Risk factors for asthma-related hospital and intensive care admissions in children, adolescents, and adults

Simms-Williams, Nikita; Nagakumar, Prasad; Thayakaran, Rasiah; Adderley, Nicola; Hotham, Richard; Mansur, Adel; Nirantharakumar, Krishnarajah; Haroon, Shamil

DOI:
10.1136/bmjresp-2023-001746

BMJ Open Respiratory Research

Risk factors for asthma-related hospital and intensive care admissions in children, adolescents and adults: a cohort study using primary and secondary care data

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

To cite: Simms-Williams N, Nagakumar P, Thayakaran R, *et al*. Risk factors for asthma-related hospital and intensive care admissions in children, adolescents and adults: a cohort study using primary and secondary care data. *BMJ Open Respir Res* 2024;**11**:e001746. doi:10.1136/bmjresp-2023-001746

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjresp-2023-001746).

Received 4 April 2023
Accepted 3 November 2023

For numbered affiliations see end of article.

Correspondence to
Dr Prasad Nagakumar; p.nagakumar@bham.ac.uk

ABSTRACT

Background Asthma remains a common cause of hospital admissions across the life course. We estimated the contribution of key risk factors to asthma-related hospital and intensive care unit (ICU) admissions in children, adolescents and adults.

Methods This was a UK-based cohort study using linked primary care (Clinical Practice Research Datalink Aurum) and secondary care (Hospital Episode Statistics Admitted Patient Care) data. Patients were eligible if they were aged 5 years and older and had been diagnosed with asthma. This included 90 989 children aged 5–11 years, 114 927 adolescents aged 12–17 years and 1 179 410 adults aged 18 years or older. The primary outcome was asthma-related hospital admissions from 1 January 2017 to 31 December 2019. The secondary outcome was asthma-related ICU admissions. Incidence rate ratios adjusted for demographic and clinical risk factors were estimated using negative binomial models. Population attributable fraction (PAF) was estimated for modifiable risk factors.

Results Younger age groups, females and those from ethnic minority and lower socioeconomic backgrounds had an increased risk of asthma-related hospital admissions. Increasing medication burden, including excessive use of short-acting bronchodilators, was also strongly associated with the primary outcome. Similar risk factors were observed for asthma-related ICU admissions. The key potentially modifiable or treatable risk factors were smoking in adolescents and adults (PAF 6.8%, 95% CI 0.9% to 12.3% and 4.3%, 95% CI 3.0% to 5.7%, respectively), and obesity (PAF 23.3%, 95% CI 20.5% to 26.1%), depression (11.1%, 95% CI 9.1% to 13.1%), gastro-oesophageal reflux disease (2.3%, 95% CI 1.2% to 3.4%), anxiety (2.0%, 95% CI 0.5% to 3.6%) and chronic rhinosinusitis (0.8%, 95% CI 0.3% to 1.3%) in adults.

Conclusions There are significant sociodemographic inequalities in the rates of asthma-related hospital and ICU admissions. Treating age-specific modifiable risk factors should be considered an integral part of asthma management, which could potentially reduce the rate of avoidable hospital admissions.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Asthma is one of the most common chronic diseases and remains an important cause of avoidable hospital and intensive care admissions.

WHAT THIS STUDY ADDS

⇒ There are significant sociodemographic inequalities in asthma-related hospital and intensive care admissions in children, adolescents and adults.

⇒ There are several addressable risk factors for asthma-related hospital admissions that differ across age groups, such as smoking, obesity, atopic disorders, depression, anxiety and gastro-oesophageal reflux disease.

⇒ Overall asthma medication burden is strongly associated with the risk of asthma-related hospital and intensive care unit admissions and should be used for assessing disease severity and monitoring asthma control and prognosis.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Sociodemographic disparities in asthma outcomes and treatable risk factors identified in this study should be addressed by policy-makers, health service commissioners and providers to improve asthma management in disadvantaged population groups.

INTRODUCTION

Asthma is the most common chronic respiratory disease affecting children and adults with an estimated worldwide prevalence of 10% and affecting over 600 million people in 2019.[1] The UK has one of the highest prevalences of asthma and associated morbidity and mortality in Western Europe, accounting for over 1000 deaths and 60 000 emergency hospital admissions per year.[2 3] This has resulted in a significant and preventable health and economic

burden that accounts for 200 000 bed days and costs the UK National Health Service £1.1 billion per year.[3] Despite efforts to improve the management of asthma through the implementation of national clinical guidelines,[4] and publication of the National Asthma Death Review recommendations,[5] there has been little reduction in asthma attacks across all age groups in the UK.[6]

Asthma attacks severe enough to require hospital admission often indicate poor management of modifiable risk factors, including comorbidities.[7 8] This includes factors such as exposure to secondhand smoke and the presence of atopic diseases.[9] However, risk factors contributing to asthma attacks have not been studied across paediatric and adult populations simultaneously in a large representative sample. Furthermore, asthma management guidelines advise stepping up medications to improve control but there is relatively little emphasis on addressing modifiable risk factors and comorbidities at each step of the treatment pathway. Identification of age-specific risk factors from a large dataset will support the development of targeted interventions to prevent severe asthma attacks across the life course.

The study aimed to investigate risk factors associated with asthma-related hospitalisations and intensive care unit (ICU) admissions. The specific objectives were to estimate the incidence rates of asthma-related hospital and intensive care admissions in children, adolescents and adults, estimate the association between demographic and clinical risk factors and these outcomes, and estimate the proportion of hospital admissions that could be prevented by addressing key modifiable risk factors.

METHODS

Setting, data source and analysis

UK primary care records were extracted from the Clinical Practice Research Datalink (CPRD) Aurum database with linked Hospital Episode Statistics (HES) Admitted Patient Care (APC) data[10] for the period from 1 January 2017 to 31 December 2019. General practices contributing to CPRD Aurum cover approximately 19% of the UK population, all of which use the EMIS clinical information system which uses Systematized Medical Nomenclature for Medicine–Clinical Terminology (SNOMED-CT) terms to code clinical data, and drug codes linked to the British National Formulary to code drug prescriptions.[11] CPRD Aurum holds data for over 13 million currently registered patients.[12] Over 90% of the data held within CPRD Aurum is linked to the HES database, which codes diagnoses using International Classification of Diseases 10th Revision (ICD-10) codes.[13] Data were extracted using the Data Extraction for Epidemiological Research[14] tool and the analyses were undertaken using Stata SE V.16 and RStudio.

Population

General practices that had contributed data to CPRD Aurum for at least 1 year prior to the index date (1 January 2017) were included in the study. Data were extracted for patients aged 5 years and older with a diagnosis of asthma registered with an eligible general practice for at least 1 year prior to the index date. Asthma was defined as the presence of a SNOMED-CT code for asthma, as listed in online supplemental table 1. The SNOMED-CT terms were selected using a systematic process with clinical input that involved checking existing code lists used by our research team, checking published code lists, searching the SNOMED-CT terminology browser and searching using free-text terms for asthma within an in-house software tool called Code Builder.

Patients with chronic obstructive pulmonary disease (COPD), bronchiectasis, obstructive sleep apnoea or interstitial lung disease were excluded to prevent misclassification of the primary diagnosis for hospitalisation. All patients were followed up from the index date (1 January 2017) and follow-up was terminated at the earliest of death, exit from the database (patient left the practice or the practice stopped contributing to the database) or the study end date (31 December 2019).

Outcomes

The primary outcome was hospital admissions for asthma, assessed using linked secondary care (HES APC) data. Asthma admissions were defined as hospital admissions with associated ICD-10 asthma diagnosis codes J45 and J46 as the primary diagnostic code for the admission. The secondary outcome was asthma-related ICU admissions.

