BMJ Open

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

Nikita Simms-Williams ,[1] Prasad Nagakumar,[2,3] Rasiah Thayakaran,[1] Nicola Adderley ,[1] Richard Hotham,[1] Adel Mansur,[3,4] Krishnarajah Nirantharakumar,[1] Shamil Haroon [1]

To cite: Simms-Williams N, Nagakumar P, Thayakaran R, *et al*. 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. *BMJ Open* 2022;**12**:e058356. doi:10.1136/bmjopen-2021-058356

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-058356).

Received 13 October 2021
Accepted 29 July 2022

For numbered affiliations see end of article.

Correspondence to
Dr Prasad Nagakumar;
P.Nagakumar@bham.ac.uk

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.

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.

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.

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.

Author affiliations
[1]Institute of Applied Health Research, University of Birmingham, Birmingham, UK
[2]Respiratory medicine, Birmingham Women's and Children's Hospitals NHS Foundation Trust, Birmingham, UK
[3]Institute of inflammation and ageing, University of Birmingham, Birmingham, UK
[4]Respiratory Medicine, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

Twitter Shamil Haroon @ShamilHaroon

Contributors SH, PN and AM led the design of the study. NS-W, SH, PN, RH, AM and RT were involved in the design of the study. NSW drafted the manuscript. SH, PN, NA, AM, RT and KN provided feedback on the manuscript; all authors approved the final version.

Funding This research was funded by the National Institute of Health and Research West Midlands Improvement and Innovation Strategic Fund. Grant number: 1 002 281.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Nikita Simms-Williams http://orcid.org/0000-0002-4926-1995
Nicola Adderley http://orcid.org/0000-0003-0543-3254
Shamil Haroon http://orcid.org/0000-0002-0096-1413

REFERENCES

1 Mukherjee M, Stoddart A, Gupta RP, *et al*. The epidemiology, healthcare and societal burden and costs of asthma in the UK and its member nations: analyses of standalone and linked national databases. *BMC Med* 2016;14:113.
2 Asthma facts and statistics [Internet], 2021. Available: https://www.asthma.org.uk/about/media/facts-and-statistics
3 National Institute of Health and Care Excellence. [Internet], 2021. Available: https://cks.nice.org.uk/topics/asthma/background-information/prevalence/
4 Sanya RE, Kirenga BJ, Worodria W, *et al*. Risk factors for asthma exacerbation in patients presenting to an emergency unit of a national referral hospital in Kampala, Uganda. *Afr Health Sci* 2014;14:707–15.
5 Sims EJ, Price D, Haughney J, *et al*. Current control and future risk in asthma management. *Allergy Asthma Immunol Res* 2011;3:217–25.
6 Fleming L. Asthma exacerbation prediction: recent insights. *Curr Opin Allergy Clin Immunol* 2018;18:117–23.
7 ten Brinke A, Sterk PJ, Masclee AAM, *et al*. Risk factors of frequent exacerbations in difficult-to-treat asthma. *Eur Respir J* 2005;26:812–8.

