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Preventing unscheduled hospitalisations from asthma: a retrospective cohort study using routine primary and secondary care data in the UK (The PUSH-Asthma Study)— protocol paper

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ABSTRACT

Introduction Asthma is the most common chronic respiratory disease in children and adults. Asthma results in significant disease-related morbidity, healthcare costs and, in some cases, death. Despite efforts through implementation of national guidelines to improve asthma care, the UK has one of the highest asthma-related morbidity and mortality rates in the western world. New approaches are necessary to prevent asthma attacks in children and adults. The objectives of this study are to assess the association between demographic and clinical factors and asthma-related hospital admissions in children and adults, describe the epidemiology of asthma phenotypes among hospital attenders, and externally validate existing asthma risk prediction models.

Methods and analysis This is a retrospective cohort study of children and adults with asthma. Data will be extracted from the Clinical Practice Research Datalink (CPRD) Aurum database, which holds anonymised primary care data for over 13 million actively registered patients and covers approximately 19% of the UK population. The primary outcome will be asthma-related hospital admissions. The secondary outcomes will be prescriptions of short courses of oral corticosteroids (as a surrogate measure for asthma exacerbations), a composite outcome measure including hospital admissions and prescriptions of short courses of oral corticosteroids and delivery of asthma care management following hospital discharge. The primary analysis will use a Poisson regression model to assess the association between demographic and clinical risk factors and the primary and secondary outcomes. Latent class analysis will be used to identify distinct subgroups, which will further our knowledge on potential phenotypes of asthma among patients at high risk of asthma-related hospital admissions. A Concordance statistic (C-statistic) and logistic regression model will also be used to externally validate existing risk prediction models for asthma-related hospitalisations to allow for the optimal model to be identified and evaluated provide evidence for potential use of the optimal performing risk prediction model in primary care.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Clinical Practice Research Datalink Aurum will be used, which has over one million registered patients with a diagnosis of asthma, providing ample statistical power for both the main and subgroup analyses.
⇒ The study will include both adults and children, allowing for age-stratified analyses of asthma-related hospital admissions.
⇒ The study will not be able to analyse emergency department attendances due to the unavailability of linked emergency department data.
⇒ Asthma is often both underdiagnosed and misdiagnosed in routine clinical care, which risks introducing misclassification bias in our analyses.

Ethics and dissemination This study was approved by the CPRD Independent Scientific Advisory Committee (reference number: 21_000512). Findings from this study will be published in a peer-reviewed journal and disseminated at national and international conferences.

INTRODUCTION
Context
Asthma is a chronic respiratory disease that affects both adults and children. It is one of the most common chronic diseases and results in significant morbidity and mortality.[1] Despite asthma being a manageable disease, the UK has one of the highest asthma-related morbidity and mortality rates in the western world, accounting for three deaths per day and approximately 60 000 emergency hospital admissions/year.[2 3] This has resulted in a significant and preventable health and economic burden that costs the UK National Health Service £1.1 billion per year.[1]

Acute asthma attacks requiring hospital attendance often indicate poor symptom control and inadequate management of risk factors. Possible risk factors for the high incidence of asthma attacks include severe disease, poor adherence to prescribed therapies, inadequate clinical care and disease monitoring, presence of comorbidities, tobacco use, socioeconomic deprivation, previous asthma attacks, and air pollution.[4–7]

Despite efforts to improve the management of asthma through implementation of national clinical guidelines published by the British Thoracic Society and the National Institute for Health and Care excellence (NICE), there has been little reduction in asthma attacks across all age groups.[2 8]