Demographic and clinical risk factors

The baseline patient demographic characteristics and behavioural risk factors extracted prior to the index date included age, sex, ethnic group, socioeconomic status (measured using the Index of Multiple Deprivation quintile (IMD)),[15] body mass index (BMI) and smoking status. The comorbidities extracted included atopic diseases (allergies, atopic eczema and allergic rhinitis), gastro-oesophageal reflux disease (GORD), chronic rhinosinusitis and mental health disorders (anxiety and depression). Asthma-related prescriptions within 1 year prior to the index date were also extracted including short-acting bronchodilators (SABA), oral corticosteroids (OCS), inhaled corticosteroids (ICS), long-acting beta-2 agonists (LABA), long-acting muscarinic antagonists (LAMA), leukotriene receptor antagonists (LTRA) and influenza vaccination.

Statistical methods

The cohort was stratified into children aged 5–11 years, adolescents aged 12– 17 years and adults aged 18 years and older. Descriptive statistics were used to describe the characteristics of the cohort. The incidence rates for asthma-related hospital and ICU admissions were calculated and stratified by age group. Partially adjusted and fully adjusted negative binomial regression models were

used to estimate the incidence rate ratios (IRR) and their 95% CIs for the association between the primary and secondary outcomes and demographic and clinical factors (see online supplemental appendix 1).

Three separate multivariable models were synthesised (model 1, model 2 and model 3) to adjust for a range of different covariates. The covariates included in model 1 were age (for adults only), sex, ethnic group, socioeconomic status, BMI and smoking status (for adolescents and adults only). Model 2 additionally included comorbidities (allergies, atopic eczema, allergic rhinitis, GORD, chronic rhinosinusitis, anxiety and depression). Model 3 additionally included asthma-related prescriptions (SABA, OCS, ICS, LABA, LAMA, LTRA and influenza vaccination). General practice was added as a random effect due to the potential variability in asthma treatment between general practices, such as differences in prescribing.

The population attributable fraction (PAF) was calculated to estimate the proportional reduction in asthma-related hospital admissions that would occur if exposure to the selected risk factors were eliminated from all people with asthma in a hypothetical scenario.[16] The PAF was calculated by fitting a fully adjusted negative binomial regression model (model 3) to estimate the IRR for the association between the primary outcome and demographic and clinical factors for each age group, before calculating the population unattributable fraction and subtracting the value and its confidence limits from 1 to obtain the PAFs.[16] The PAF was only calculated for modifiable risk factors or treatable comorbidities that had statistically significant IRRs above 1.

Study size

All eligible patients with asthma aged 5 years and above in the CPRD Aurum database were included. The sample size was determined by the available data.

Missing data

Missing data were addressed by creating a separate 'missing' category for each binary or categorical variable, including ethnicity, IMD quintile, BMI and smoking status. This method was chosen to retain patient data and avoid introducing any biases by omitting patients with missing data from the analyses. The absence of clinical codes for diagnoses or drug treatment codes was taken to indicate the absence of the condition or drug.

Patient and public involvement

Patients and members of the public were not involved in the design or conduct of the study.

RESULTS

Baseline characteristics

1 385 326 patients were included in the study, comprising 90 989 children, 114 927 adolescents and 1 179 410 adults (figure 1). The mean follow-up was 2.7 years. Baseline characteristics, stratified by age group, are summarised in table 1.

Incidence rates of primary and secondary outcomes

2898 of 90 989 (3.2%) children, 1422 of 114 927 (1.2%) adolescents and 13 186 of 1 179 410 (1.1%) adults experienced at least one asthma-related hospital admission during the 3-year follow-up period (online supplemental figure 1). Asthma-related hospital admission rates were highest in children (20.1 per 1000 person-years, 95% CI 19.5 to 20.6), followed by adolescents (10.1, 95% CI 9.7 to 10.4) and adults (6.9, 95% CI 6.8 to 7.0) (table 2). Similarly, ICU admissions were higher in children (0.5 per 1000 person-years, 95% CI 0.5 to 0.6) compared with adolescents (0.3, 95% CI 0.2 to 0.4) and adults (0.2, 95% CI 0.1 to 0.2) (table 2).

Risk factors for asthma-related hospital admissions

The association between demographic and clinical risk factors and the risk of asthma-related hospital admissions is shown in figures 2–4. Younger patients with asthma generally had a higher risk of asthma-related hospital admissions than older patients, except in patients aged 80 years and older, whose risk was similar to those aged 18–24 years (online supplemental table 2c). Females had a higher risk than males (IRR 1.83, 95% CI 1.61 to 2.08 in adolescents and 1.61, 95% CI 1.54 to 1.68 in adults) (online supplemental table 2b,c, respectively).

Patients from ethnic minority groups were at increased risk of hospital admissions compared with patients from white ethnic groups. This was particularly prominent among those from black ethnic minority groups, who had an almost twofold increased risk compared with white patients among children and adolescents (IRR 1.91, 95% CI 1.58 to 2.30 in children and 1.74, 95% CI 1.31 to 2.32 in adolescents) (online supplemental table 2a,b, respectively). There was also a socioeconomic gradient in risk, with those from the most deprived quintile having between a 43% and 52% (depending on age group) relative increase in the rate of asthma-related hospital admissions compared with patients from the most affluent quintile.

Smoking was associated with an increased risk in adolescents (IRR 1.26, 95% CI 1.05 to 1.53 for former smokers compared with non-smokers) and adults (1.19, 95% CI 1.12 to 1.25 for current smokers). Approximately 7% of asthma-related hospital admissions in adolescents (PAF 6.8%, 95% CI 0.9% to 12.3%) and 4% in adults (PAF 4.3%, 95% CI 3.0% to 5.7%), could potentially be prevented by eliminating smoking (online supplemental table 3).

In adults, BMI was significantly associated with the risk of asthma-related hospital admissions. Being underweight (IRR 1.21, 95% CI 1.06 to 1.38), overweight (1.12, 95% CI 1.06 to 1.18) and obese (1.51, 95% CI 1.43 to 1.59) were all associated with an increased risk compared

