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

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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

Re: INPRACTICE-D-16-00283R1, Identifying risk of future asthma attacks using UK medical record data: a Respiratory Effectiveness Group initiative

EDITOR'S SPECIFIC COMMENTS:

Thank you for submitting your revised manuscript to JACI: In Practice. As you know, we want to publish your work. However, your responses have not satisfied our biostatistical (Reviewer #3). We will accept your paper for publication after the biostatistical reviewer comments have been adequately addressed in a further revision.

RESPONSE:
We thank the Editor for the opportunity to address the additional comments from Reviewer 3 regarding our manuscript. Our point-by-point response to the comments is provided below.
We hope that you will now find this second revised version of our manuscript suitable for publication in *JACI: In Practice*.
Many thanks for your reconsideration.
Best wishes,
John Blakey, for the authors

Reviewer #1:
The authors have responded very well to reviewer input in their revised manuscript.

RESPONSE: Thank you.

Reviewer #3 (Biostatistical Reviewer)
3.1. COMMENT: The authors have presented some strong analyses due to sample sizes. There are still a few important points to address and revisions needed to the presentation and discussion of analyses to improve this submission. Many of these issues were identified on the first review but not addressed.

3.1 RESPONSE: We thank the Reviewer for these additional comments and suggestions. We hope the following responses address these concerns to the satisfaction of the editorial team.

3.2. COMMENT-Methods section:
-I do not really understand the study design regarding how the years were selected and why? There has to be more input put into this; otherwise it looks like a random collection of years from a prior study.

3.2. RESPONSE: This is a retrospective (historical) cohort design of an observational study, with prospectively followed patients and recorded data. The data were recorded in, and then extracted from, an anonymized database (OPCR database, or OPCRD). The source of the data is the patient records from the GP practices from which all data have been sourced into and stored in the database "OPCRD." The selection (extraction) of the patients for this cohort analysis is by "exposure," that is, based on the data in Year 1. These patients then had had their outcomes (asthma attacks) in the subsequent 2 years (Year 2 and Year 3) after Year 1.
The study years (February 2005 through September 2014) were not selected randomly. As noted in the Methods section, the study period began after the institution of the UK Quality and Outcomes Framework (QOF) in 2004. We ended it at the time of data extraction in September

2014. Within that period (Feb. 2005 to Sept. 2014), we analyzed the most recent 3-year interval of data for eligible patients to include their most current and, as complete as possible, available data.
Our approach in selecting the most recent data for each patient within an established time period is commonly employed in such observational studies. We would refer the Reviewer to these two of several other similar examples of study design:

1. Janson C, Larsson K, Lisspers KH, Stallberg B, Stratelis G, Goike H, et al. Pneumonia and pneumonia related mortality in patients with COPD treated with fixed combinations of inhaled corticosteroid and long acting beta2 agonist: observational matched cohort study (PATHOS). BMJ 2013;346:f3306.
2. Suissa S, Patenaude V, Lapi F, Ernst P. Inhaled corticosteroids in COPD and the risk of serious pneumonia. Thorax 2013;68:1029-36.

We have added the following extended explanation in the Discussion:
"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.[21,40,41] Within that period, we analyzed the most recent 3-year interval of data for eligible patients to include their most current available data."

3.3. COMMENT: -Was any sort of power analysis done? Information on the power of the sample is needed

3.3. RESPONSE: This was an observational, single-cohort exploratory study, not a hypothesis-driven trial or experimental study design of one or multiple arms. Therefore, we have not performed *a priori* sample size and power calculations, but instead we explored all available follow-up data over a 3-year interval from a registry database, with a large number of patients included in the study (N=118, 981). The main aim of the study was to identify risk factors and establish associations, rather than to test them.
We understand the importance of providing power calculation information and, to satisfy the Reviewer's request, we have now included *post-hoc* power analysis of the established associations. We have added a statement in the Discussion indicating that post-hoc power calculations can be found in the Online Repository, the text of which is as follows:
"Post-hoc power calculations showed that the large study population of 118,981 patients provided sufficient statistical power (≥80%; α=0.05) to detect an association with an odds ratio of 1.10 for the risk of two or more asthma attacks, assuming a risk of 11% in patients without the characteristic of the predictor and a prevalence of the characteristic of at least 8%. For the risk of four or more asthma attacks, the study population size would allow detecting an odds ratio of 1.17, assuming a risk of 3.0% in patients without the characteristic for predictors with a prevalence of at least 9%."

3.4. COMMENT: -One can only assume you are using logistic regression because the outcome(s) is binary, but the rational for using logistic regression is not sufficiently defined (though should be).

3.4. RESPONSE: We agree with the Reviewer's comment that a binary outcome can also be predicted (classified) by a ROC curve analysis alone (including calculation of 95% CIs) without the need for a logistic regression model. However, the ROC curve alone is a univariate (single factor) approach and, as such, it does not allow us to build multivariable (multifactor) associations with

the outcome nor to assess model parameters or the parsimony or robustness of potentially identifiable multivariable associations. As mentioned above, our aim was to build a prediction model that could be used to estimate an individual patient's risk of having repeated asthma attacks. Logistic regression analysis is a model- and parameter-based approach that employs an appropriate link function to relate a set of predictors to the presence (repeated attacks) or absence (no repeated attacks) of the binary outcome. Using logistic regression carries the possibility of using criteria to assess the information loss of inclusion/exclusion of different variables in a multivariable framework (AIC).

We do indeed state clearly in the "Model building" subsection of the Methods that we used logistic regression. We leave it the editorial team's discretion to decide whether the above rationale for using logistic regression should be added to the revised manuscript.

3.5. COMMENT: -Please specifically indicate in the Methods section that you have a binary outcome.

3.5. RESPONSE: We have added the underlined words in the following text to the Methods section:
"Univariable logistic regression analysis was used to identify individual characteristics that were predictive of <u>two different binary outcomes</u> (1) two or more <u>(yes/no) asthma attacks during the 2-year outcome period</u> and (2) four or more <u>(yes/no)</u> asthma attacks during the 2-year outcome period."

3.6. COMMENT: -You claim that the variables are rank-ordered but do not state that the variables themselves were rank-ordered.

3.6. RESPONSE: Because some of the candidate variables, such as the number of baseline asthma attacks and its component variable, the number of baseline oral corticosteroid courses, are highly correlated we included only one of these variables in the model to avoid collinearity giving less precise estimates. The choice was based on model fit and clinical input. To detect potential collinearity a non-parametric Spearman correlation coefficient was calculated for each pair of predictors. The values of variables were rank-ordered only for calculating these correlation coefficients and not for other purposes. We have now added the following underlined phrase to the "Model Building" subsection
"<u>The values of variables were rank-ordered for calculating these correlation coefficients, and</u> relationships with rank correlation coefficients greater than 0.30 were defined as being collinear."

3.7. COMMENT: -You now state that you used AICs in model building, but previously stated you used backward selection. Did you redo your analyses?

3.7. RESPONSE: The analyses were not redone, but evidently we did not describe them adequately. We did indeed include the use of AICs for model building in the Methods section of our original submission. Backwards selection was performed manually, based on *P*-values, and the choice of which one of any two collinear (covariate) variables to include was made based on model fit (Akaike). As the number of candidate predictors was large, we used backward elimination to find the model that produced the lowest AIC criterion. We have tried to make this clearer, adding the underlined text as follows:
"All predictors with a significant univariable association ($P<.05$) were entered into a multiple logistic regression analysis with backwards selection of the model<u>, performed manually based</u>

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."

3.8. COMMENT: -Results section:
-A summary of the important risk factors with odds ratio and confidence intervals would still be helpful besides the exhaustive tables that are provided for the two models.

3.8. RESPONSE: As we noted in our prior response to this request: *Tables IV and V summarize all significant predictors included in the two risk models. We believe that the tables are the most succinct and efficient means of summarizing the important risk factors. It would be difficult, and arbitrary, to select the most important ones without lengthy text explanations duplicating information in the tables.*
May we add to this that the aim of the study was not to compare the relative importance of risk factors, but to take steps toward a risk assessment tool comprising many important factors. We would also like to clarify that clinical "importance" is not synonymous with magnitude of effect size: modifiable factors (such as current smoking or obesity) may be considered to be relatively more important than non-modifiable risk factors (such as age or sex) depending on the context in which such data are being viewed.
We have reported in the Results text and Abstract, together with lists of other significant predictors, that the "number of acute OCS courses in the baseline year had the strongest association."
We would be grateful to the Editor for guidance as to whether more results from the tables should be detailed, and thus duplicated, in the body of the text.

3.9. COMMENT: -Discussion section:
-The authors claim they have developed a risk model but there would need to be more testing shown for that to accomplished and presented. Please make this available.

3.9. RESPONSE: We agree with the reviewer that further testing is needed and will be relevant and interesting; however, more testing (e.g., external validation, impact) is outside the scope of the current study. The aim of our study was to assess which predictors were associated with the outcome and to build predictive model(s). What could have been done in terms of internal validation, beyond cross-validation and bootstrapping, was to analyze the models for potential "optimism" in estimated performance or models overfitting in such a large dataset, but no such patterns were found. This gives additional credence to the robustness of the identified associations and the created risk models.
Publishing these analyses in a high-quality journal such as *JACI: In Practice* will facilitate testing these findings in other datasets and settings.