8 Nuffield Trust [Internet], 2021. Available: https://www.nuffieldtrust.org.uk/research/international-comparisons-of-health-and-wellbeing-in-adolescence-and-early-adulthood
9 Arrotta N, Hill J, Villa-Roel C, *et al*. Factors associated with hospital admission in adult patients with asthma exacerbations: a systematic review. *J Asthma* 2019;56:34–41.
10 Ardura-Garcia C, Stolbrink M, Zaidi S, *et al*. Predictors of repeated acute Hospital attendance for asthma in children: a systematic review and meta-analysis. *Pediatr Pulmonol* 2018;53:1179–92.
11 Kang H-R, Song HJ, Nam JH, *et al*. Risk factors of asthma exacerbation based on asthma severity: a nationwide population-based observational study in South Korea. *BMJ Open* 2018;8:e020825.
12 Lin MP, Vargas-Torres C, Schuur JD, *et al*. Trends and predictors of hospitalization after emergency department asthma visits among U.S. adults, 2006-2014. *J Asthma* 2020;57:811–9.
13 Tay TR, Wong HS, Tee A. Predictors of future exacerbations in a multi-ethnic Asian population with asthma. *J Asthma* 2019;56:380–7.
14 Suruki RY, Daugherty JB, Boudiaf N, *et al*. The frequency of asthma exacerbations and healthcare utilization in patients with asthma from the UK and USA. *BMC Pulm Med* 2017;17:74.
15 Johnson LH, Beck AF, Kahn RS, *et al*. Characteristics of pediatric emergency Revisits after an asthma-related hospitalization. *Ann Emerg Med* 2017;70:277–87.
16 Buelo A, McLean S, Julious S, *et al*. At-Risk children with asthma (ARC): a systematic review. *Thorax* 2018;73:813–24.
17 Kao Y-H, Wu S-C, Yu-Hsiang K. STROBE-compliant article: is continuity of care associated with avoidable hospitalization among older asthmatic patients? *Medicine* 2016;95:e4948.
18 Smiley M, Sicignano N, Rush T, *et al*. Outcomes of follow-up care after an emergency department visit among pediatric asthmatics in the military health system. *J Asthma* 2016;53:816–24.
19 Herrera AM, Brand P, Cavada G, *et al*. Treatment, outcomes and costs of asthma exacerbations in Chilean children: a prospective multicenter observational study. *Allergol Immunopathol* 2019;47:282–8.
20 Turner SW, Murray C, Thomas M, *et al*. Applying UK real-world primary care data to predict asthma attacks in 3776 well-characterised children: a retrospective cohort study. *NPJ Prim Care Respir Med* 2018;28:28: 28.
21 Saglani S, Fleming L, Sonnappa S, *et al*. Advances in the aetiology, management, and prevention of acute asthma attacks in children. *Lancet Child Adolesc Health* 2019;3:354–64.
22 Lo D, Beardsmore C, Roland D, *et al*. Risk factors for asthma attacks and poor control in children: a prospective observational study in UK primary care. *Arch Dis Child* 2022;107:26–31.
23 Loymans RJB, Debray TPA, Honkoop PJ, *et al*. Exacerbations in adults with asthma: a systematic review and external validation of prediction models. *J Allergy Clin Immunol Pract*. In Press 2018;6:1942–52.
24 Luo G, He S, Stone BL, *et al*. Developing a model to predict Hospital encounters for asthma in asthmatic patients: secondary analysis. *JMIR Med Inform* 2020;8:e16080.
25 Noble M, Burden A, Stirling S, *et al*. Predicting asthma-related crisis events using routine electronic healthcare data: a quantitative database analysis study. *Br J Gen Pract* 2021;71:e948–57.
26 Huang Y, Li W, Macheret F, *et al*. A tutorial on calibration measurements and calibration models for clinical prediction models. *J Am Med Inform Assoc* 2020;27:621–33.
27 Hingorani AD, Windt DAvander, Riley RD, *et al*. Prognosis research strategy (progress) 4: stratified medicine research. *BMJ* 2013;346:e5793.
28 CPRD Aurum March 2021 dataset. [Internet], 2021. Available: https://www.cprd.com/cprd-aurum-march-2021
29 NHS Digital. Terminology and Classifications. [internet], 2021. Available: https://digital.nhs.uk/services/terminology-and-classifications
30 British National Formulary. [Internet], 2021. Available: https://www.bnf.org/
31 Clinical Classifications. [Internet], 2021. Available: https://digital.nhs.uk/services/terminology-and-classifications/clinical-classifications
32 Marston L, Carpenter JR, Walters KR, *et al*. Issues in multiple imputation of missing data for large general practice clinical databases. *Pharmacoepidemiol Drug Saf* 2010;19:618–26.
33 Gokhale KM, Chandan JS, Toulis K, *et al*. Data extraction for epidemiological research (Dexter): a novel tool for automated clinical epidemiology studies. *Eur J Epidemiol* 2021;36:165–78.
34 Hussain Z, Shah SA, Mukherjee M, *et al*. Predicting the risk of asthma attacks in children, adolescents and adults: protocol for a machine learning algorithm derived from a primary care-based retrospective cohort. *BMJ Open* 2020;10:e036099.
35 Shah SA, Quint JK, Nwaru BI, *et al*. Impact of COVID-19 national lockdown on asthma exacerbations: interrupted time-series analysis of English primary care data. *Thorax* 2021;76:860–6.
36 Signorini DF. Sample size for Poisson regression. *Biometrika* 1991;78:446–50.
37 Zhang Z, Yuan K-H. *Practical statistical power analysis using Webpower and R (Eds)*. Granger, IN: ISDSA Press, 2018.
38 Mansur AH. Clinical spectrum of patients assessed in primary care respiratory diagnostic hub; informing referral criteria. *Thorax BMJ* 2021;76.
39 Yang CL, Simons E, Foty RG, *et al*. Misdiagnosis of asthma in schoolchildren. *Pediatr Pulmonol* 2017;52:293–302.