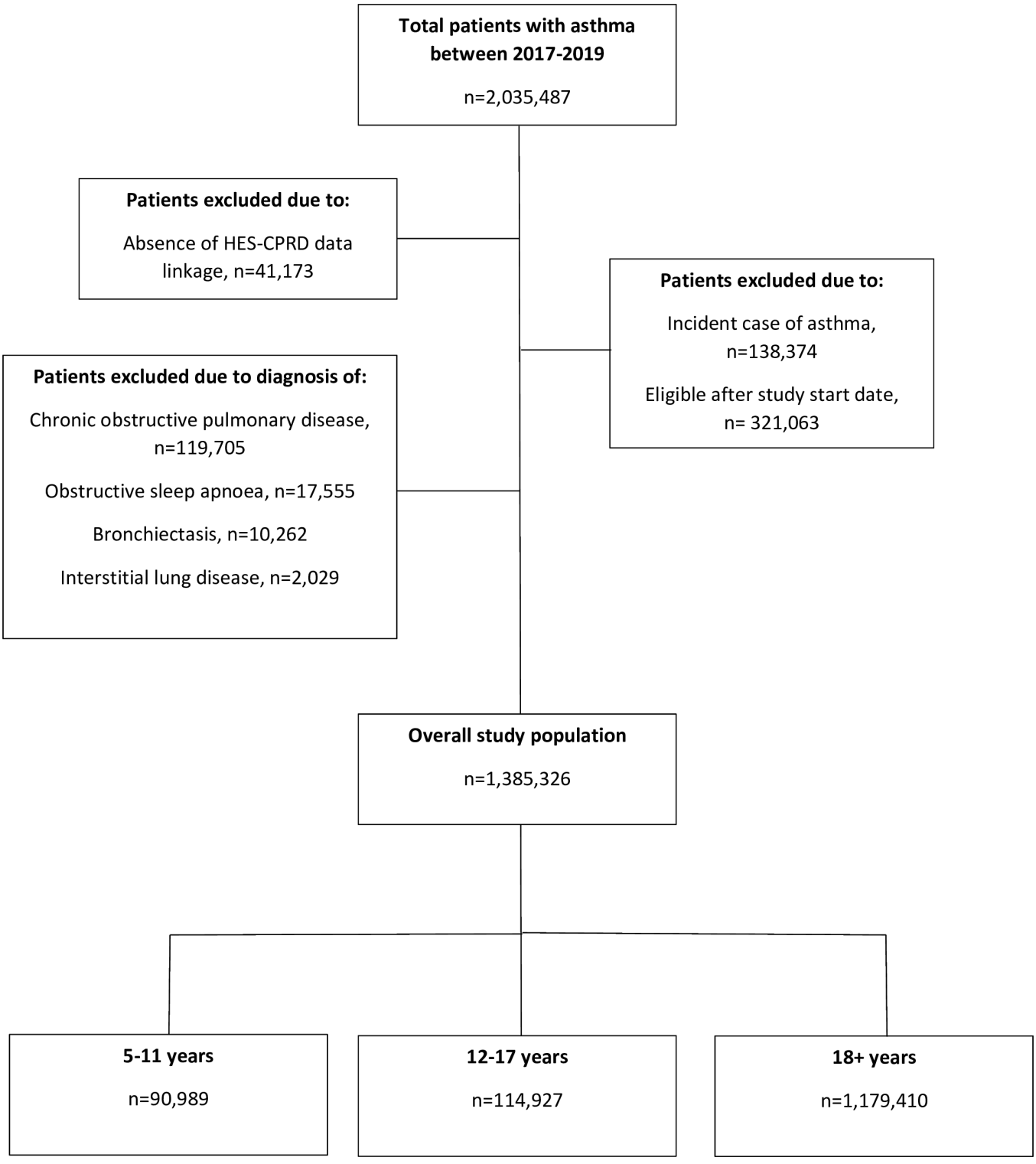


Figure 1 Participant flow diagram. CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics.

with those with a normal BMI. Eliminating obesity in the adult population could potentially prevent a fifth of all asthma-related hospital admissions (PAF 23.3%, 95% CI 20.5% to 26.1%).

Allergies and atopic conditions (atopic eczema, allergic rhinitis) were associated with an increased risk in all age groups. In adults, comorbidities had a greater associated risk with asthma-related hospital admissions, particularly with depression (IRR 1.28, 95% CI 1.22 to 1.34), chronic rhinosinusitis (1.21, 95% CI 1.08 to 1.35), GORD (1.14, 1.07 to 1.20) and anxiety (1.07, 95% CI 1.02 to 1.12). Depression potentially contributed to 11% of all asthma-related hospital admissions in adults (11.1%, 95% CI 9.1% to 13.1%).

Table 1 Baseline characteristics

Characteristic	Children (n=90 989)	Adolescents (n=114 927)	Adults (n=1 179 410)
Age (years), median (IQR)	9.1 (7.4–10.6)	15.5 (13.5–16.5)	41.5 (29.5–56.5)
Age categories (years), n (%)			
18–24	–	–	175 957 (14.9)
25–39	–	–	375 254 (31.8)
40–59	–	–	392 801 (33.3)
60–79	–	–	192 344 (16.3)
≥80	–	–	43 054 (3.7)
Sex, n (%)			
Male	54 559 (60.0)	67 825 (59.0)	555 856 (47.1)
Female	36 430 (40.0)	47 102 (41.0)	623 554 (52.9)
Ethnicity			
White	55 659 (61.2)	56 275 (49.0)	780 056 (66.1)
Black	4252 (4.7)	4527 (3.9)	29 490 (2.5)
Mixed	3386 (3.7)	2905 (2.5)	17 803 (1.5)
Asian	9834 (10.8)	9392 (8.2)	68 409 (5.8)
Other	1375 (1.5)	1260 (1.1)	11 304 (1.0)
Missing	16 483 (18.1)	40 568 (35.3)	272 348 (23.1)
IMD score, n (%)			
1—least deprived	17 312 (19.0)	22 938 (20.0)	253 814 (21.5)
2	15 788 (17.4)	20 923 (18.2)	239 399 (20.3)
3	15 681 (17.2)	20 377 (17.7)	226 015 (19.2)
4	18 686 (20.5)	23 186 (20.2)	233 339 (19.8)
5—most deprived	23 470 (25.8)	27 404 (23.8)	225 673 (19.1)
Missing	52 (0.1)	99 (0.1)	1170 (0.1)
BMI, n (%)			
Underweight	5454 (6.0)	15 859 (13.8)	34 438 (2.9)
Normal weight	31 496 (34.6)	37 788 (32.9)	379 089 (32.1)
Overweight	7151 (7.9)	10 889 (9.5)	334 266 (28.3)
Obese	3216 (3.5)	5604 (4.9)	297 323 (25.2)
Missing	43 672 (48.0)	44 787 (39.0)	134 294 (11.4)
Smoking status, n (%)			
Current smoker	–	11 749 (10.2)	324 947 (27.6)
Former smoker	–	11 970 (10.4)	439 116 (37.2)
Never smoked	–	60 832 (52.9)	397 038 (33.7)
Missing		30 376 (26.4)	18 309 (1.6)
Comorbidities, n (%)			
Allergies	18 457 (20.3)	29 658 (25.8)	317 054 (26.9)
Atopic eczema	40 808 (44.9)	51 067 (44.4)	317 822 (27.0)
Allergic rhinitis	14 963 (16.4)	29 492 (25.7)	320 075 (27.1)
Gastro-oesophageal reflux disease	5235 (5.8)	3503 (3.1)	119 111 (10.1)
Chronic rhinosinusitis	66 (0.1)	243 (0.2)	27 039 (2.3)
Anxiety	946 (1.0)	5552 (4.8)	260 258 (22.1)
Depression	917 (1.0)	2949 (2.6)	357 277 (30.3)
Medication use, n (%)			

Continued

Table 1 Continued

Characteristic	Children (n=90 989)	Adolescents (n=114 927)	Adults (n=1 179 410)
SABA	59 321 (65.2)	52 212 (45.4)	464 123 (39.4)
SABA prescriptions within last year			
0	31 668 (34.8)	62 715 (54.6)	715 287 (60.7)
1–3	42 416 (46.6)	37 236 (32.4)	288 395 (24.5)
4–6	11 390 (12.5)	8822 (7.7)	90 047 (7.6)
≥7	5515 (6.1)	6154 (5.4)	85 681 (7.3)
OCS	10 476 (11.5)	6333 (5.5)	114 033 (9.7)
ICS	48 865 (53.7)	39 549 (34.4)	445 349 (37.8)
LABA	938 (1.0)	1245 (1.1)	59 643 (5.1)
LAMA	0 (0)	6 (0.01)	7628 (0.7)
LTRA	9404 (10.3)	4920 (4.3)	33 247 (2.8)
Influenza vaccine	33 464 (36.8)	22 256 (19.4)	389 583 (33.0)

BMI, body mass index; ICS, inhaled corticosteroid; IMD, Index of Multiple Deprivation; LABA, Long-acting beta-2 agonists; LAMA, long-acting muscarinic antagonists; LTRA, leukotriene receptor antagonists; OCS, oral corticosteroid; SABA, short acting beta-2 agonist.