3.10. COMMENT: -There is no real assessment of how variables were important post-analyses, just that the overall models are predictive.

3.10. RESPONSE: Yes, we agree with the Reviewer that more testing is needed and will be relevant and important. While our population was large and our analyses robust, further testing in other datasets is warranted (e.g., external validation). To follow this comment of the

Reviewer and include this potential limitation, we have now added the underlined phrase to the Conclusions of the revised version of the manuscript, as follows:
"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."

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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Word count: 3251

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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~~fed~~ 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 β_2 agonist

LTRA: leukotriene receptor antagonist

OCS: oral corticosteroids

PEF: peak expiratory flow

QOF: Quality and Outcomes Framework

ROC: receiver operating characteristic

SABA: short-acting β_2 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 physical[4] 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 factors[16] 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 criteria[19] 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 β_2 agonist [SABA], inhaled corticosteroids [ICS], long-acting β_2 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),[~~21~~ 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).[~~22,23~~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,[~~24~~ 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 ~~R~~relationships with rank correlation coefficients greater than 0.30 were defined as being collinear.

All predictors with a significant univariable association ($P<.05$) were ~~fed~~ entered into a multiple logistic regression analysis with backwards selection of the model, performed manually based on significant *P* values. ~~including all significant independent predictors.~~ 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 ~~giving~~ 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 ~~model~~ 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 ~~were performed by comparing~~ showing the correlation of the mean observed risk with mean predicted risk among 500 groups ~~of ~238 patients,~~ encompassing all patients in the study (n=118,981).

~~**Role of the funding source**~~

~~This study was funded by the Respiratory Effectiveness Group, an investigator-led, not-for-profit, real-life respiratory research and advocacy initiative.[25] Access to data from the Optimum Patient Care Research Database was co-funded by Research in Real-Life Ltd, UK, under a subcontract by Observational and Pragmatic Research Institute Pte Ltd, Singapore. The corresponding author had full access to all the data in the study and takes final responsibility for the decision to submit for publication.~~

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) ~~frequency~~ 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 Deaths[29]; 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 10^9/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 al[37] 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.[40,41~~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~~; f~~. Further ~~analysis~~ analyses will be required to ~~create~~ 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/m^2; 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 10^9cell/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 β_2 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 β_2 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 10^9/L	64,803 (55)
>0.4 x 10^9/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 β_2 agonist; LTRA, leukotriene receptor antagonist; NSAIDs, nonsteroidal anti-inflammatory drugs; OCS, oral corticosteroid; PEF, peak expiratory flow; SABA, short-acting β_2 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.

~~The category 'Years 2 & 3 combined' includes those patients who had a single exacerbation in year 2 and/or in year 3.~~

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)

The category 'Years 2 & 3 combined' includes those patients who had a single exacerbation in year 2 and/or in year 3.

545 **TABLE IV.** Independent baseline predictors (~~in study~~ year 1) of two or more asthma attacks
546 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)	1.00	<.001
19–34 years	1.27 (1.14–1.40)	
35–54 years	1.43 (1.29–1.57)	
55–80 years	1.47 (1.33–1.62)	
Sex, female	1.35 (1.29–1.41)	<.001
Body mass index – normal (ref)	1.00	<.001
Underweight	1.10 (0.95–1.27)	
Overweight	1.16 (1.09–1.22)	
Obese	1.27 (1.21–1.34)	
Unknown	0.96 (0.86–1.08)	
Smoking status – non-smoker (ref)	1.00	<.001
Current smoker	1.17 (1.11–1.24)	
Ex-smoker	1.01 (0.96–1.06)	
Unknown	1.02 (0.93–1.11)	
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)	1.00	<.001
≤60%	1.62 (1.52–1.27)	
61–79%	1.21 (1.15–1.27)	
Unknown	1.25 (1.17–1.33)	
Blood eosinophil count – ≤0.4x10^9/L (ref)	1.00	<.001
>0.4 x10^9/L	1.21 (1.14–1.29)	
Missing	0.88 (0.83–0.93)	
Mean SABA dose‡ – 0 µg/d (ref)	1.00	<.001
1–200 µg/d	1.05 (0.97–1.14)	
201–400 µg/d	1.28 (1.16–1.39)	
>400 µg/d	1.63 (1.45–1.77)	
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)	1.00	<.001
>0–39.9%	0.88 (0.82–0.94)	
40–59.9%	0.88 (0.82–0.95)	
60–79.9%	0.94 (0.86–1.02)	
≥100%	0.92 (0.86–0.98)	
No ICS prescribed	0.65 (0.59–0.71)	
Acute OCS courses – 0 (ref)	1.00	<.001
1	3.34 (3.37–3.71)	
≥2	9.50 (8.94–10.08)	
Asthma-related ED admission, ≥1	1.76 (1.45–2.13)	<.001
Primary care consultations – 0 (ref)	1.00	<.001

Year 1 predictors	Adjusted OR (95% CI)	*P* value*
1–5	1.29 (1.13–1.48)	
6–12	1.66 (1.45–1.90)	
≥13	2.05 (1.78–2.36)	

Collinearity of variables is described in the Online Repository. ED, emergency department; GERD, gastroesophageal reflux disease; ICS, inhaled corticosteroid; LABA, long-acting β_2 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 β_2 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.

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

Age –12–18 years (ref)	1.0	<.001
19–34 years	1.13 (0.91–1.40)	
35–54 years	1.45 (1.19–1.77)	
55–80 years	1.61 (1.31–1.97)	
Sex, female	1.31 (1.20–1.43)	<.001
Body mass index – normal (ref)	1.0	<.001
Underweight	0.89 (0.65–1.22)	
Overweight	1.18 (1.06–1.31)	
Obese	1.27 (1.15–1.41)	
Unknown	0.95 (0.76–1.20)	
Smoking status – non-smoker (ref)	1.0	<.001
Current smoker	1.29 (1.16–1.43)	
Ex-smoker	1.02 (0.93–1.12)	
Unknown	1.19 (1.01–1.39)	
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)	1.0	<.001
≤60%	1.67 (1.50–1.86)	
61–79%	1.29 (1.17–1.43)	
Unknown	1.26 (1.10–1.43)	
Blood eosinophil count – ≤0.4x10^9/L (ref)	1.0	<.001
>0.4 x10^9/L	1.37 (1.24–1.53)	
Missing	0.95 (0.86–1.05)	
Mean SABA dose‡ – 0 µg/d (ref)	1.0	<.001
1–200 µg/d	0.89 (0.76–1.05)	
201–400 µg/d	1.13 (0.96–1.33)	
>400 µg/d	1.68 (1.43–1.97)	
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)	1.00	<.001
>0–39.9%	0.81 (0.71–0.92)	
40–59.9%	0.90 (0.79–1.02)	
60–79.9%	1.01 (0.87–1.17)	
≥100%	0.95 (0.84–1.07)	
No ICS prescribed	0.71 (0.59–0.84)	
Acute OCS courses – 0 (ref)	1.0	<.001
1	4.34 (3.94–4.79)	
≥2	15.49 (14.09–17.04)	
Asthma-related ED admissions, ≥1	2.01 (1.55–2.62)	<.001
Primary care consultations – 0 (ref)	1.0	<.001
1–5	0.94 (0.71–1.23)	
6–12	1.39 (1.06–1.82)	
≥13	1.81 (1.38–2.39)	

Collinearity of variables is described in the Online Repository. ED, emergency department; ICS, inhaled corticosteroid; LABA, long-acting β_2 agonist; LTRA, leukotriene receptor antagonist; MPR, medication possession ratio; OCS, oral corticosteroid; PEF, peak expiratory flow; ref, reference category; SABA, short-acting β_2 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~~ A 35-year-old woman who is obese, takes NSAIDs, and uses a lot of her SABA (mean, >400 µg/d)	8.9%	1.1%
– Non-smoker, PEFR ≥80%, no comorbidities, no OCS courses the prior year, 80–100% MPR, 1–5 primary care consultations, no blood eosinophilia		
~~a~~ 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	4.7%	0.7%
– 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		
~~an~~ An 18-year-old woman with rhinitis and eczema who has had 2 attacks in the last year and is on LTRA	49.7%	17.1%
– 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		
~~a~~ A 23-year-old man who smokes, has had a couple of ED attendances in the last year , and takes 25% of his ICS	38.8%	12.0%
– PEFR ≥80%, normal weight, no comorbidities, ≥2 OCS courses, 6–12 primary care consultations, SABA mean dose 1–200 µg/d, no blood eosinophilia		

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 β_2 agonist.

582 **Figure legends**

583 **FIGURE 1.** Calibration plot of mean observed risk versus mean predicted risk of ***A,*** ≥2 asthma

584 attacks and ***B,*** ≥4 asthma attacks in the outcome period ~~for groups of ~238 patients~~; each dot

585 represents one of the 500 groups encompassing all patients in the study (n=118,981).