Current knowledge

Previous studies have found that female sex,[9–12] previous exacerbations requiring hospital admission,[9 11 13] increased disease severity,[9 14] older age (≥45 years),[9 11 12] younger age (<18),[10 15] ethnic minorities (African-American, Black and Indian),[10 13 15] history of inhaled corticosteroids (ICS) (defined as ICS use in the preceding year),[15] over-use of short-acting beta agonists[16] and comorbidities such as chronic rhinitis and gastro-oesophageal reflux disease (GORD)[11] are associated with asthma exacerbations including those requiring hospitalisation in children and adults. Previous studies also suggest that continued care and follow-up after hospitalisation reduce future asthma-related hospitalisations.[17–19]

Most of the existing evidence on the association between asthma and hospitalisations is based on patient data from the USA and Asia, and the evidence from these studies is unlikely to be generalisable to a UK population, partly due to significant differences in healthcare provision. Risk factors for exacerbations are likely to differ across age groups, but there is a paucity of studies describing risk factors for asthma exacerbations stratified by age.

A UK-based study describing the characteristics of 3776 children aged 5–12 years in primary care record databases (Clinical Practice Research Datalink (CPRD) and Optimum Patient Care Research Database) showed that previous history of asthma attacks was the strongest predictor for future asthma attacks.[20] A similar study using data from over 200 000 patients in CPRD showed that the risk of subsequent asthma attacks requiring hospitalisation increased with disease severity.[14] A study of 460 children aged 5–16 years from 10 UK general practices showed that recent asthma attacks, high fractional exhaled nitric oxide, socioeconomic deprivation and poor symptom control in the previous 6 months was associated with a higher risk of future asthma attacks.[21 22]

Two previous studies have used UK data from CPRD to assess asthma outcomes; however, one study included only children[20] and the other investigated the association with disease severity alone.[14] There is currently no evidence published using UK primary care data in a population of adults and children stratified by important demographic characteristics, including age and sex. A UK representative population-based cohort study using primary care data is needed to understand the multiple risk factors present for future asthma exacerbations requiring hospital admission, in addition to understanding the primary care management of patients after hospitalisation in the UK.

A recent systematic review summarised a number of risk prediction models that have been developed to estimate the risk of asthma exacerbations requiring hospitalisation.[23–25] The main parameters used in these risk prediction models included age, sex, smoking history, comorbidities, course of systemic corticosteroids, emergency department visits and previous hospitalisation for asthma exacerbations. A more recent study used data from a subset of CPRD to generate a risk prediction model for asthma exacerbations.[25] The model included patients aged 12–80 years and did not demonstrate if the risk prediction model was able to accurately predict the risk of asthma exacerbation-related hospitalisations in children below the age of 12 years.

External validation of existing risk prediction models is needed in a common data set to identify the model with optimal performance in a UK primary care population to accurately predict asthma exacerbation risk. There is a need to assess both the discrimination and calibration of these models.[26] This could help guideline developers and clinicians to determine whether the models are appropriate for use in UK primary care. This would also help to identify the most promising models to prospectively evaluate in randomised controlled impact trials.[27]

Study aims and objectives

We aim to describe detailed characteristics of patients with asthma and their association with asthma-related hospital admissions to identify a comprehensive range of risk factors for high-risk patients. The aim is to enable primary care services to use these findings on risk factors to identify and flag high-risk patients for the delivery of targeted interventions to prevent future hospitalisations. We also aim to identify distinct risk factor clusters to describe the clinical heterogeneity in high-risk patients with asthma and delineate potential phenotypes that may help better target therapies. The treatment and care delivered following hospitalisation will be analysed to aid the identification of the gaps and discontinuity between primary and secondary care services, which could then be targeted for intervention and service improvement. We also aim to externally validate existing risk prediction models for asthma exacerbations in a UK-based primary population.

The specific objectives for this study are to (1) define and characterise a cohort of adults and children with asthma, (2) assess the incidence of asthma-related hospitalisations, (3) identify risk factors for asthma-related hospitalisations, (4) phenotype asthma patients at high risk of asthma-related hospitalisations, (5) externally validate existing risk prediction models for hospitalisations for asthma, (6) assess the primary care management of

patients following hospital discharge after an asthma exacerbation.