Across all age group, asthma medication prescriptions issued in the previous year were strongly associated with an increased risk of asthma-related hospital admissions. This was seen most prominently in those with prior SABA prescriptions. For example, children who had received more than six SABA prescriptions in the previous year had a fivefold increased risk in hospital admission compared with those who had not received any (IRR 4.97, 95% CI 4.06 to 6.09) (online supplemental table 2a). Similar trends were seen in adolescents and adults and were also seen for other asthma medications such as oral and ICS.

Risk factors for ICU admissions

Younger age was associated with a higher risk of asthma-related ICU admissions. Among adults, the highest asthma-related ICU admission was in the 18–25 years age group. Adolescent females were at increased risk of asthma-related ICU admissions compared with males (IRR 1.54, 95% CI 1.00 to 2.36) (online supplemental table 4b). Similar trends were seen in adults (1.46, 95% CI 1.17 to 1.81) (online supplemental table 4c) but not in children (online supplemental table 4a).

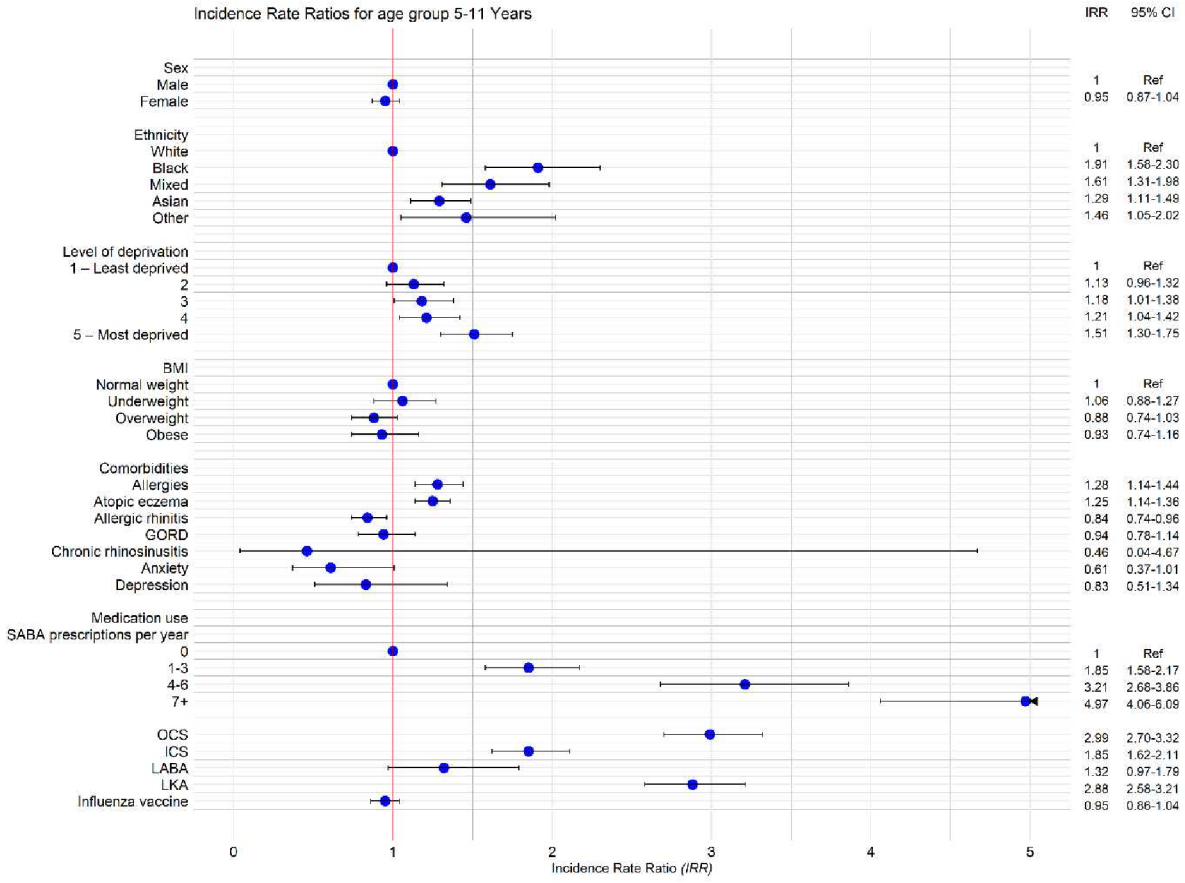
Among ethnic groups, black patients had the highest risk of asthma-related hospital admissions (IRR 4.07, 95% CI 2.35 to 7.05 in children, 3.51, 95% CI 1.62 to 7.59 in adolescents and 2.69, 95% CI 1.75 to 4.13 in adults). Socioeconomic deprivation was also associated with an increased risk in children with those in the most deprived quintile having a 98% increased risk (IRR 1.98, 95% CI 1.03 to 3.79) compared with those in the least deprived quintile. These trends were not statistically significant in adolescents or adults.

Table 2 Incidence rates of the primary and secondary outcomes

Outcome	5–11 years	12–17 years	≥18 years
Asthma-related hospital admissions			
Incident asthma-related hospital admissions	5105	3228	21 925
Person years	254 526	320 086	3 184 183
Incidence rate (per 1000 person years)	20.06 (95% CI 19.51 to 20.61)	10.08 (95% CI 9.74 to 10.44)	6.89 (95% CI 6.79 to 6.98)
Asthma-related ICU admissions			
Incident asthma-related ICU admissions	137	92	474
Person years	254 526	320 086	3 184 183
Incidence rate (per 1000 person years)	0.54 (95% CI 0.45 to 0.64)	0.29 (95% CI 0.23 to 0.35)	0.15 (95% CI 0.14 to 0.16)

ICU, intensive care unit.

Adjusted* Incidence Rate Ratios (IRR) for asthma-related hospital admissions among children aged 5-11 years



* Adjusted for all covariates including sex, ethnic group, socioeconomic status, BMI, allergies, atopic eczema, allergic rhinitis, GORD, Chronic rhinosinusitis, anxiety, depression and use of SABA, OCS, ICS, LABA, LAMA, LKA, and influenza vaccine.

GORD; Gastro Oesophageal Reflux Disease, SABA; Short-Acting Beta-Agonist, OCS; Oral Corticosteroids, ICS; Inhaled Corticosteroids, LABA; Long-Acting Beta-Agonist, LKA; Leukotriene Receptor Antagonist

Figure 2 Forest plot showing adjusted IRR for hospital admissions among children. BMI, body mass index.

The only comorbidity associated with an increased rate of ICU admissions was depression in adults, which was associated with a 60% increased risk (1.60, 95% CI 1.28 to 2.00). Similar to the trend for hospital admissions, previous asthma medication prescriptions, including SABAs were associated with a significantly increased risk of ICU admissions. For example, in children, seven or more SABA prescriptions in the previous year were associated with an approximately sevenfold increase in risk compared with those who had not received any (IRR 6.97, 95% CI 2.91 to 16.68). Similar associations were also seen for other asthma-related medications prescribed in the previous year in all age groups.