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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 β_2 agonist

LTRA: leukotriene receptor antagonist

OCS: oral corticosteroids

PEF: peak expiratory flow

QOF: Quality and Outcomes Framework

ROC: receiver operating characteristic

SABA: short-acting β_2 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 physical[4] 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 factors[16] 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 criteria[19] 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 β_2 agonist [SABA], inhaled corticosteroids [ICS], long-acting β_2 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 Deaths[29]; 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 10^9/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 al[37] 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/m^2; 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 10^9cell/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 β_2 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 β_2 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 10^9/L	64,803 (55)
>0.4 x 10^9/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 β_2 agonist; LTRA, leukotriene receptor antagonist; NSAIDs, nonsteroidal anti-inflammatory drugs; OCS, oral corticosteroid; PEF, peak expiratory flow; SABA, short-acting β_2 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)

The category 'Years 2 & 3 combined' includes those patients who had a single exacerbation in year 2 and/or in year 3.

533 **TABLE IV.** Independent baseline predictors (year 1) of two or more asthma attacks during the
534 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)	1.00	<.001
19–34 years	1.27 (1.14–1.40)	
35–54 years	1.43 (1.29–1.57)	
55–80 years	1.47 (1.33–1.62)	
Sex, female	1.35 (1.29–1.41)	<.001
Body mass index – normal (ref)	1.00	<.001
Underweight	1.10 (0.95–1.27)	
Overweight	1.16 (1.09–1.22)	
Obese	1.27 (1.21–1.34)	
Unknown	0.96 (0.86–1.08)	
Smoking status – non-smoker (ref)	1.00	<.001
Current smoker	1.17 (1.11–1.24)	
Ex-smoker	1.01 (0.96–1.06)	
Unknown	1.02 (0.93–1.11)	
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)	1.00	<.001
≤60%	1.62 (1.52–1.27)	
61–79%	1.21 (1.15–1.27)	
Unknown	1.25 (1.17–1.33)	
Blood eosinophil count – ≤0.4x10^9/L (ref)	1.00	<.001
>0.4 x10^9/L	1.21 (1.14–1.29)	
Missing	0.88 (0.83–0.93)	
Mean SABA dose‡ – 0 µg/d (ref)	1.00	<.001
1–200 µg/d	1.05 (0.97–1.14)	
201–400 µg/d	1.28 (1.16–1.39)	
>400 µg/d	1.63 (1.45–1.77)	
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)	1.00	<.001
>0–39.9%	0.88 (0.82–0.94)	
40–59.9%	0.88 (0.82–0.95)	
60–79.9%	0.94 (0.86–1.02)	
≥100%	0.92 (0.86–0.98)	
No ICS prescribed	0.65 (0.59–0.71)	
Acute OCS courses – 0 (ref)	1.00	<.001
1	3.34 (3.37–3.71)	
≥2	9.50 (8.94–10.08)	
Asthma-related ED admission, ≥1	1.76 (1.45–2.13)	<.001
Primary care consultations – 0 (ref)	1.00	<.001

Year 1 predictors	Adjusted OR (95% CI)	*P* value*
1–5	1.29 (1.13–1.48)	
6–12	1.66 (1.45–1.90)	
≥13	2.05 (1.78–2.36)	

Collinearity of variables is described in the Online Repository. ED, emergency department; GERD, gastroesophageal reflux disease; ICS, inhaled corticosteroid; LABA, long-acting β_2 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 β_2 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.

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

Age –12–18 years (ref)	1.0	<.001
19–34 years	1.13 (0.91–1.40)	
35–54 years	1.45 (1.19–1.77)	
55–80 years	1.61 (1.31–1.97)	
Sex, female	1.31 (1.20–1.43)	<.001
Body mass index – normal (ref)	1.0	<.001
Underweight	0.89 (0.65–1.22)	
Overweight	1.18 (1.06–1.31)	
Obese	1.27 (1.15–1.41)	
Unknown	0.95 (0.76–1.20)	
Smoking status – non-smoker (ref)	1.0	<.001
Current smoker	1.29 (1.16–1.43)	
Ex-smoker	1.02 (0.93–1.12)	
Unknown	1.19 (1.01–1.39)	
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)	1.0	<.001
≤60%	1.67 (1.50–1.86)	
61–79%	1.29 (1.17–1.43)	
Unknown	1.26 (1.10–1.43)	
Blood eosinophil count – ≤0.4x10^9/L (ref)	1.0	<.001
>0.4 x10^9/L	1.37 (1.24–1.53)	
Missing	0.95 (0.86–1.05)	
Mean SABA dose‡ – 0 µg/d (ref)	1.0	<.001
1–200 µg/d	0.89 (0.76–1.05)	
201–400 µg/d	1.13 (0.96–1.33)	
>400 µg/d	1.68 (1.43–1.97)	
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)	1.00	<.001
>0–39.9%	0.81 (0.71–0.92)	
40–59.9%	0.90 (0.79–1.02)	
60–79.9%	1.01 (0.87–1.17)	
≥100%	0.95 (0.84–1.07)	
No ICS prescribed	0.71 (0.59–0.84)	
Acute OCS courses – 0 (ref)	1.0	<.001
1	4.34 (3.94–4.79)	
≥2	15.49 (14.09–17.04)	
Asthma-related ED admissions, ≥1	2.01 (1.55–2.62)	<.001
Primary care consultations – 0 (ref)	1.0	<.001
1–5	0.94 (0.71–1.23)	
6–12	1.39 (1.06–1.82)	
≥13	1.81 (1.38–2.39)	

Collinearity of variables is described in the Online Repository. ED, emergency department; ICS, inhaled corticosteroid; LABA, long-acting β_2 agonist; LTRA, leukotriene receptor antagonist; MPR, medication possession ratio; OCS, oral corticosteroid; PEF, peak expiratory flow; ref, reference category; SABA, short-acting β_2 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)	8.9%	1.1%
– Non-smoker, PEFR ≥80%, no comorbidities, no OCS courses the prior year, 80–100% MPR, 1–5 primary care consultations, no blood eosinophilia		
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	4.7%	0.7%
– 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		
An 18-year-old woman with rhinitis and eczema who has had 2 attacks in the last year and is on LTRA	49.7%	17.1%
– 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		
A 23-year-old man who smokes, has had a couple of ED attendances in the last year , and takes 25% of his ICS	38.8%	12.0%
– PEFR ≥80%, normal weight, no comorbidities, ≥2 OCS courses, 6–12 primary care consultations, SABA mean dose 1–200 µg/d, no blood eosinophilia		

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 β_2 agonist.

570 **Figure legends**

571 **FIGURE 1.** Calibration plot of mean observed risk versus mean predicted risk of ***A,*** ≥2 asthma

572 attacks and ***B,*** ≥4 asthma attacks in the outcome period ; each dot represents one of the 500

573 groups encompassing all patients in the study (n=118,981).

574

575

Figure No.1A

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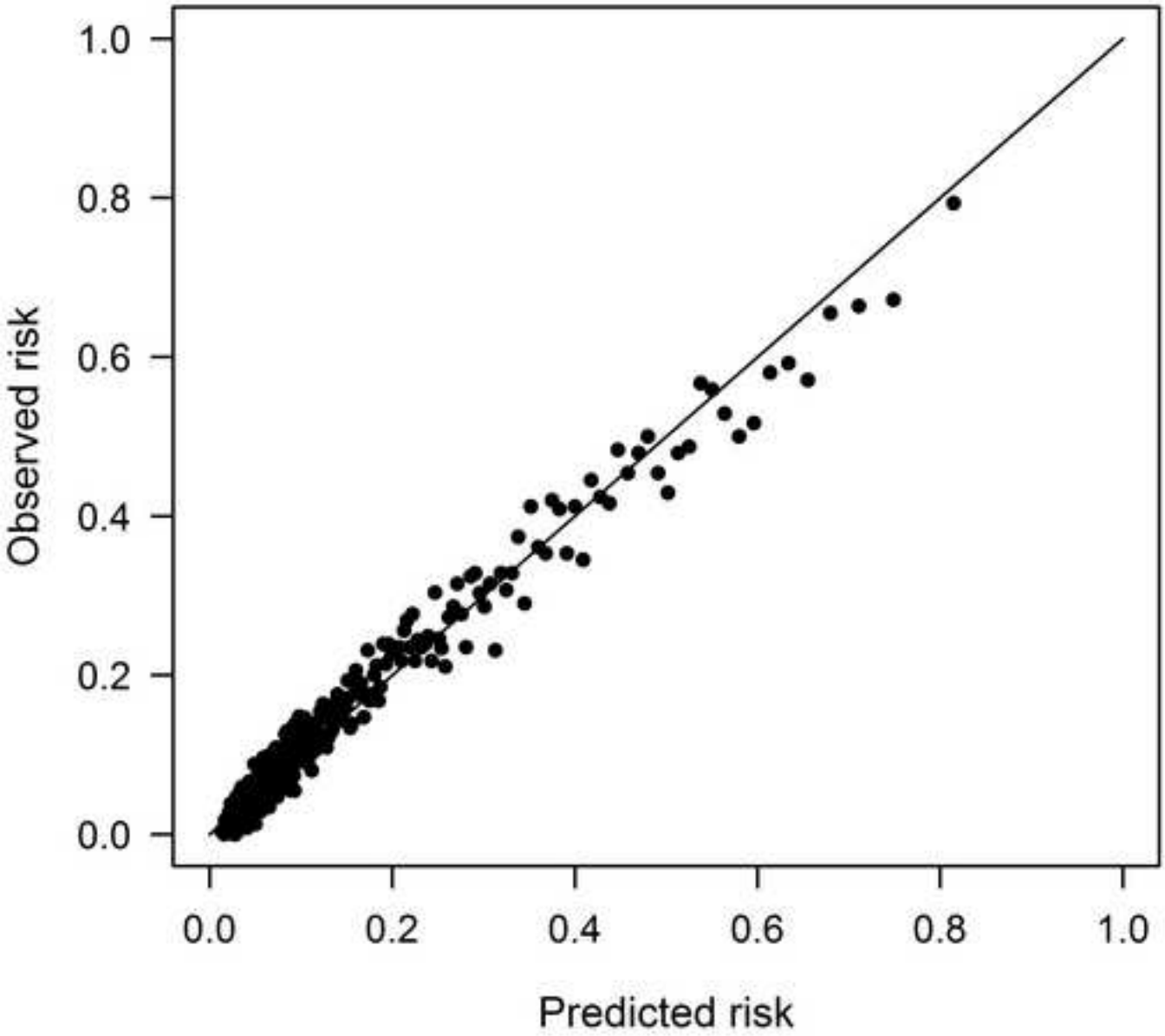

