking status | 7712 (6) |
| Recorded comorbidity† |  |
| Rhinitis diagnosis, active\* | 3567 (3) |
| Rhinitis diagnosis/therapy, active | 36,312 (31) |
| Nasal polyps, ever\* | 3933 (3) |
| Eczema diagnosis, active\* | 4321 (4) |
| Anaphylaxis diagnosis, ever\* | 512 (0.4) |
| GERD diagnosis, active\* | 1444 (1) |
| Anxiety or depression diagnosis, ever | 5812 (5) |
| ≥1 prescription during baseline |  |
| NSAIDs\* | 27,862 (23) |
| %predicted PEF, median (IQR)\* | 80 (68–91) |
| ≤60% | 13,808 (12) |
| 61–79% | 33,850 (28) |
| ≥80% | 47,780 (40) |
| Unknown | 23,543 (20) |
| Blood eosinophil count\* |  |
| ≤0.4 x 109/L | 64,803 (55) |
| >0.4 x 109/L | 13,184 (11) |
| Missing | 40,994 (34) |
| Mean daily SABA dose\*‡ |  |
| 0 μg/d | 11,992 (10) |
| 1–200 μg/d | 50,467 (42) |
| 201–400 | 29,866 (26) |
| >400 μg/d | 26,656 (22) |
| Last ICS dose prescribed in baseline year‡ |  |
| 0 μg/d | 14,636 (12) |
| <400 μg/d | 56,693 (48) |
| ≥400 μg/d | 47,652 (40) |
| ICS medication possession ratio\* |  |
| >0–39.9% | 37,723 (32) |
| 40–59.9% | 23,374 (20) |
| 60–79.9% | 9385 (8) |
| 80–100% | 15,493 (13) |
| >100% | 18,370 (15) |
| No ICS prescribed | 14,636 (12) |
| ≥1 prescription during baseline |  |
| LTRA\* | 6995 (6) |
| LABA (standalone)\* | 8253 (7) |
| Acute OCS courses\* |  |
| 0 | 98,270 (83) |
| 1 | 14,554 (12) |
| ≥2 | 6157 (5) |
| Primary care consultation\* |  |
| 0 | 5618 (5) |
| 1–5 | 56,023 (47) |
| 6–12 | 40,074 (34) |
| ≥13 | 17,266 (14) |
| ≥1 Asthma-related ED admission\* | 696 (0.6) |
| Asthma attacks¶ |  |
| 0 | 97,583 (82) |
| 1 | 15,058 (13) |
| 2 | 4202 (4) |
| ≥3 | 2138 (2) |

Data are n (%) unless otherwise noted.

ED, emergency department; GERD, gastroesophageal reflux disease; ICS, inhaled corticosteroid; LABA, long-acting β2 agonist; LTRA, leukotriene receptor antagonist; NSAIDs, nonsteroidal anti-inflammatory drugs; OCS, oral corticosteroid; PEF, peak expiratory flow; SABA, short-acting β2 agonist.

\*Variables included in the final model for risk of ≥2 asthma attacks during the outcome 2 years. Age and PEF %predicted were included as categorized variables.

†For comorbidities, ‘active’ refers to those for which a diagnosis was recorded within the baseline year and/or a prior diagnosis was accompanied by a prescription for the comorbidity within the baseline year. Comorbidity recorded ‘ever’ was defined as a diagnostic Read code during the baseline year or at any time before baseline. ‘Rhinitis’ included allergic and nonallergic rhinitis.

‡The SABA dose is the albuterol-equivalent dose; the ICS dose is the fluticasone-equivalent ICS dose.

§ICS adherence was calculated as number of days’ supply of drug/365 \* 100

¶Asthma attacks were defined as occurrence of asthma-related hospital or emergency department attendance, inpatient admission, or acute OCS course

**TABLE III.** Number of asthma attacks (severe exacerbations) in the baseline and outcome years for 118,981 patients with asthma.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Asthma attacks | Year 1 | Year 2 | Year 3 | Years 2 & 3 combined |
| ≥1, n (%) | 21,398 (18.0) | 20,132 (16.9) | 17,984 (15.1) | 30,234 (25.4) |
| ≥2, n (%) | 6340 (5.3) | 6169 (5.2) | 5517 (4.6) | 12,736 (10.7) |
| ≥4, n (%) | 770 (0.6) | 732 (0.6) | 681 (0.6) | 3198 (2.7) |