METHODS AND ANALYSIS
Study design
A retrospective open cohort study using routine primary and secondary healthcare data, consisting of patients with asthma between 1 January 2011 and 1 January 2021.

Data source
The data used to conduct this study will be UK primary care records extracted from the Clinical Practice Research Datalink —Aurum (CPRD Aurum) database with linked Hospital Episode Statistics (HES). Over 1000 general practices contribute to CPRD Aurum, covering approximately 19% of the UK population. The database holds data for over 39 million patients, approximately 13 million of whom are current patients.[28] Over 90% of patient data contributing to CPRD Aurum have linked HES data. The general practices that contribute to CPRD Aurum use a patient records software called EMIS, which codes clinical data using Read Code clinical classification (V.3) and Systematized Nomenclature of Medicine - Clinical Terms (SNOMED-CT) codes,[29] and codes for drug prescriptions using medical drug codes, which are linked to the British National Formulary.[30] The linked HES data uses ICD-10 codes to code diagnoses.[31]

Population
General practices that have contributed to CPRD on or after the index date (1 January 2011) will be eligible for inclusion in the study. Data will be extracted for adults and children aged 5 years and over diagnosed with asthma who have been registered to an eligible general practice for at least 1 year prior to the index date to allow for the collection of baseline data. Patients will be included in the study if they have received a diagnosis of asthma before the index date as well as incident cases diagnosed after the index date. Asthma will be defined as the presence of a Read code or SNOMED-CT code for asthma, as listed in online supplemental file 1. The recruitment/study period will be 1 January 2011 to 1 January 2021. There are no exclusion criteria for this study.

Study variables
Exposure variables
Asthma will be defined as the presence of a Read code or SNOMED-CT code for asthma. An extensive list of relevant clinical codes for asthma has been developed to identify eligible patients eligible for inclusion (see online supplemental file 1).

Outcome variables
The primary outcome will be the number of hospital admissions for asthma, assessed with linked HES Admitted Patient Care (APC) data (defined by the ICD-10 asthma diagnosis codes J45 and J46). The secondary outcomes will be prescriptions of short courses of oral corticosteroids

for asthma exacerbations, delivery of clinical care for asthma after discharge from hospital (including prescriptions of ICS, smoking cessation counselling, provision of an asthma management plan, demonstration of inhaler technique and provision of an asthma review) and a composite outcome measure including hospital admissions or prescriptions of short courses of oral corticosteroids. The outcomes will be defined by the relevant clinical codes (ICD-10) or drug/SNOMED-CT codes.

Predictor variables
The baseline patient demographics and characteristics to be extracted include age (at index date), sex, ethnic group, socioeconomic status, smoking status (smoker, ex-smoker, never smoked), body mass index (BMI) and alcohol consumption. Current comorbidities will also be extracted. A literature search was conducted in addition to obtaining expert opinions to identify the most relevant comorbidities to be included in the study. This included atopic dermatitis, allergic rhinitis, allergies, GORD, cardiovascular disease, chronic obstructive pulmonary disease (COPD), obstructive sleep apnoea, non-cystic fibrosis bronchiectasis, interstitial lung disease, chronic rhinosinusitis, anxiety, depression, obesity and diabetes mellitus. Asthma-related prescriptions including short-acting bronchodilators, ICS and leukotriene receptor antagonists and other medical prescriptions unrelated to asthma diagnosis such as beta blockers and non-steroidal anti-inflammatory drugs will also be reported due to their likely association with asthma hospitalisations. All covariates will be captured before the index date at baseline from CPRD data.

Follow-up period
The recruitment/study period will be from 1 January 2011 to 1 January 2021. The start of follow-up for patients will be the latest of 12 months after registration with general practice, study start date or the date of patient diagnosis of asthma. The end of follow-up for patients will be the earliest of at least one study outcome reached, death, exit from the database or study end date (1 January 2021).