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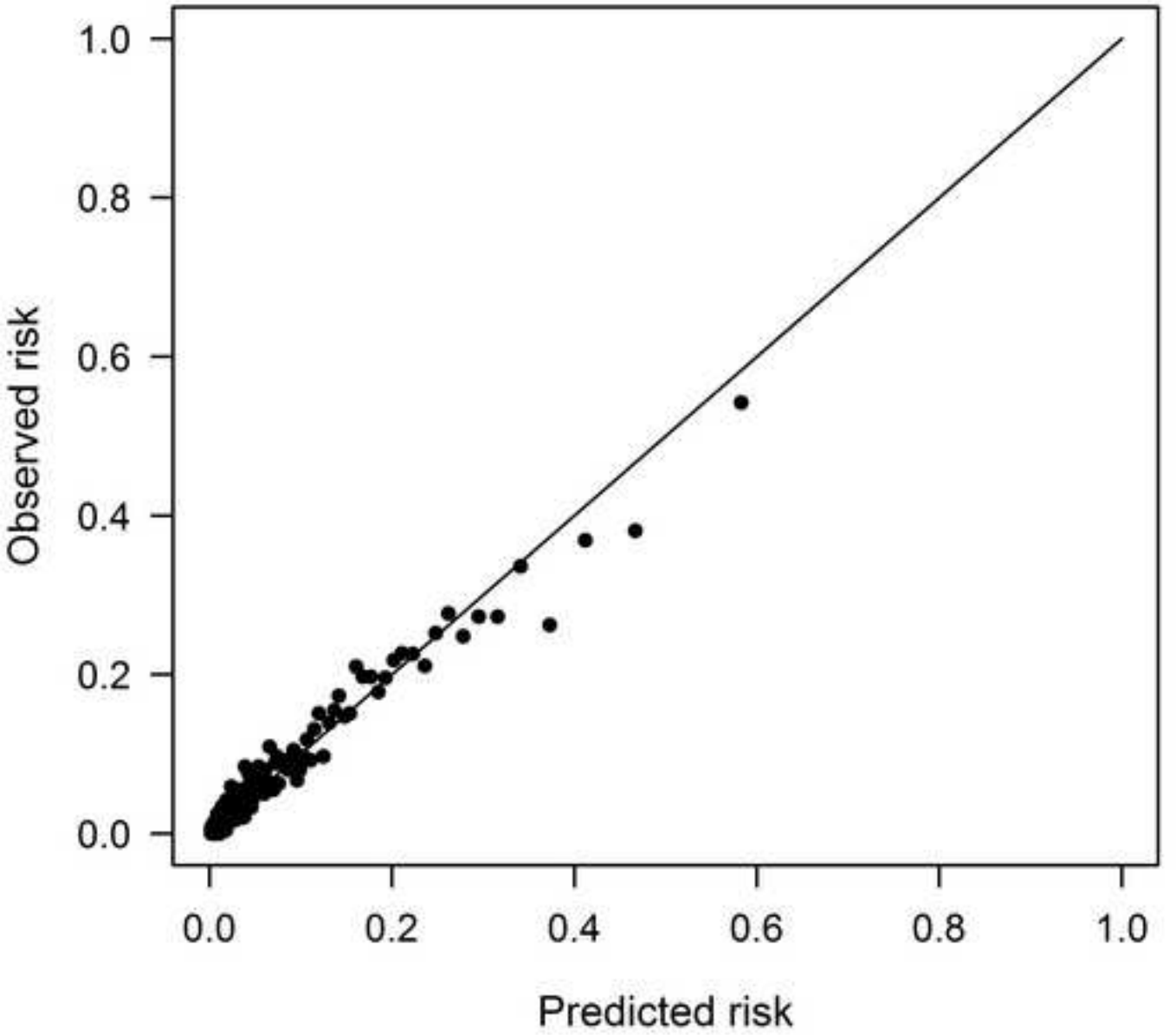

Online Repository

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

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Supplementary Methods

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.[E1,E2] The study protocol was approved by the Anonymised Data Ethics Protocols and Transparency (ADEPT) committee, the independent scientific advisory committee for the OPCRD, and was registered with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP http://www.encepp.eu/encepp/viewResource.htm?id=6303).[E3]

The Charlson comorbidity index (CCI) score[E4] in the baseline year was categorized as 0, 1–4, 5–9, ≥10, with comorbidity weights taken from the Hospital Standardised Mortality Ratios.[E5]

Post-hoc power calculations showed that the large study population of 118,981 patients provided sufficient statistical power (≥80%; α=0.05) to detect an association with an odds ratio of 1.10 for the risk of two or more asthma attacks, assuming a risk of 11% in patients without the characteristic of the predictor and a prevalence of the characteristic of at least 8%. For the risk of four or more asthma attacks, the study population size would allow detecting an odds ratio of 1.17, assuming a risk of 3.0% in patients without the characteristic for predictors with a prevalence of at least 9%.

Supplementary Results

Additional patient demographic and clinical characteristics are depicted in Online Repository Table E1.[E6]

Univariable analyses

All of the potential baseline risk factors tested in univariable analyses with the exception of beta blocker prescriptions (yes/no) were significantly associated with the presence of asthma attacks (≥2 or ≥4 attacks) in the follow-up period (study years 2 and 3; Online Repository Table E2).[E6–E9]

Multivariable analyses

Age was collinear with gastroesophageal reflux disease (GERD) diagnosis (active/ever) and/or GERD drugs, cardiovascular disease diagnosis, and prescriptions for statins.

Acute oral corticosteroid (OCS) courses were collinear with acute OCS courses with evidence of lower respiratory consultation, antibiotic courses (with evidence of lower respiratory consultation), acute respiratory events, and severe exacerbations (baseline year).

Inhaled corticosteroid (ICS) adherence was collinear with number of ICS prescriptions and inhalers, ICS average daily dose, ICS prescribed and actual duration, and number of SABA prescriptions and inhalers.

ICS prescribed dose was collinear with ICS device type.

Rhinitis diagnosis (active) was collinear with rhinitis diagnosis (ever), rhinitis diagnosis (active)/drugs, and rhinitis diagnosis (ever)/drugs.

Eczema diagnosis (active) was collinear with eczema (ever).

GERD diagnosis (active) was collinear with GERD diagnosis (ever).

Primary care consultations were collinear with diabetes diagnosis, asthma consultations, CCI score, paracetamol prescriptions, antibiotic courses, and asthma control status.

NSAID prescriptions were collinear with paracetamol prescriptions.

During the stepwise backward logistic regression, heart failure and anxiety/depression were dropped from the ~~full~~ final model for two or more attacks; and diagnoses of

gastroesophageal reflux disease (GERD, active), heart failure, eczema (active), and anxiety/depression, as well as prescriptions for nonsteroidal anti-inflammatory drugs were dropped from the ~~full~~ final model for four or more attacks.

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E1. Roche N, Reddel H, Martin R, Brusselle G, Papi A, Thomas M, et al. Quality standards for real-world research. Focus on observational database studies of comparative effectiveness. Ann Am Thorac Soc 2014;11 Suppl 2:S99-S104.

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FIGURE E1. Patient flow chart showing selection of eligible patients in the Optimum Patient Care Database.

COPD, chronic obstructive pulmonary disease; OPCRD, Optimum Patient Care Research Database.

FIGURE E2. Receiver operating characteristic curve for the model predicting risk of ≥2 asthma attacks in the 2-year outcome period.

FIGURE E3. Receiver operating characteristic curve for the model predicting risk of ≥4 asthma attacks in the 2-year outcome period.

Online Repository

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

John D Blakey, PhD, David B Price, MD, Emilio Pizzichini, MD, Todor A Popov, MD, Borislav D Dimitrov, DM/PhD, Dirkje S Postma, MD, Lynn K Josephs, DM, Alan Kaplan, MD, Alberto Papi, MD, Marjan Kerkhof, PhD, Elizabeth V Hillyer, DVM, Alison Chisholm, MSc, Mike Thomas, PhD

Supplementary Methods

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.[E1,E2] The study protocol was approved by the Anonymised Data Ethics Protocols and Transparency (ADEPT) committee, the independent scientific advisory committee for the OPCRD, and was registered with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP http://www.encepp.eu/encepp/viewResource.htm?id=6303).[E3]

The Charlson comorbidity index (CCI) score[E4] in the baseline year was categorized as 0, 1–4, 5–9, ≥10, with comorbidity weights taken from the Hospital Standardised Mortality Ratios.[E5]

Post-hoc power calculations showed that the large study population of 118,981 patients provided sufficient statistical power (≥80%; α=0.05) to detect an association with an odds ratio of 1.10 for the risk of two or more asthma attacks, assuming a risk of 11% in patients without the characteristic of the predictor and a prevalence of the characteristic of at least 8%. For the risk of four or more asthma attacks, the study population size would allow detecting an odds ratio of 1.17, assuming a risk of 3.0% in patients without the characteristic for predictors with a prevalence of at least 9%.