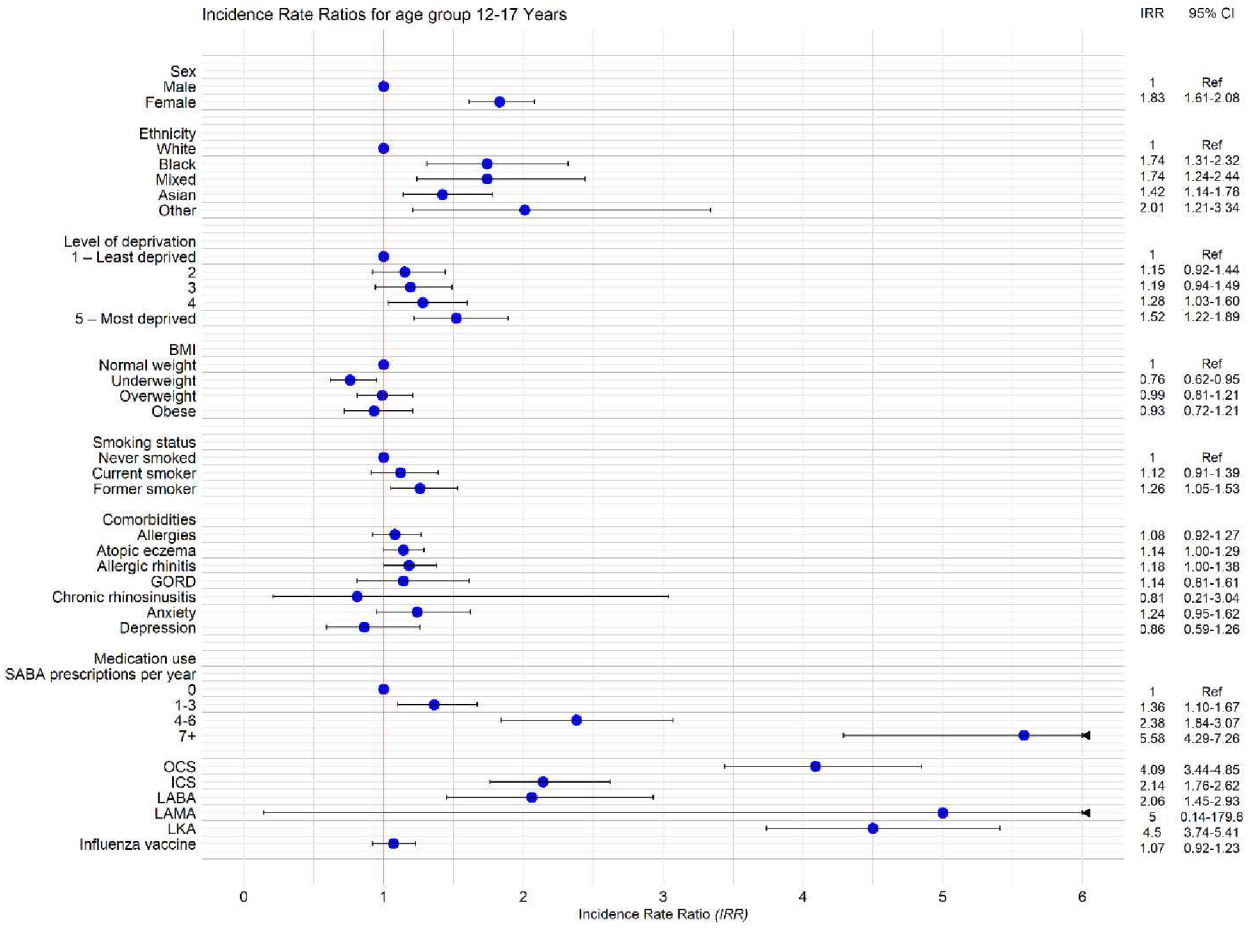
DISCUSSION

Main findings

Our analysis of over one million patients with a diagnosis of asthma in their primary care record showed that there are significant demographic disparities in the risk of asthma-related hospital and ICU admissions in England. Our analysis also shows an association between behavioural risk factors, comorbidities, and medication history, and the risk of these adverse outcomes. Furthermore, these associations vary across the life course.

Younger age groups were typically at higher risk of asthma-related hospital admissions than older adults. Females were at higher risk than males, except in children. Ethnic minority groups were at greater risk than patients from white ethnic groups, with those from

Adjusted* Incidence Rate Ratios (IRR) for asthma-related hospital admissions among adolescents aged 12-17 years



* Adjusted for all covariates including sex, ethnic group, socioeconomic status, BMI, smoking status, allergies, atopic eczema, allergic rhinitis, GORD, Chronic rhinosinusitis, anxiety, depression and use of SABA, OCS, ICS, LABA, LAMA, LKA, and influenza vaccine.

GORD; Gastro Oesophageal Reflux Disease, SABA; Short-Acting Beta-Agonist, OCS; Oral Corticosteroids, ICS; Inhaled Corticosteroids, LABA; Long-Acting Beta-Agonist, LAMA; Long-Acting Muscarinic Antagonist, LKA; Leukotriene Receptor Antagonist

Figure 3 Forest plot showing adjusted IRR for hospital admissions among adolescents. BMI, body mass index.

black ethnic minority groups being at the highest risk, including for ICU admissions. Socioeconomic deprivation was also an important risk factor.

Smoking in adults and adolescents was an important behavioural risk factor, the elimination of which could theoretically prevent 7% of hospital admissions in adolescents and 4% in adults. Obesity was a significant risk factor in adults, potentially contributing to over a fifth of hospital admissions in this age group.

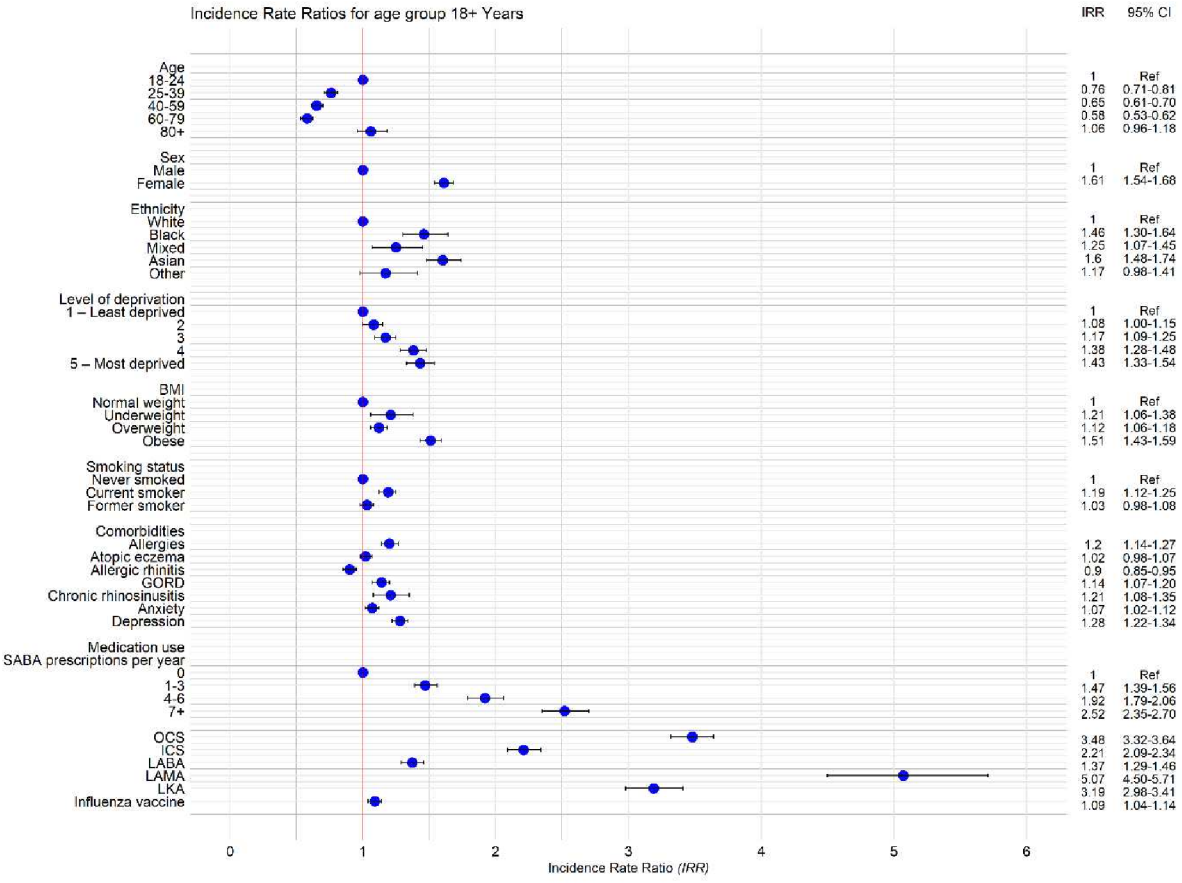
Atopic diseases were associated with an increased risk of hospital admissions across all age groups. However, our analysis suggests that comorbidities play a more significant role in adverse outcomes in adults, where significant associations with hospital admissions were found for several conditions including depression, anxiety, GORD and rhinosinusitis.