List of Appendices

Appendix 1: Asthma code list

CPRD AURUM MEDCODES	DESCRIPTION	READ CODE	SNOMED-CT CODE
95786019	Occupational asthma	173c.00	57607007
301485011	Asthma	H33..00	195967001
338238011	Brittle asthma	H334.00	225057002
396114013	Intrinsic asthma	H331.00	266361008
456163018	Asthma - currently active	663j.00	312453004
1208969012	Mild asthma	663V100	370218001
1483199016	Allergic asthma	H330.11	389145006
1488421017	Asthma annual review	66YJ.00	394700004
1488436019	Asthma medication review	8B3j.00	394720003
885291000006115	Extrinsic asthma - atopy	H330.99	389145006
955631000006116	Occupational asthma	null	955631000006100
2010041000006110	Acute non-infective exacerbation of asthma	null	2010041000006100
216186011	Asthma accident and emergency attendance since last visit	663m.00	708373002
264565016	Emergency asthma admission since last appointment	663d.00	708358003
301508013	Intrinsic asthma NOS	H331z00	266361008
350149018	Late-onset asthma	H33z200	233679003
350151019	Extrinsic asthma with asthma attack	H330111	708093000
409865018	Asthma attack NOS	H33z111	708038006
655601000006113	Exercise induced asthma	173A.00	31387002
655611000006111	Exercise induced asthma	H33zz11	31387002
660351000006118	Extrinsic (atopic) asthma	H330.00	389145006
419211018	Acute exacerbation of asthma	H333.00	708038006
145961000006117	Severe asthma attack	H33z011	708090002
396118011	Status asthmaticus NOS	H33z000	734904007
283550015	Emergency admission, asthma	8H2P.00	183478001
12485061000006100	Emergency admission, asthma	null	183478001
8465401000006110	Life threatening acute exacerbation of non-allergic asthma	null	1086711000000100
6720721000006110	Asthmatic bronchitis	null	405944004
7628271000006110	Acute exacerbation of extrinsic asthma	null	708093000
3435971000006110	Industrial asthma	null	57607007
3005801000006110	EIA - Exercise-induced asthma	null	31387002
4723761000006110	Emergency hospital admission for asthma	null	183478001
7627241000006110	Acute exacerbation of asthma	null	708038006
7628191000006110	Acute severe exacerbation of asthma	null	708090002
8465381000006110	Life threatening acute exacerbation of extrinsic asthma	null	1086701000000100
5492441000006110	Non-allergic asthma	null	266361008
7628281000006110	Acute exacerbation of immunoglobulin E-mediated allergic asthma	null	708093000
7030341000006110	IgE mediated allergic asthma	null	424643009

7030351000006110	Immunoglobulin E-mediated allergic asthma	null	424643009
3005811000006110	Exercise induced asthma	null	31387002
4781531000006110	Asthmatic	null	195967001
6512381000006110	Atopic asthma	null	389145006
2009981000006110	Difficult asthma	null	2009981000006100
1821521000006110	Occasional asthma exacerbations	null	1821521000006100
1208970013	Moderate asthma	663V200	370219009
1208971012	Occasional asthma	663V000	370220003
350153016	Hay fever with asthma	H330011	233683003
301509017	Mixed asthma	H332.00	195977004
301499010	Extrinsic asthma NOS	H330z00	424643009
350152014	Allergic asthma NEC	H33zz12	389145006
11903851000006100	Severe asthma attack	null	708038006
7030311000006110	IgE-mediated allergic asthma	null	424643009
7030321000006110	IgE mediated asthma	null	424643009
2240591000000110	Chronic asthma with fixed airflow obstruction	H335.00	866881000000101
1208972017	Severe asthma	663V300	370221004
1488422012	Asthma follow-up	66YK.00	394701000
301450011	Chronic asthmatic bronchitis	H312000	195949008
301480018	Bronchial asthma	H33..11	195967001
264541019	Asthma causing night waking	663N000	170632009
264544010	Asthma not disturbing sleep	663O.00	170635006
5054341000006110	Late-onset asthma	null	233679003
264550017	Asthma management plan given	663U.00	406162001
301511014	Asthma unspecified	H33z.00	195967001
2117771000000110	Asthma self-management plan agreed	661M100	811921000000103
2010031000006110	Acute infective exacerbation of asthma	null	2010031000006100
1780388018	Asthma confirmed	1O2..00	401193004
396119015	Asthma attack	H33z100	708038006
350148014	Late onset asthma	H331.11	233679003
264568019	Asthma severely restricts exercise	6.63E100	170657004
350156012	Intrinsic asthma with asthma attack	H331111	708094006
396120014	Asthma NOS	H33zz00	195967001
98546013	Intrinsic asthma with status asthmaticus	H331100	1086711000000100
817361000006114	Hay fever with asthma	H330.13	233683003