Supplementary Results

Additional patient demographic and clinical characteristics are depicted in Online Repository Table E1.[E6]

Univariable analyses

All of the potential baseline risk factors tested in univariable analyses with the exception of beta blocker prescriptions (yes/no) were significantly associated with the presence of asthma attacks (≥2 or ≥4 attacks) in the follow-up period (study years 2 and 3; Online Repository Table E2).[E6–E9]

Multivariable analyses

Age was collinear with gastroesophageal reflux disease (GERD) diagnosis (active/ever) and/or GERD drugs, cardiovascular disease diagnosis, and prescriptions for statins.

Acute oral corticosteroid (OCS) courses were collinear with acute OCS courses with evidence of lower respiratory consultation, antibiotic courses (with evidence of lower respiratory consultation), acute respiratory events, and severe exacerbations (baseline year).

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Primary care consultations were collinear with diabetes diagnosis, asthma consultations, CCI score, paracetamol prescriptions, antibiotic courses, and asthma control status.

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During the stepwise backward logistic regression, heart failure and anxiety/depression were dropped from the final model for two or more attacks; and diagnoses of

gastroesophageal reflux disease (GERD, active), heart failure, eczema (active), and anxiety/depression, as well as prescriptions for nonsteroidal anti-inflammatory drugs were dropped from the final model for four or more attacks.

References

E1. Roche N, Reddel H, Martin R, Brusselle G, Papi A, Thomas M, et al. Quality standards for real-world research. Focus on observational database studies of comparative effectiveness. Ann Am Thorac Soc 2014;11 Suppl 2:S99-S104.

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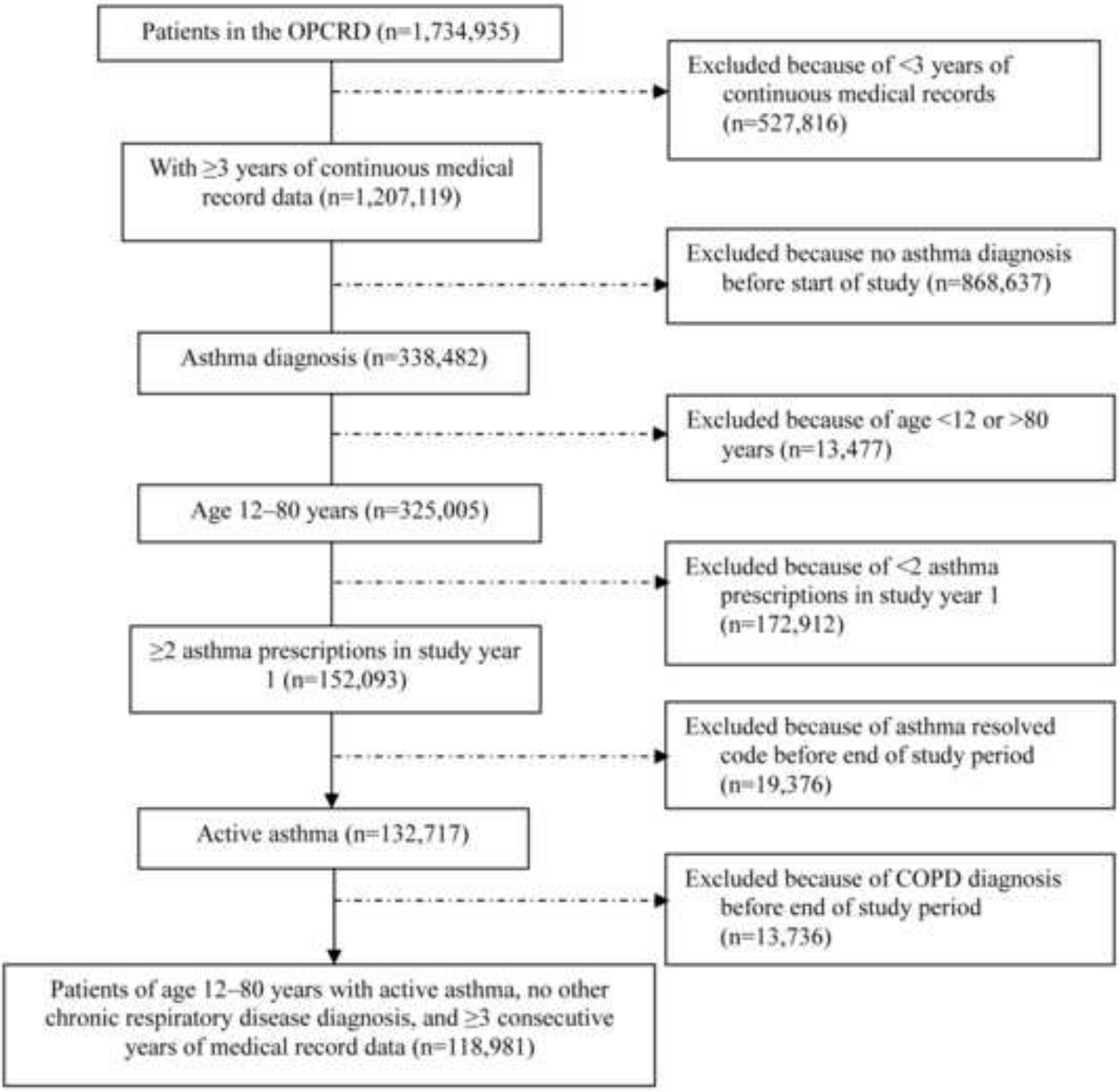

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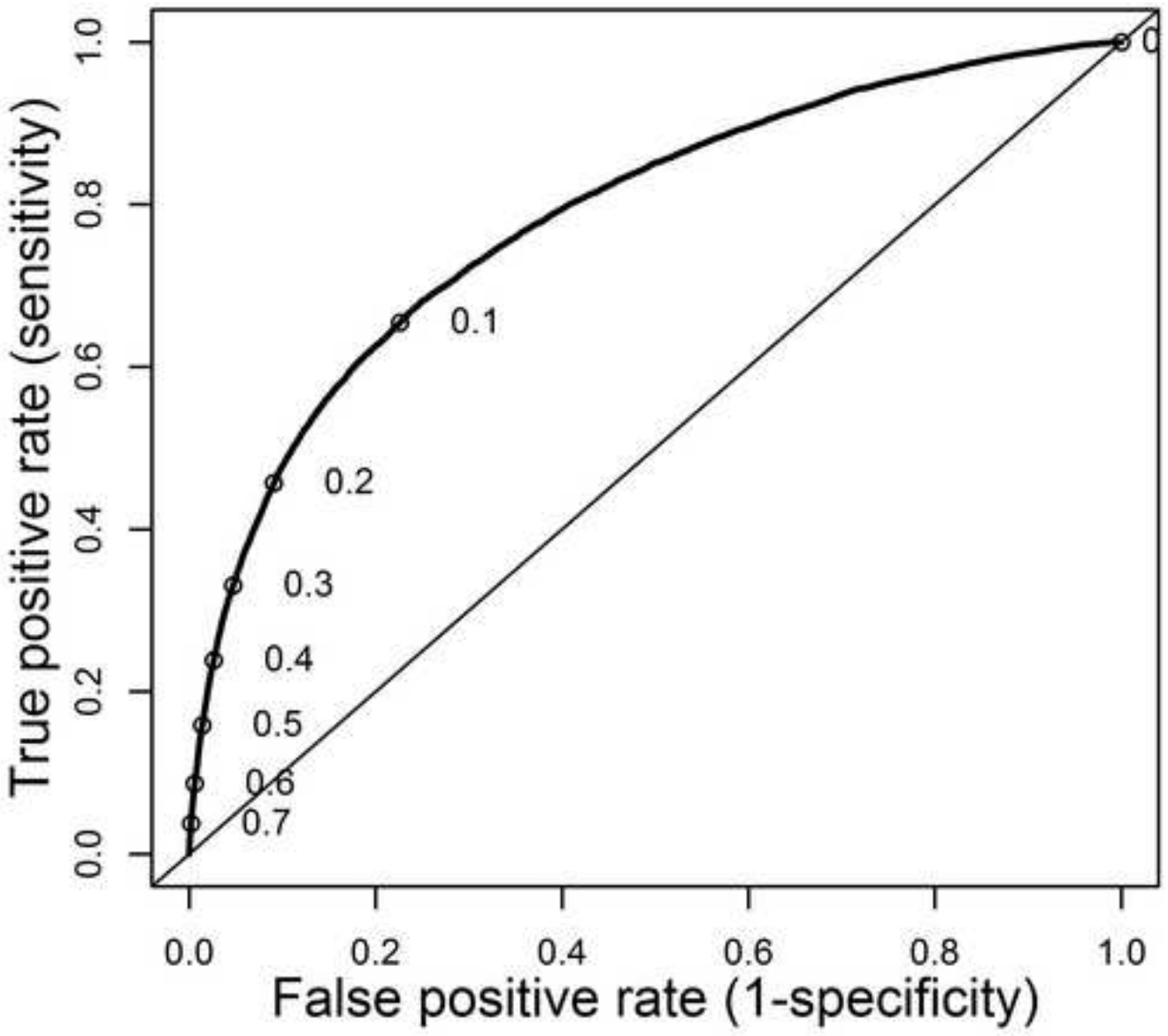