**TABLE IV.** Independent baseline predictors (year 1) of two or more asthma attacks during the 2-year follow-up period as identified in the final multivariable model

| Year 1 predictors | Adjusted OR (95% CI) | *P* value\* |
| --- | --- | --- |
| Age –12–18 years (ref)  19–34 years  35–54 years  55–80 years | 1.00  1.27 (1.14–1.40)  1.43 (1.29–1.57)  1.47 (1.33–1.62) | <.001 |
| Sex, female | 1.35 (1.29–1.41) | <.001 |
| Body mass index – normal (ref)  Underweight  Overweight  Obese  Unknown | 1.00  1.10 (0.95–1.27)  1.16 (1.09–1.22)  1.27 (1.21–1.34)  0.96 (0.86–1.08) | <.001 |
| Smoking status – non-smoker (ref)  Current smoker  Ex-smoker  Unknown | 1.00  1.17 (1.11–1.24)  1.01 (0.96–1.06)  1.02 (0.93–1.11) | <.001 |
| Rhinitis diagnosis, active\* | 1.14 (1.03–1.27) | .015 |
| Eczema diagnosis, active | 1.13 (1.02–1.25) | .017 |
| GERD diagnosis, active | 1.29 (1.11–1.50) | .017 |
| Nasal polyps, ever | 1.60 (1.46–1.76) | <.001 |
| Anaphylaxis diagnosis, ever | 1.66 (1.29–2.13) | <.001 |
| NSAID prescription, ≥1 | 1.13 (1.08–1.18) | <.001 |
| PEF % predicted – ≥80% (ref)  ≤60%  61–79%  Unknown | 1.00  1.62 (1.52–1.27)  1.21 (1.15–1.27)  1.25 (1.17–1.33) | <.001 |
| Blood eosinophil count – ≤0.4x109/L (ref)  >0.4 x109/L  Missing | 1.00  1.21 (1.14–1.29)  0.88 (0.83–0.93) | <.001 |
| Mean SABA dose‡ – 0 µg/d (ref)  1–200 µg/d  201–400 µg/d  >400 µg/d | 1.00  1.05 (0.97–1.14)  1.28 (1.16–1.39)  1.63 (1.45–1.77) | <.001 |
| LTRA prescription, ≥1 | 2.05 (1.92–2.18) | <.001 |
| LABA prescription (stand alone), ≥1 | 1.21 (1.13–1.30) | <.001 |
| ICS MPR (%) – 80–100% (ref)  >0–39.9%  40–59.9%  60–79.9%  ≥100%  No ICS prescribed | 1.00  0.88 (0.82–0.94)  0.88 (0.82–0.95)  0.94 (0.86–1.02)  0.92 (0.86–0.98)  0.65 (0.59–0.71) | <.001 |
| Acute OCS courses – 0 (ref)  1  ≥2 | 1.00  3.34 (3.37–3.71)  9.50 (8.94–10.08) | <.001 |
| Asthma-related ED admission, ≥1 | 1.76 (1.45–2.13) | <.001 |
| Primary care consultations – 0 (ref)  1–5  6–12  ≥13 | 1.00  1.29 (1.13–1.48)  1.66 (1.45–1.90)  2.05 (1.78–2.36) | <.001 |

Collinearity of variables is described in the Online Repository. ED, emergency department; GERD, gastroesophageal reflux disease; ICS, inhaled corticosteroid; LABA, long-acting β2 agonist; LTRA, leukotriene receptor antagonist; MPR, medication possession ratio; NSAID, nonsteroidal anti-inflammatory drug; OCS, oral corticosteroid; PEF, peak expiratory flow; ref, reference category; SABA, short-acting β2 agonist.

\*Overall *P* value of the association between the predictor and the outcome.

†For comorbidities, ‘active’ refers to those for which a diagnosis was recorded within the baseline year and/or a prior diagnosis was accompanied by a prescription for the comorbidity within the baseline year. ‘Ever’ refers to diagnosis at any time before or during the baseline period.

‡albuterol-equivalent dose.

**TABLE V.** Independent baseline predictors (year 1) of four or more asthma attacks during the 2-year follow-up period as identified in the final multivariable model