Across all age groups, prior asthma medication history was associated with an increased risk of both hospital and ICU admissions. This could be seen most clearly with an increasing number of SABA prescriptions but was also seen for several other asthma medications, which is likely to reflect increasing disease severity and potentially poor medication compliance.

Relationship to other studies

Some previous studies have demonstrated an increasing risk of hospital admissions, readmissions and severe exacerbations with age.[17 18] In unadjusted analyses, we found a similar association; however, after adjusting for demographic and behavioural confounders, our findings showed that the highest incidence rates for hospital

Adjusted* Incidence Rate Ratios (IRR) for asthma-related hospital admissions among adults aged 18+ years



* Adjusted for all covariates including age, sex, ethnic group, socioeconomic status, BMI, smoking status, allergies, atopic eczema, allergic rhinitis, GORD, Chronic rhinosinusitis, anxiety, depression and use of SABA, OCS, ICS, LABA, LAMA, LKA, and influenza vaccine.

GORD; Gastro Oesophageal Reflux Disease, SABA; Short-Acting Beta-Agonist, OCS; Oral Corticosteroids, ICS; Inhaled Corticosteroids, LABA; Long-Acting Beta-Agonist, LAMA; Long-Acting Muscarinic Antagonist LKA; Leukotriene Receptor Antagonist

Figure 4 Forest plot showing adjusted IRR for hospital admissions among adults. BMI, body mass index.

and ICU admissions are in children and adolescents. Among adults, the risk of hospitalisation decreased with increasing age up until 80 years and older, when the risk was similar to those aged 18–24 years.

Ethnic disparities in asthma-related hospital admissions and readmissions have been found in several previous studies, particularly in patients from black ethnic minority groups who appear to have the highest risk.[19–21] Differences in socioeconomic status and access to health and poor living conditions may partially explain these ethnic disparities. Beck *et al* found that social hardships and socioeconomic status explained approximately 40%–50% of the racial disparity observed for paediatric asthma-related hospital admissions in one study in the USA.[21] In addition, higher BMI, airway inflammatory responses to early life exposures and genetic predisposition have been implicated in increasing the risk of asthma exacerbations in ethnic minority children.[22]

Several studies have previously demonstrated that increased socioeconomic deprivation is a risk factor for asthma-related hospital admissions and readmissions in children and adults.[23–25] The risk of hospital admissions has previously been shown to be between one and two times higher in those who are most deprived compared with those who are least. This is consistent with the findings from our study and may be explained by the many adverse factors that are associated with low socioeconomic status such as poor housing conditions,[26] which may be particularly marked in urban areas.[24]

Studies have investigated the association between exposure to tobacco smoke and risk of hospitalisation, readmission and severe asthma exacerbations.[27–29] Two studies

found that detectable serum or salivary cotinine was significantly associated with a 59% and 135% increase in asthma-related hospital readmissions, respectively,[30] and a 40% increase in severe asthma exacerbations (defined as hospitalisation, emergency department (ED) visit or prescription of an OCS).[31]

Several studies have found that obesity is associated with an up to fourfold increased risk of asthma-related hospitalisations and readmissions in children and adults,[27–29] whereas in our study, we only found this association in adults. The lack of association between obesity and asthma-related hospitalisations in younger people in our study could be partly attributable to the high level of missing BMI data for children and adolescents. However, a meta-analysis of observational studies similarly found that overweight and obesity are not associated with asthma-related hospitalisations in children and adolescents.[32] The association between obesity and increased risk in hospital admissions in adults may be explained by the inflammatory effects of obesity and the impact on airway calibre and bronchial hyper-reactivity.[33–35] However, it is also possible that this association is at least partly mediated by obesity being a risk factor for GORD, which may worsen asthma outcomes.

An association between affective disorders, such as anxiety and depression, and the risk of asthma-related ED visits and hospitalisations, has been observed in some studies.[27–29] However, there is a scarcity of literature on the role of depressive disorders in children and young people, which may be partly due to depressive symptoms being relatively undiagnosed or untreated in younger age groups.[32–34] Furthermore, the relationship between asthma and affective disorders is likely to be bidirectional, adding further complexity to modelling the association between mental health disorders and asthma outcomes.

The presence of allergies or atopic illnesses was associated with asthma-related hospitalisations in all three age groups in our study. The role of allergens in triggering IgE-mediated inflammation, eosinophilia and release of inflammatory cytokines, to promote airway inflammation and bronchial mucous hypersecretion in asthma, is well established.[36] However, the evaluation of allergy is usually only performed in patients with severe asthma. Our findings suggest that more effective management of allergies may contribute to reducing asthma-related hospitalisation in children and adults.[37–39] However, in practice, it can often be challenging to reduce allergic exposures.

A recent systematic review and meta-analysis of observational studies showed that GORD is a risk factor for severe asthma.[35] The findings from the meta-analysis showed that the overall odds of severe asthma exacerbations were 27% higher in those with GORD. Furthermore, children with GORD were more at risk of severe asthma exacerbations than adults.[35] This is in contrast to our study, which found an increased risk in asthma-related hospitalisations associated with GORD only in adults and not in children or adolescents. This may potentially be due to under recognition of GORD in children and adolescents, leading to exposure misclassification bias in our analysis and dilution of the associated effect size. However, it is also possible that GORD plays a more dominant role in asthma outcomes in adults, in which it is a more common comorbidity and may be less significant in children. We would expect GORD to be associated with worse asthma control since acid reflux can induce cough and induce airway inflammation through pulmonary aspiration, and vagus-mediated bronchoconstriction may occur in response to reflux, worsening asthma symptoms.[40] However, it remains unclear whether treating GORD has a significant impact on asthma exacerbations.

There are a number of studies in the literature which support our findings that previous use of SABAs and OCS are associated with an increased risk of hospital admissions.[19 41 42] The use of three or more SABA inhalers per year has been associated with up to a fivefold increase in risk of asthma exacerbations.[19 43] Medication burden in general is a marker of poor asthma control, potentially poor medication compliance and greater disease severity.[44] A longitudinal study which followed over 1000 New Zealanders from birth to 26 years of age similarly found that asthma-related hospital admissions were overall more likely in patients who had been treated with a SABA, ICS or any other asthma medication, which is in keeping with our findings.[45]

Strengths and limitations

Our study used linked primary and secondary care data from over a million patients with diagnosed asthma, making this one of the largest analyses of asthma-related hospital and ICU admissions. The large sample size provided adequate power to investigate several important risk factors and stratify analyses by age subgroups. We evaluated a range of risk factors and estimated PAFs for key modifiable risk factors. This enabled us to identify the most important risk factors responsible for these outcomes at a population level.