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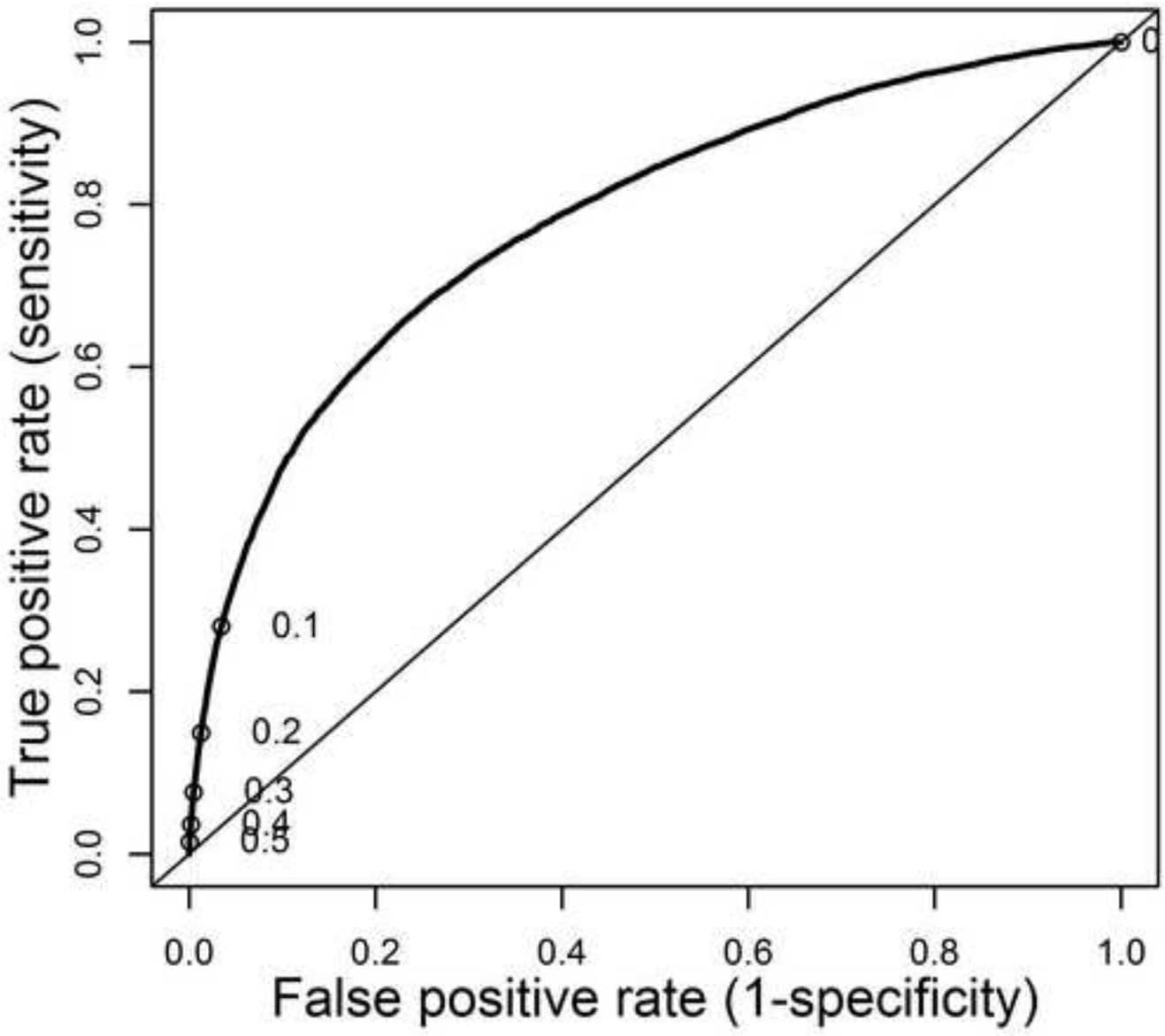

TABLE E1. Additional patient demographic and clinical characteristics during the baseline year

Variable	All patients (n=118,981)
Charlson comorbidity index score	
0	54,974 (46)
1–4	58,034 (49)
5–9	3351 (3)
≥10	2622 (2)
Recorded comorbidity†	
Rhinitis diagnosis, active*	3567 (3)
Rhinitis diagnosis/therapy, active	36,312 (31)
Rhinitis diagnosis, ever	30,644 (26)
Rhinitis diagnosis/therapy, ever	81,991 (69)
Nasal polyps, ever*	3933 (3)
Eczema diagnosis, active*	4321 (4)
Eczema diagnosis, ever	32,213 (27)
GERD diagnosis, active*	1444 (1)
GERD diagnosis/therapy, active	23,861 (20)
GERD diagnosis, ever	9640 (8)
GERD diagnosis/therapy, ever	40,593 (34)
Diabetes (type 1 or 2), ever	15,105 (13)
Cardiovascular disease, ever	29,688 (25)
Ischemic heart disease, ever	6208 (5)
Heart failure, ever	873 (0.7)
Asthma education, ever	47,356 (40)
Mean daily ICS dose‡	
0 μg/d	14,636 (12)
<400 μg/d	87,543 (74)
≥400 μg/d	16,802 (14)
≥1 prescription during baseline	
Paracetamol	28,166 (24)
Beta-blockers	3334 (3)
Statins	18,159 (15)
BTS step§	
No therapy	0 (0)
Step 1	13,761 (12)
Step 2	39,222 (33)
Step 3	27,837 (23)
Step 4	36,004 (30)
Step 5	2144 (2)
Not assignable	13 (0.01)
ICS or FDC inhaler device type, last prescription	
pMDI	69,604 (59)
DPI	28,920 (24)
BAI	5821 (5)

No ICS	14,636 (12)
Spacer device prescribed with ICS pMDI	6212 (9)
Acute OCS courses with lower respiratory consultation	
0	115,117 (97)
1	3436 (3)
≥2	428 (0.4)
Primary care consultation for asthma	
0	37,367 (31)
1	51,115 (43)
≥2	30,499 (26)
Acute respiratory events	
0	81,387 (68)
1	24,538 (21)
≥2	13,056 (11)
Antibiotics with lower respiratory consult	
0	90,247 (76)
1	19,692 (17)
≥2	9042 (7)
Asthma limiting daily activities, *n with data*	35,526
yes	7784 (22)
Asthma limiting night-time activities, *n with data*	36,250
yes	6261 (17)
Asthma is causing daytime symptoms, *n with data*	43,762
yes	27,690 (63)

Data are n (%) unless otherwise noted.

BAI, breath-actuated inhaler; BTS, British Thoracic Society; DPI, dry powder inhaler; FDC, fixed-dose combination; FP, fluticasone propionate; GERD, gastroesophageal reflux disease; ICS, inhaled corticosteroid; LABA, long-acting β_2 agonist; LTRA, leukotriene receptor antagonist; NSAIDs, nonsteroidal anti-inflammatory drugs; OCS, oral corticosteroid; PEF, peak expiratory flow; pMDI, pressurized metered-dose inhaler; SABA, short-acting β_2 agonist;

*Variables included in the final model for risk of ≥2 asthma attacks during the outcome 2 years.

†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.

‡fluticasone-equivalent ICS dose

§BTS steps were defined as 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.[E6]

1 **TABLE E2.** Results of univariable logistic regression analyses of asthma attack frequency (n=118,981)