Missing data
Missing data are not likely to be missing at random.[32] Therefore, multiple imputation will not be used. A separate 'missing' category will be created for missing data for each variable. Continuous variables will be converted into categorical variables to allow for the addition of the 'missing' category. Data will likely be missing for ethnic group, BMI and smoking status. The absence of clinical codes for diagnoses (eg, comorbidities) or drug treatment codes will indicate the absence of the condition or drug.

Data analysis
The data will be extracted using the Data extraction for epidemiological research (DExtER)[33] tool and the analysis will be undertaken using STATA SE V.16. The asthma cohort will be stratified into the following age-groups: 5–11,

12–17, 18+ years. The primary analysis will use descriptive statistics to describe the characteristics of the cohort including age, sex, ethnic group, socioeconomic status, smoking status (smoker, ex-smoker, never smoked), BMI, comorbidities (including allergies and atopic diseases), prescriptions of short-acting bronchodilators, ICS, oral corticosteroids and blood eosinophil levels (counts and percentage where these are available). Categorical data at baseline will be described using proportions, and continuous data will be described using means with SD, where the data follow a normal distribution or median with IQR, where the distribution is skewed.

The incidence rates for asthma-related hospitalisations will be calculated for the entire cohort and stratified by demographic and clinical characteristics. Poisson regression models will be used to assess the association between the prespecified covariates and the primary and secondary outcomes. The models will be fitted with the prespecified covariates as the independent variables and asthma-related hospital admissions (primary outcome) as the dependent variable. The secondary outcomes, prescriptions of short courses of oral corticosteroids and the composite outcome of hospital admissions or short courses of oral corticosteroids, will also be analysed using separate Poisson regression models.

A latent class analysis will be used to identify clusters of characteristics based on demographic and clinical factors that differentiate patients with asthma. This will allow us to phenotype subgroups of patients with asthma at high risk of asthma-related hospital admissions.

To quantify the performance of existing risk prediction models, we will conduct an external validation on models derived from primary care where there has been sufficient reporting of model parameters. The models will be identified from the literature and recent systematic reviews. The variables used in the models that are also available in CPRD include age, sex, smoking history, comorbidities, prescriptions of systemic corticosteroids and previous hospitalisation for asthma exacerbations. A novel risk prediction model that has been developed by the University of Edinburgh will also be externally validated in CPRD Aurum.[34]

The discrimination and calibration of the prediction models will be assessed. The concordance statistic (C-statistic) will be used to calculate discrimination, which will assess how well the model differentiates between patients who experience the outcome and patients who do not. Calibration will be used to assess how closely the predictions of the model match the observed outcomes in the data. Calibration will be assessed by fitting a logistic regression model with the outcome variable set as the observed outcomes and the independent variable set as the log odd-transformed model predictors. We will assess these measures using both the primary and secondary outcomes.

An analysis of hospitalised patients with asthma will be conducted to assess the primary care management of patients following discharge from hospital after an asthma exacerbation. We will report the frequency and percentages of asthma-related drug prescriptions and any other interventions delivered before and after discharge from hospital. We will use χ^2 tests to test for statistically significant differences between the frequency of drug prescriptions and other interventions before and after hospitalisation. An ordinal logistic regression model will be used to assess the association between patient risk factors and the delivery of clinical care after discharge from hospital. The items of clinical care management to be included are prescriptions of ICS, smoking cessation counselling, provision of an asthma management plan, demonstration of inhaler technique and provision of an asthma review. A composite management score will be derived as the sum of the number of clinical care management items recorded.