There were also several limitations. First, asthma is commonly misdiagnosed in primary care.[46] We defined asthma as a coded diagnosis using prespecified SNOMED-CT terms that had been systematically selected. However, studies have demonstrated that asthma can be accurately defined within electronic health record data.[47] In addition, there may also be misclassification bias in the coding of asthma-related hospital admissions, as exacerbations could be due to other comorbidities with overlapping symptoms, such as heart failure. However, we attempted to limit this by excluding patients with common chronic respiratory diseases such as COPD, which might otherwise present similarly to asthma during acute exacerbations.

The study was also limited by the lack of data on some key risk factors, such as BMI and smoking status in children and adolescents, as well as lacking data on

environmental risk factors such as air quality, including data on secondhand smoke exposure. Furthermore, some conditions such as depression and anxiety may be underdiagnosed in children and adolescents, thus making them underrepresented in our dataset.[34] We also lacked data on key physiological measures such as peak expiratory flow rate, spirometry, airway eosinophilia, fractional exhaled nitric oxide and other physiological measures of disease severity or patient-reported outcome measures.

Drug prescriptions were modelled on individual medicinal components, and we did not model potential interactions between drug constituents from dual therapy inhalers. In addition, although we had accurate data on prescriptions, we did not have data on medication compliance.

Moreover, our statistical models did not incorporate interactions between the included risk factors. Incorporation of interaction terms increases the complexity of statistical models and reduces their interpretability. We were principally interested in assessing the association between potentially modifiable risk factors and the risk of hospital admissions, and therefore, kept our models as parsimonious as possible. However, future research aiming to produce predictive models of asthma admissions should ideally explore interactions between the risk factors presented in this study.

This study did not use directed acyclic graphs (DAGs) to model the causal relationship between the various risk factors explored. Future research could employ DAGs to model the causal relationships between the risk factors explored in this study. Given causal diagrams were not used to build the regression models, a degree of overadjustment bias is possible. Although we have indicated that eliminating or treating risk factors has the potential to reduce asthma-related hospital admissions, further research is needed to determine whether treating or preventing these risk factors leads to a reduction in exacerbations.

Finally, although we were able to include outcome data on hospital and ICU admissions, we did not have access to data on ED attendances, which also constitutes an important measure of asthma control and secondary care use.

Implications for practice, policy and future research

Our study provides novel insights into age specific risk factors and population groups experiencing severe asthma exacerbations requiring hospital and ICU admission. These disparities require urgent attention through a whole system approach to promote improvements in asthma management in disadvantaged population groups.

We have provided estimates of the proportion of asthma-related hospital admissions that could potentially be prevented by eliminating modifiable risk factors. Our findings suggest that treating allergies and atopic conditions should be considered an important component of asthma management and has the potential to significantly reduce asthma-related hospital admissions in all age groups. In adolescents and adults, smoking cessation also has the potential to significantly reduce hospital admissions, emphasising the need to integrate smoking cessation with asthma care. In adults, supporting weight management and treating comorbid depression, anxiety and GORD should also be considered an integral part of general asthma management as they are likely to significantly contribute to avoidable asthma-related hospital admissions.

We also show the importance of medication burden as a key measure of poor asthma control. In addition to monitoring SABA prescriptions, clinicians should also monitor the prescription frequency of other asthma medications. Specifically, patients prescribed three or more salbutamol inhalers in the previous 12 months should be reviewed promptly to optimise asthma management. Confirming the asthma diagnosis, demonstrating good inhaler technique, and emphasising adherence to preventative therapies such as ICS could improve asthma control and reduce over reliance on short-acting bronchodilators. High medication burden should be considered an important measure of disease severity and predictor of asthma-related hospital and ICU admissions. Measures of global asthma medication burden, incorporating the findings of this study, could be used by electronic prescribing systems to highlight high-risk patients requiring regular review and support.

CONCLUSIONS

There remain significant sociodemographic inequalities in the rates of asthma-related hospital and ICU admissions, with younger patients, females and those from black ethnic minority and lower socioeconomic groups being at the highest risk. The management of modifiable risk factors such as smoking and obesity and the treatment of comorbidities, including atopic diseases, depression, anxiety and GORD should be integrated with the clinical management of asthma. Finally, asthma medication burden is an important prognostic measure of asthma severity that could be used for disease monitoring.

Transparency statement

The manuscript's guarantor affirms that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Author affiliations
[1]University of Birmingham Institute of Applied Health Research, Birmingham, UK
[2]Birmingham Women's and Children's Hospitals NHS Foundation Trust, Birmingham, UK
[3]Institute of Inflammation and Ageing University, University of Birmingham, Birmingham, UK
[4]University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

Contributors SH and PN led the design of the study with input from NS-W, RH, AHM and RT. NS-W conducted the analyses with expert input from RT and NJA. RT produced the forest plots. NS-W and SH drafted the initial manuscript with input from NJA and PN. All authors approved the final version. SH is the guarantor for this study. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding This research was funded by the National Institute for Health and Research Clinical Research Network West Midlands Improvement and Innovation Strategic Funding, grant number: 1002281.

Disclaimer The researchers were independent from the funders and all authors had access to the study data and took responsibility for the integrity of the analyses.

Competing interests SH reports receiving funding from NIHR and UKRI. KN has been awarded research grants from NIHR, UKRI/MRC, Kennedy Trust for Rheumatology Research, Health Data Research UK, Wellcome Trust, European Regional Development Fund, Institute for Global Innovation, Boehringer Ingelheim, Action Against Macular Degeneration Charity, Midlands Neuroscience Teaching and Development Funds, South Asian Health Foundation, Vifor Pharma, College of Police and CSL Behring, with all payments made to his academic institution; KN received consulting fees from BI, Sanofi, CEGEDIM, MSD and holds a leadership/fiduciary role with NICST, a charity and OpenClinical, a Social Enterprise. AHM received personal and institution funds for talks, consultancy fees, education or research grants from GSK, AZ, Sanofi, Teva, BI, Novartis, Chiesi. NJA reports receiving funding from NIHR outside the submitted work. PN reports receiving grants from NIHR and fees for educational talks and consultancy from Novartis, GSK and Astrazaneca.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval 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.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are not publicly available. Access to anonymised patient data from CPRD is subject to a data sharing agreement containing detailed terms and conditions of use following protocol approval from the MHRA Independent Scientific Advisory Committee. This study-specific analysable dataset is, therefore, not publicly available but can be requested from the corresponding author subject to research data governance approvals. Details about Independent Scientific Advisory Committee applications and data costs are available on the CPRD website (cprd.com).