Year 1 predictors	Asthma attacks within the 2-year outcome period					
	<2 n (%)	**≥2 n (%)**	**OR (95% CI)**	**<4, n (%)**	**≥4, n (%)**	**OR (95% CI)**
Sex, female	58,816 (55)	8718 (68)	1.75 (1.69–1.82)	65,282 (56)	2252 (70)	1.85 (1.72–2.00)
Age, years						
12–18	12,753 (12)	699 (6)	1.0	13,312 (12)	140 (4)	1.0
19–34	19,520 (18)	1861 (14)	1.74 (1.59–1.90)	20,984 (18)	397 (12)	1.80 (1.48–2.18)
35–54	39,459 (37)	4916 (39)	2.27 (2.09–2.47)	43,134 (37)	1241 (39)	2.74 (2.29–3.26)
55–80	34,513 (32)	5260 (41)	2.78 (2.56–3.02)	38,353 (33)	1420 (44)	3.52 (2.96–4.19)
Body mass index						
Normal	32,339 (30)	3061 (24)	1.0	34,685 (30)	715 (22)	1.0
Underweight	3221 (3)	259 (2)	0.85 (0.75–0.97)	3430 (3)	50 (2)	0.71 (0.53–0.94)
Overweight	32,700 (31)	3908 (31)	1.26 (1.20–1.33)	35,629 (31)	979 (31)	1.33 (1.21–1.47)
Obese	30,536 (29)	5008 (39)	1.73 (1.65–1.82)	34,200 (29)	1344 (42)	1.91 (1.74–2.09)
Unknown	7449 (7)	500 (4)	0.71 (0.64–0.78)	7839 (7)	110 (3)	0.68 (0.56–0.83)
Smoking status						
Non-smoker	59,015 (56)	6474 (51)	1.0	63,941 (55)	1548 (48)	1.0
Current smoker	16,655 (16)	2367 (19)	1.30 (1.23–1.36)	18,394 (16)	628 (20)	1.41 (1.28–1.55)
Ex-smoker	23,631 (22)	3127 (24)	1.21 (1.15–1.26)	25,951 (22)	807 (25)	1.28 (1.18–1.40)
Unknown	6944 (6)	768 (6)	1.01 (0.93–1.09)	7497 (6)	215 (7)	1.19 (1.03–1.37)
Charlson comorbidity index score						
0	50,250 (47)	4724 (37)	1.0	53,925 (47)	1049 (33)	1.0
1–4	50,853 (48)	7181 (56)	1.50 (1.44–1.56)	56,116 (48)	1918 (60)	1.76 (1.63–1.89)
5–9	2876 (3)	475 (4)	1.76 (1.59–1.95)	3218 (3)	133 (4)	2.12 (1.77–2.56)
≥10	2266 (2)	356 (3)	1.67 (1.49–1.88)	2524 (2)	98 (3)	1.99 (1.62–2.46)
Asthma education	42,009 (40)	5347 (42)	1.11 (1.07–1.15)	45,900 (40)	1456 (46)	1.27 (1.18–1.37)
PEF % predicted						
≤60	11,045 (11)	2763 (22)	2.87 (2.72–3.02)	12,931 (11)	877 (27)	3.90 (3.54–4.30)
61–79	29,804 (28)	4046 (32)	1.56 (1.48–1.63)	32,797 (28)	1053 (33)	1.85 (1.69–2.03)
≥80	43,945 (41)	3835 (30)	1.0	46,964 (41)	816 (26)	1.0
Unknown	21,451 (20)	2092 (16)	1.12 (1.06–1.18)	23,091 (20)	452 (14)	1.13 (1.00–1.26)
Blood eosinophil count ($x10^9$/L)						

≤0.4	56,856 (54)	7947 (62)	1.0	62,834 (54)	1969 (62)	1.0
>0.4	11,271 (10)	1913 (15)	1.21 (1.15–1.28)	12,608 (11)	576 (18)	1.46 (1.33–1.60)
Unknown	38,118 (36)	2876 (23)	0.54 (0.52–0.56)	40,341 (35)	653 (20)	0.52 (0.47–0.57)
Rhinitis diagnosis, active*	3060 (3)	507 (4)	1.39 (1.27–1.54)	3415 (3)	152 (5)	1.64 (1.39–1.94)
Rhinitis diagnosis /drugs, active	31,073 (29)	5239 (41)	1.69 (1.63–1.76)	34,792 (30)	1520 (48)	2.11 (1.96–2.26)
Rhinitis diagnosis, ever*	26,921 (25)	3723 (29)	1.22 (1.17–1.27)	29,633 (26)	1011 (32)	1.34 (1.25–1.45)
Rhinitis diagnosis /drugs, ever	72,082 (68)	9909 (78)	1.66 (1.59–1.74)	79,389 (69)	2602 (81)	2.0 (1.83–2.19)
Eczema diagnosis, active	3741 (4)	580 (5)	1.31 (1.19–1.43)	4159 (4)	162 (5)	1.43 (1.22–1.68)
Eczema diagnosis, ever	28,570 (27)	3643 (29)	1.09 (1.05–1.14)	31,281 (27)	932 (29)	1.11 (1.03–1.20)
GERD diagnosis, active	1188 (1)	256 (2)	1.82 (1.58–2.08)	1373 (1.2)	71 (2.2)	1.89 (1.49–2.41)
GERD diagnosis/ drugs, active	19,890 (19)	3971 (32)	1.97 (1.89–2.05)	22,667 (20)	1194 (37)	2.45 (2.28–2.63)
GERD diagnosis, ever	8130 (8)	1510 (12)	1.62 (1.53–1.72)	9217 (8)	423 (13)	1.76 (1.59–1.96)
GERD diagnosis/ drugs, ever	34,421 (32)	6172 (48)	1.96 (1.89–2.04)	38,853 (34)	1740 (54)	2.36 (2.20–2.54)
Cardiovascular disease, ever	25,616 (24)	4072 (32)	1.48 (1.42–1.54)	28,590 (25)	1098 (34)	1.59 (1.48–1.72)
Ischemic heart disease diagnosis, ever	5297 (5)	911 (7)	1.47 (1.36–1.58)	5948 (5)	260 (8)	1.63 (1.44–1.86)
Diabetes diagnosis, ever	12,983 (12)	2122 (17)	1.44 (1.37–1.51)	14,496 (13)	611 (19)	1.65 (1.51–1.81)
Heart failure diagnosis, ever	731 (0.7)	142 (1.1)	1.63 (1.36–1.95)	835 (0.7)	38 (1.2)	1.66 (1.19–2.29)
Anxiety or depression diagnosis, ever	4909 (5)	903 (7)	1.57 (1.46–1.69)	5558 (5)	254 (8)	1.71 (1.50–1.95)
Nasal polyps, ever	3159 (3)	774 (6)	2.11 (1.95–2.29)	3672 (3)	261 (8)	2.71 (2.38–3.09)
Anaphylaxis diagnosis, ever	414 (0.4)	98 (0.8)	1.98 (1.59–2.47)	482 (0.4)	30 (0.9)	2.27 (1.57–3.29)
Beta blockers	2964 (3)	370 (3)	1.04 (0.93–1.16)	3248 (2.8)	86 (2.7)	0.96 (0.77–1.19)
Nonsteroidal anti-inflammatory drugs	23,930 (23)	3932 (31)	1.54 (1.47–1.60)	26,859 (23)	1003 (31)	1.51 (1.40–1.63)
Paracetamol	23,519 (22)	4647 (36)	2.02 (1.94–2.10)	26,841 (23)	1325 (41)	2.34 (2.18–2.52)
Statins	15,709 (15)	2450 (19)	1.37 (1.31–1.44)	17,531 (15)	628 (20)	1.37 (1.25–1.49)
Preventer device						
No ICS	13,697 (13)	939 (7)	0.59 (0.55–0.63)	14,434 (12)	202 (6)	0.55 (0.47–0.63)
MDI	62,370 (59)	7234 (57)	1.0	67,861 (59)	1743 (55)	1.0
BAI	5385 (5)	436 (3)	0.70 (0.63–0.77)	5745 (5)	76 (2)	0.52 (0.41–0.65)
DPI	24,793 (23)	4127 (33)	1.44 (1.38–1.50)	27,743 (24)	1177 (37)	1.65 (1.53–1.78)
% ICS medication possession ratio						

>0–39.9	34,519 (32)	3204 (25)	0.57 (0.54–0.61)	37,098 (32)	625 (19)	0.42 (0.38–0.47)
40–59.9	20,930 (20)	2444 (19)	0.72 (0.68–0.77)	22,775 (20)	599 (19)	0.66 (0.59–0.74)
60–79.9	8144 (8)	1241 (10)	0.94 (0.87–1.01)	9029 (8)	356 (11)	0.98 (0.86–1.13)
80–100	13,328 (12)	2165 (17)	1.0	14,896 (13)	597 (19)	1.0
≥100	15,627 (15)	2743 (22)	1.08 (1.02–1.15)	17,551 (15)	819 (26)	1.16 (1.05–1.30)
No ICS prescribed	13,697 (13)	939 (7)	0.42 (0.39–0.46)	14,434 (12)	202 (6)	0.35 (0.30–0.41)
ICS prescriptions						
0	13,697 (13)	939 (8)	1.0	14,434 (13)	202 (6)	1.0
1–3	46,896 (44)	3999 (31)	1.24 (1.16–1.34)	50,142 (43)	753 (24)	1.07 (0.92–1.26)
≥4	45,652 (43)	7798 (61)	2.49 (2.32–2.67)	51,207 (44)	2243 (70)	3.13 (2.71–3.62)
ICS inhalers						
0	13,697 (13)	939 (8)	1.0	14,434 (13)	202 (6)	1.0
1–3	38,220 (36)	3100 (24)	1.18 (1.10–1.28)	40,761 (35)	559 (18)	0.98 (0.84–1.16)
≥4	54,328 (51)	8697 (68)	2.34 (2.18–2.52)	60,588 (52)	2437 (76)	2.87 (2.49–3.34)
ICS prescribed dose†						
0	13,697 (13)	939 (7)	1.0	14,434 (13)	202 (6)	1.0
<400	52,506 (49)	4187 (33)	1.16 (1.08–1.25)	55,906 (48)	787 (25)	1.01 (0.86–1.18)
≥400	40,042 (38)	7610 (60)	2.77 (2.58–2.98)	45,443 (39)	2209 (69)	3.47 (3.00–4.02)
ICS average daily dose†						
0	13,697 (13)	939 (7)	1.0	14,434 (13)	202 (6)	1.0
<400	79,400 (75)	8143 (64)	1.49 (1.39–1.60)	85,778 (74)	1765 (55)	1.47 (1.27–1.71)
≥400	13,148 (12)	3654 (29)	4.05 (3.76–4.37)	15,571 (13)	1231 (38)	5.65 (4.86–6.56)
ICS actual duration (days)						
≤100	43,117 (41)	3374 (26)	1.0	45,837 (40)	654 (21)	1.0
101–219	34,177 (32)	4454 (35)	1.67 (1.59–1.75)	37,503 (32)	1128 (35)	2.11 (1.92–2.33)
≥300	28,951 (27)	4908 (39)	2.17 (2.07–2.27)	32,443 (28)	1416 (44)	3.06 (2.79–3.36)
ICS prescribed duration (days)						
≤200	37,484 (35)	3116 (24)	1.0	39,966 (35)	634 (20)	1.0
201–319	33,676 (32)	4025 (32)	1.44 (1.37–1.51)	36,725 (32)	976 (30)	1.67 (1.52–1.86)
≥320	35,085 (33)	5595 (44)	1.92 (1.84–2.01)	39,092 (34)	1588 (50)	2.56 (2.34–2.82)
SABA prescriptions						
0	11,051 (10)	941 (7)	1.0	11,783 (10)	209 (6)	1.0
1–3	55,143 (52)	4897 (39)	1.04 (0.97–1.12)	59,060 (51)	980 (31)	0.94 (0.81–1.09)