| Year 1 predictors | Adjusted OR (95% CI) | *P* value\* |
| --- | --- | --- |
| Age –12–18 years (ref)  19–34 years  35–54 years  55–80 years | 1.0  1.13 (0.91–1.40)  1.45 (1.19–1.77)  1.61 (1.31–1.97) | <.001 |
| Sex, female | 1.31 (1.20–1.43) | <.001 |
| Body mass index – normal (ref)  Underweight  Overweight  Obese  Unknown | 1.0  0.89 (0.65–1.22)  1.18 (1.06–1.31)  1.27 (1.15–1.41)  0.95 (0.76–1.20) | <.001 |
| Smoking status – non-smoker (ref)  Current smoker  Ex-smoker  Unknown | 1.0  1.29 (1.16–1.43)  1.02 (0.93–1.12)  1.19 (1.01–1.39) | <.001 |
| Rhinitis diagnosis, active† | 1.24 (1.03–1.49) | .023 |
| Nasal polyps, ever | 1.65 (1.42–1.93) | <.001 |
| Anaphylaxis diagnosis, ever | 1.77 (1.17–2.68) | .007 |
| PEF % predicted – ≥80% (ref)  ≤60%  61–79%  Unknown | 1.0  1.67 (1.50–1.86)  1.29 (1.17–1.43)  1.26 (1.10–1.43) | <.001 |
| Blood eosinophil count – ≤0.4x109/L (ref)  >0.4 x109/L  Missing | 1.0  1.37 (1.24–1.53)  0.95 (0.86–1.05) | <.001 |
| Mean SABA dose‡ – 0 µg/d (ref)  1–200 µg/d  201–400 µg/d  >400 µg/d | 1.0  0.89 (0.76–1.05)  1.13 (0.96–1.33)  1.68 (1.43–1.97) | <.001 |
| LTRA prescription, ≥1 | 2.22 (2.01–2.45) | <.001 |
| LABA prescription (stand alone), ≥1 | 1.15 (1.03–1.30) | .018 |
| ICS MPR (%) – 80–100% (ref)  >0–39.9%  40–59.9%  60–79.9%  ≥100%  No ICS prescribed | 1.00  0.81 (0.71–0.92)  0.90 (0.79–1.02)  1.01 (0.87–1.17)  0.95 (0.84–1.07)  0.71 (0.59–0.84) | <.001 |
| Acute OCS courses – 0 (ref)  1  ≥2 | 1.0  4.34 (3.94–4.79)  15.49 (14.09–17.04) | <.001 |
| Asthma-related ED admissions, ≥1 | 2.01 (1.55–2.62) | <.001 |
| Primary care consultations – 0 (ref)  1–5  6–12  ≥13 | 1.0  0.94 (0.71–1.23)  1.39 (1.06–1.82)  1.81 (1.38–2.39) | <.001 |

Collinearity of variables is described in the Online Repository. ED, emergency department; ICS, inhaled corticosteroid; LABA, long-acting β2 agonist; LTRA, leukotriene receptor antagonist; MPR, medication possession ratio; OCS, oral corticosteroid; PEF, peak expiratory flow; ref, reference category; SABA, short-acting β2 agonist.

\*Overall *P* value of the association between the predictor and the outcome.

†For comorbidities, ‘active’ refers to those for which a diagnosis was recorded within the baseline year and/or a prior diagnosis was accompanied by a prescription for the comorbidity within the baseline year. ‘Ever’ refers to diagnosis at any time before or during the baseline period.

‡albuterol-equivalent dose.

**TABLE VI.** Predicted risk (over 2 years) as calculated for four hypothetical patients with asthma

|  |  |  |
| --- | --- | --- |
| **Patient description** | **Risk of ≥2 attacks** | **Risk of ≥4 attacks** |
| A 35-year-old woman who is obese, takes NSAIDs, and uses a lot of her SABA (mean, >400 µg/d)   * Non-smoker, PEFR ≥80%, no comorbidities, no OCS courses the prior year, 80–100% MPR, 1–5 primary care consultations, no blood eosinophilia | 8.9% | 1.1% |
| A 56-year-old man at step 4 who has a PEFR of 65% predicted and an incident finding of a high blood eosinophil count   * Non-smoker, normal weight, no comorbidities, no OCS courses the prior year, 80–100% MPR, 1–5 primary care consultations, SABA mean dose 1–200 µg/d | 4.7% | 0.7% |
| An 18-year-old woman with rhinitis and eczema who has had 2 attacks in the last year and is on LTRA   * Non-smoker, PEFR ≥80%, normal weight, no other comorbidities, 80–100% MPR, 6–12 primary care consultations, SABA mean dose 1–200 µg/d, no blood eosinophilia | 49.7% | 17.1% |
| A 23-year-old man who smokes, has had a couple of ED attendances in the last year , and takes 25% of his ICS   * PEFR ≥80%, normal weight, no comorbidities, ≥2 OCS courses, 6–12 primary care consultations, SABA mean dose 1–200 µg/d, no blood eosinophilia | 38.8% | 12.0% |

ED, emergency department; ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist; MPR, medication possession ratio; NSAIDs, nonsteroidal anti-inflammatory drugs; OCS, oral corticosteroid; PEFR, peak expiratory flow rate; SABA, short-acting β2 agonist.

**Figure legends**

**FIGURE 1.** Calibration plot of mean observed risk versus mean predicted risk of ***A*,** ≥2 asthma attacks and ***B*,** ≥4 asthma attacks in the outcome period ; each dot represents one of the 500 groups encompassing all patients in the study (n=118,981).