A sensitivity analysis will be conducted to assess the effect of the COVID-19 pandemic on the results of the primary analysis. The events of the COVID-19 pandemic are likely to have had an impact on the frequency of asthma-related exacerbations and hospital admissions due to self-isolations and national lockdowns being implemented over the past year. A recent study found that asthma exacerbations significantly decreased during the pandemic across all age groups, both sexes and across most regions in England.[35] The sensitivity analysis will be conducted in two parts. The first part includes restricting the analysis to all patients eligible for inclusion prior to 31 January 2020 (patients eligible for inclusion after this date will be excluded). Therefore, the study start date for the analysis will be 1 January 2011 and the study end date will be 31 January 2020. The second part includes restricting the analysis to all patients eligible for inclusion after 31 January 2020 to the latest available date. The sensitivity analysis will allow any differences in outcome results attributed to COVID-19 to be identified and compared with that of the primary analyses.

In older adults, COPD can be misdiagnosed as asthma. Smoking is a known key risk factor for COPD. We will, therefore, undertake a subgroup analysis by smoking status and COPD status to assess whether the observed associations differ between these two groups. Additionally, we will conduct a subgroup analysis focusing on patients with eosinophilia on their blood count (peripheral blood eosinophil count >3%, or absolute count >300 cells/μl) as eosinophilia can be used as an indicator for potential corticosteroid responsiveness in airway diseases; this is mainly in the form of asthma and also includes a proportion of patients with COPD.

Sample size calculation

Based on the sample size calculation derived by Signorini and Zhang and Yuan,[36 37] we have determined that, for the smallest outcome baseline rate considered (0.5%), in order to have 80% power at an alpha level of 0.05 to detect the smallest effect size (incidence rate ratio 0.2), we will need a sample size of approximately 360 000. Based on data from NICE and Asthma UK, we expect a

cumulative incidence of asthma-related hospital admissions of approximately 0.75% in a single year.[2][3] Therefore, we will have a sufficient sample size for this study. The population size of current patients within CPRD Aurum is 13 320 051. We estimate that approximately 1 600 000 patients will meet the criteria for inclusion in this study.

Patient and public involvement

We will be working closely with members of the Patient and Public Involvement groups of Asthma UK and the NIHR Children and Young Persons Steering Group for dissemination of the study findings. Patients and members of the public were not involved in the design of the study.

STRENGTHS AND LIMITATIONS

The study will have a large sample size and data will be generalisable to the UK population as CPRD contains data that covers approximately 20% of the UK population.[28] In contrast with previous studies, we will stratify patients across three age groups to describe risk factors and adjust for a broader range of relevant risk factors and confounders in the analysis. This will enable us to identify at risk patients across multiple age groups and provide a comprehensive evaluation of the impact of various comorbidities on asthma-related hospital admissions. The large sample size also provides sufficient statistical power to perform several relevant subgroup analyses. The HES APC data linkage to primary care records provides a unique opportunity to characterise patients admitted to hospital due to asthma exacerbations.

Limitations of the study include the potential inaccuracy of asthma diagnoses. We acknowledge that patients with asthma can often be misdiagnosed, which may result in the potential misclassification of asthma.[38][39] The misclassification of asthma could result in the dilution of effect sizes and, therefore, the effect sizes in this study are likely to be relatively conservative, as will model performance.

A limitation of using data from primary care databases is that ethnicity is often poorly recorded with approximately 30% of individuals having missing ethnicity data. However, for those without an ethnicity recording, a separate category will be created for the missing data values. Another limitation is that oral corticosteroids may be prescribed for a number of alternative conditions such as other atopic diseases (eg, atopic dermatitis), COPD and rheumatoid arthritis, leading to potential misclassification bias of the secondary outcome. We also acknowledge that a prescription recorded in primary care records does not necessitate that the prescribed drug was actually consumed by the patient or reflect medication compliance. We will acknowledge these study limitations in our main study report.

A further limitation to the study includes the lack of accident and emergency (A&E) data use. Some asthmatic patients may require A&E but may not be admitted to hospital or visit their GP; therefore, data from these patients may be missed. However, this is likely to be a small proportion of patients with asthma and is unlikely to affect the results of this study.

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