≥4	40,051 (38)	6898 (54)	2.03 (1.88–2.17)	44,940 (39)	2009 (63)	2.52 (2.19–2.92)
SABA inhalers						
0	11,051 (11)	941 (7)	1.0	11,783 (10)	209 (7)	1.0
1–3	45,978 (43)	3925 (31)	1.00 (0.93–1.08)	49,151 (43)	752 (24)	0.86 (0.74–1.01)
≥4	49,216 (46)	7870 (62)	1.88 (1.75–2.02)	54,849 (47)	2237 (70)	2.29 (1.99–2.66)
SABA dose†						
0	11,051 (10)	941 (7)	1.0	11,783 (10)	209 (7)	1.0
1–200	46,452 (44)	4015 (32)	1.02 (0.94–1.09)	49,692 (43)	775 (24)	0.88 (0.76–1.03)
201–400	26,490 (25)	3376 (27)	1.50 (1.39–1.62)	29,057 (25)	809 (25)	1.57 (1.35–1.84)
>400	22,252 (21)	4404 (35)	2.33 (2.16–2.51)	25,251 (22)	1405 (44)	3.14 (2.71–3.63)
LTRA prescriptions						
0	101,223 (95)	10,763 (85)	1.0	109,546 (95)	2440 (76)	1.0
≥1	5022 (5)	1973 (15)	3.69 (3.49–3.91)	6237 (5)	758 (24)	5.46 (5.01–5.95)
LABA prescriptions						
0	99,401 (94)	11,327 (89)	1.0	107,950 (93)	2778 (87)	1.0
≥1	6844 (6)	1409 (11)	1.81 (1.70–1.92)	7833 (7)	420 (13)	2.08 (1.87–2.32)
Spacer use						
No	100,138 (94)	11,523 (91)	1.0	108,812 (94)	2849 (89)	1.0
Yes	6107 (6)	1213 (10)	1.73 (1.62–1.84)	6971 (6)	349 (11)	1.91 (1.71–2.14)
BTS step therapy (missing n=13)§						
1	12,983 (12)	778 (6)	1.0	13,615 (12)	146 (5)	1.0
2	36,863 (35)	2359 (19)	9.91 (8.85–11.10)	38,869 (34)	353 (11)	21.32 (17.5–25.9)
3	25,354 (24)	2483 (20)	9.28 (8.42–10.23)	27,335 (24)	502 (16)	25.18 (21.7–29.3)
4	29,689 (28)	6315 (50)	6.07 (5.51–6.68)	34,207 (30)	1797 (56)	12.45 (10.8–14.3)
5	1345 (1)	799 (7)	2.79 (2.55–3.06)	1745 (2)	399 (12)	4.35 (3.97–4.9)
Asthma attacks						
<2	103,116 (97)	9525 (75)	1.0	110,875 (96)	1766 (55)	1.0
≥2	3129 (3)	3211 (25)	11.11 (10.5–11.7)	4908 (4)	1432 (45)	18.32 (17.0–19.8)
<4	106 055 (99.8)	12 156 (95)	1.0	115 409 (99.7)	2802 (88)	1.0
≥4	190 (0.2)	580 (5)	26.6 (22.6–31.4)	374 (0.3)	396 (12)	43.6 (37.7–50.5)
Acute respiratory events						
0	77,098 (73)	4289 (34)	1.0	80,779 (70)	608 (19)	1.0
1	20,828 (20)	3710 (29)	3.20 (3.06–3.36)	23,791 (21)	747 (23)	4.17 (3.74–4.65)

≥2	8319 (8)	4737 (37)	10.20 (9.77–10.74)	11,213 (10)	1843 (58)	21.84 (19.9–23.9)
Acute OCS courses						
0	92,120 (87)	6150 (48)	1.0	97,310 (84)	960 (30)	1.0
1	11,106 (10)	3448 (27)	4.65 (4.44–4.87)	13,717 (12)	837 (26)	6.18 (5.63–6.80)
≥2	3019 (3)	3138 (25)	15.57 (14.7–16.5)	4756 (4)	1401 (44)	29.86 (27.4–32.6)
Acute OCS courses (with lower respiratory consultation)						
0	103,833 (98)	11284 (89)	1.0	112,499 (97)	2618 (82)	1.0
1	2252 (2.1)	1184 (9)	4.84 (4.50–5.21)	3004 (2.6)	432 (13)	6.18 (5.55–6.88)
≥2	160 (0.2)	268 (2)	15.41 (12.7–18.8)	280 (0.2)	148 (5)	22.7 (18.5–27.8)
Antibiotics (with lower respiratory consultation)						
0	83,644 (79)	6603 (52)	1.0	88,966 (77)	1281 (40)	1.0
1	16,441 (15)	3251 (26)	2.51 (2.39–2.62)	18,886 (16)	806 (25)	2.96 (2.71–3.24)
≥2	6160 (6)	2882 (23)	5.93 (5.64–6.24)	7931 (7)	1111 (35)	9.73 (8.95–10.6)
Asthma-related ED admissions‡						
0	105,760 (99)	12525 (98)	1.0	115,177 (99)	3108 (97)	1.0
≥1	485 (1)	211 (2)	3.67 (3.12–4.33)	606 (1)	90 (3)	5.51 (4.40–6.89)
Asthma consultations						
0	34,564 (32)	2803 (22)	1.0	36,776 (32)	591 (18)	1.0
1	46,704 (44)	4411 (35)	1.16 (1.11–1.22)	50,219 (43)	896 (28)	1.11 (1.00–1.23)
≥2	24,977 (24)	5522 (43)	2.73 (2.59–2.86)	28,788 (25)	1711 (54)	3.70 (3.36–4.07)
Primary care consultations						
0	5363 (5)	255 (2)	1.0	5557 (5)	61 (2)	1.0
1–5	52,274 (49)	3749 (29)	1.51 (1.32–1.72)	55,348 (48)	675 (21)	1.11 (0.85–1.44)
6–12	34,909 (33)	5165 (41)	3.11 (2.73–3.54)	38,760 (33)	1314 (41)	3.09 (2.39–3.99)
≥13	13,699 (13)	3567 (28)	5.47 (4.80–6.24)	16,118 (14)	1148 (36)	6.49 (5.01–8.41)
Asthma is limiting daily activities¶	6388 (6)	1396 (11)	2.14 (1.99–2.29)	7327 (6)	457 (14)	2.88 (2.55–3.27)
Asthma is limiting night activities¶	5199 (5)	1062 (8)	1.83 (1.69–1.98)	5905 (5)	356 (11)	2.46 (2.16–2.80)
Asthma is causing daytime symptoms¶	24,270 (23)	3420 (27)	1.63 (1.52–1.74)	26,754 (63)	936 (29)	2.26 (1.96–2.60)

GINA control‖						
Not available	30,739 (29)	3520 (28)		33,363 (29)	896 (28)	
Controlled	12,833 (17)	881 (10)	1.0	13,562 (16)	152 (7)	1.0
Partly controlled	53,889 (71)	6376 (69)	1.72 (1.60–1.85)	58,765 (71)	1500 (65)	2.27 (1.93–2.69)
Uncontrolled	8784 (12)	1959 (21)	3.25 (2.98–3.53)	10,093 (12)	650 (28)	5.75 (4.81–6.87)

BAI, breath-actuated inhaler; BMI, body mass index; DPI, dry powder inhaler; ED, emergency department; FP, fluticasone propionate; GERD, gastroesophageal reflux disease; ICS, inhaled corticosteroid; LABA, long-acting β_2 agonist; LRTI, lower respiratory tract infection; LTRA, leukotriene receptor antagonist; MDI, metered-dose inhaler; OCS, oral corticosteroid; PEF, peak expiratory flow; SABA, short-acting β_2 agonist;

*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.

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

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

§BTS steps were defined as 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.[E6]

¶Based on Royal College of Physicians 3 questions (RCP3)[E7,E8]

‖Determined from results of patient-completed questionnaires and based on GINA recommendations (May 2015) for adults and children ≥12 years.[E9]