ORCID iD
Nikita Simms-Williams http://orcid.org/0000-0002-4926-1995

REFERENCES

1 Song P, Adeloye D, Salim H, *et al*. Global, regional, and national prevalence of asthma in 2019: a systematic analysis and modelling study. *J Glob Health* 2022;12:04052.
2 National Institute of Health and Care Excellence. Available: https://cks.nice.org.uk/topics/asthma/background-information/prevalence/ [Accessed 7 Jul 2021].
3 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.
4 NICE Guideline. Asthma: diagnosis, monitoring and chronic asthma management. Available: https://www.nice.org.uk/guidance/ng80 [Accessed 7 Jul 2021].
5 Levy ML. The National review of asthma deaths: what did we learn and what needs to change. *Breathe (Sheff)* 2015;11:14–24.
6 Nuffield Trust. Available: https://www.nuffieldtrust.org.uk/research/international-comparisons-of-health-and-wellbeing-in-adolescence-and-early-adulthood [Accessed 7 Jul 2021].
7 Fleming Louise. Asthma exacerbation prediction: recent insights. *Curr Opin Allergy Clin Immunol* 2018;18:117–23.
8 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.
9 Aggarwal S, Cepalo T, Gill S, *et al*. Factors associated with future hospitalization among children with asthma: a systematic review. *J Asthma* 2023;60:425–45.
10 Wolf A, Dedman D, Campbell J, *et al*. Data resource profile: clinical practice research Datalink (CPRD) Aurum. *Int J Epidemiol* 2019;48:1740–1740g.
11 Herrett E, Gallagher AM, Bhaskaran K, *et al*. Data resource profile: clinical practice research Datalink (CPRD). *Int J Epidemiol* 2015;44:827–36.
12 CPRD Aurum March 2021 Dataset. Available: https://www.cprd.com/cprd-aurum-march-2021 [Accessed 7 Jul 2021].
13 Clinical classifications. Available: https://digital.nhs.uk/services/terminology-and-classifications/clinical-classifications [Accessed 7 Jul 2021].
14 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.
15 Noble M, Wright G, Smith G, *et al*. Measuring multiple deprivation at the small-area level. *Environ Plan A* 2006;38:169–85.
16 Newson RB. Attributable and unattributable risks and fractions and other scenario comparisons. *The Stata Journal* 2013;13:672–98.
17 Bloom CI, Nissen F, Douglas IJ, *et al*. Exacerbation risk and characterisation of the UK's asthma population from infants to old age. *Thorax* 2018;73:313–20.
18 Hasegawa K, Gibo K, Tsugawa Y, *et al*. Age-related differences in the rate, timing, and diagnosis of 30-day readmissions in hospitalized adults with asthma exacerbation. *Chest* 2016;149:1021–9.
19 Hull SA, McKibben S, Homer K, *et al*. Asthma prescribing, Ethnicity and risk of hospital admission: an analysis of 35,864 linked primary and secondary care records in East London. *NPJ Prim Care Respir Med* 2016;26:16049.
20 Fisher-Owens SA, Turenne WM, Chavanu K, *et al*. Racial disparities in children hospitalized with asthma at academic childrens' hospitals. Pediatr Asthma Allergy Immunol 2006;19:162–71.
21 Beck AF, Huang B, Simmons JM, *et al*. Role of financial and social hardships in asthma racial disparities. *Pediatrics* 2014;133:39:431–9:.
22 Whitrow MJ, Harding S. Asthma in black African, black Caribbean and South Asian adolescents in the MRC DASH study: a cross sectional analysis. *BMC Pediatr* 2010;10:18.
23 Grecian S, Grecian R, Dermott S, *et al*. The relationship between social deprivation and hospital admissions with asthma. *Eur Respir J* 2013;42:957.
24 Purdy S, Griffin T, Salisbury C, *et al*. Emergency respiratory admissions: influence of practice, population and hospital factors. *J Health Serv Res Policy* 2011;16:133–40.
25 Alsallakh MA, Rodgers SE, Lyons RA, *et al*. Association of socioeconomic deprivation with asthma care, outcomes, and deaths in Wales: a 5-year national linked primary and secondary care cohort study. *PLoS Med* 2021;18:e1003497.
26 Bryant-Stephens T. Asthma disparities in urban environments. *J Allergy Clin Immunol* 2009;123:1199–206.
27 Bardach NS, Neel C, Kleinman LC, *et al*. Depression, anxiety, and emergency department use for asthma. *Pediatrics* 2019;144:e20190856.

28 Ahmedani BK, Peterson EL, Wells KE, *et al*. Examining the relationship between depression and asthma exacerbations in a prospective follow-up study. *Psychosom Med* 2013;75:305–10.
29 Mancuso CA, Peterson MG, Charlson ME. Effects of depressive symptoms on health-related quality of life in asthma patients. *J Gen Intern Med* 2000;15:301–10.
30 Howrylak JA, Spanier AJ, Huang B, *et al*. Cotinine in children admitted for asthma and readmission. *Pediatrics* 2014;133:e355–62.
31 Neophytou AM, Oh SS, White MJ, *et al*. Secondhand smoke exposure and asthma outcomes among African American and Latino children with asthma. *Thorax* 2018;73:1041–8.
32 De Groot EP, Duiverman EJ, Brand PLP. Comorbidities of asthma during childhood: possibly important, yet poorly studied. *Eur Respir J* 2010;36:671–8.
33 Shams MR, Bruce AC, Fitzpatrick AM. Anxiety contributes to poorer asthma outcomes in inner-city black adolescents. *J Allergy Clin Immunol Pract* 2018;6:227–35.
34 Mullen S. Major depressive disorder in children and adolescents. *Ment Health Clin* 2018;8:275–83.
35 Mallah N, Turner JM, González-Barcala F-J, *et al*. Gastroesophageal reflux disease and asthma exacerbation: a systematic review and meta-analysis. *Pediatr Allergy Immunol* 2022;33:e13655.
36 Singh AM, Busse WW. Asthma exacerbations 2: aetiology. *Thorax* 2006;61:809–16.
37 Teague WG, Iqbal A, Ding Y, *et al*. The added burden of allergen sensitization among children with severe or poorly controlled asthma. *J Allergy Clin Immunol Pract* 2021;9:853–61.
38 Rosas I, McCartney HA, Payne RW, *et al*. Analysis of the relationships between environmental factors (Aeroallergens, air pollution, and weather) and asthma emergency admissions to a hospital in Mexico city. *Allergy* 1998;53:394–401.
39 O'Hollaren MT, Yunginger JW, Offord KP, *et al*. Exposure to an aeroallergen as a possible precipitating factor in respiratory arrest in young patients with asthma. *N Engl J Med* 1991;324:359–63.
40 Ates F, Vaezi MF. Insight into the relationship between gastroesophageal reflux disease and asthma. *Gastroenterol Hepatol (N Y)* 2014;10:729–36.
41 Paris J, Peterson EL, Wells K, *et al*. Relationship between recent short-acting beta-agonist use and subsequent asthma exacerbations. *Ann Allergy Asthma Immunol* 2008;101:482–7.
42 Adams RJ, Smith BJ, Ruffin RE. Factors associated with hospital admissions and repeat emergency department visits for adults with asthma. *Thorax* 2000;55:566–73.
43 Stanford RH, Shah MB, D'Souza AO, *et al*. Short-acting B-agonist use and its ability to predict future asthma-related outcomes. *Ann Allergy Asthma Immunol* 2012;109:403–7.
44 Engelkes M, Janssens HM, de Jongste JC, *et al*. Medication adherence and the risk of severe asthma exacerbations: a systematic review. *Eur Respir J* 2015;45:396–407.
45 Rasmussen F, Taylor DR, Flannery EM, *et al*. Risk factors for hospital admission for asthma from childhood to young adulthood: a longitudinal population study. *J Allergy Clin Immunol* 2002;110:220–7.
46 Kavanagh J, Jackson DJ, Kent BD. Over- and under-diagnosis in asthma. *Breathe (Sheff)* 2019;15:e20–7.
47 Nissen F, Morales DR, Mullerova H, *et al*. Validation of asthma recording in the clinical practice research Datalink (CPRD). *BMJ Open* 2017;7:e017474.