Short-acting β_2-agonists and exacerbations in children with asthma in England: SABINA Junior

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Shareable abstract (@ERSpublications)
High SABA prescriptions (⩾3 canisters per year) are associated with an increased risk of exacerbations in the paediatric asthma population, as observed in adults with asthma. Careful monitoring of asthma symptoms and SABA use can identify at-risk patients. https://bit.ly/3ITusJl

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Abstract

Background Prescription of three or more short-acting β_2-agonist (SABA) canisters per year in adult and adolescent asthma populations is associated with a risk of severe exacerbations; however, evidence in children aged <12 years is limited.

Methods This study analysed data on children and adolescents with asthma in three age cohorts: 1–5 years, 6–11 years and 12–17 years from the Clinical Practice Research Datalink Aurum database for the period 1 January 2007 to 31 December 2019. Associations between SABA prescriptions (three or more *versus* fewer than three canisters per year) at baseline, defined as 6 months after an asthma diagnosis as a binary exposure variable, and the rate of future asthma exacerbations, defined as oral corticosteroid burst therapy, an emergency department visit or hospital admission, were assessed by multilevel negative binomial regression, adjusted for relevant demographic and clinical confounders.

Results Overall 48 560, 110 091 and 111 891 paediatric patients with asthma were aged 1–5, 6–11 and 12–17 years, respectively. During the baseline period, 22 423 (46.2%), 42 137 (38.3%) and 40 288 (36.0%) in these three age cohorts, respectively, were prescribed three or more SABA canisters per year. Across all age ranges, the rate of future asthma exacerbations in those prescribed three or more *versus* fewer than three SABA canisters per year was at least two-fold higher. >30% of patients across all age cohorts were not prescribed inhaled corticosteroids (ICS), and the median proportion of days covered was only 33%, suggesting inadequate prescribing of ICS

Conclusion In children, higher SABA prescriptions at baseline were associated with increased future exacerbation rates. These findings highlight the need for monitoring prescription of three or more SABA canisters per year to identify children with asthma at risk of exacerbations.

Introduction

Asthma, a chronic heterogeneous, inflammatory, respiratory disease [1], is common across Europe, with ∼30 million diagnosed cases among children and adults aged <45 years [2]. Countries such as Sweden and the United Kingdom (UK) have reported some of the highest levels of disease-related morbidity among children and young adults in the region [3]. In the UK, ∼5.4 million people currently receive treatment for asthma, including 1.1 million children. In 2016/2017, >75 000 people spanning all age groups experienced an asthma exacerbation that warranted hospitalisation [4].

To achieve symptom control and minimise exacerbation risk, the Global Initiative for Asthma (GINA) and the British Thoracic Society (BTS) recommend a stepwise approach to the pharmacological management

of asthma, entailing medication titration and/or add-on treatments until disease control is achieved [1, 5]. Although historically, short-acting β_2-agonists (SABAs) had been recommended as the first-line treatment for rapid symptom relief across asthma severity, addition of an inhaled corticosteroid (ICS)-containing agent has proven clinically effective relative to SABA monotherapy, in reducing the risk of exacerbations, even in cases of mild disease [6–8]. Efficacy of these anti-inflammatory medications together with the safety concerns related to high SABA use have prompted a major reassessment of available asthma pharmacotherapies [9–11].

The *Lancet* commission on asthma recommends an anti-inflammatory medication (such as ICS) as first-line treatment, regardless of asthma severity, rather than symptom-based management with a bronchodilator [12, 13]. Moreover, since 2019, GINA has advised against the use of SABA monotherapy in adolescents and adults with asthma [14]. Instead, GINA track 1 (preferred) recommends ICS–formoterol as the reliever across all treatment steps: as-needed at steps 1–2 (mild asthma), and as both maintenance and reliever therapy (MART) for steps 3–5 (moderate-to-severe asthma) [1]. ICS-containing treatment is now also recommended for children aged 6–11 years at steps 1 and 2 whenever SABA is taken for symptom relief, or as daily low-dose ICS [1]. The option of using ICS–formoterol as MART was recommended by GINA for children aged 6–11 years in 2021 [15] and the subsequent 2022 revision [1]. The 2019 BTS guidelines also recommend initiation of very low-dose ICS or a leukotriene receptor antagonist at the outset of asthma symptoms for those aged <5 years) [5].

Despite these updated treatment recommendations, studies across the globe, including in the UK, have reported a widespread reluctance to adopt ICS-containing therapies and an apparent continued reliance on SABA to control the frequency and intensity of symptoms [16–18]. Indeed, a systematic review commissioned by Asthma UK, which was undertaken to identify risk factors associated with asthma exacerbations in children aged 5–12 years, reported that suboptimal drug regimens were associated with a moderately increased risk [19]. In this review, five of the seven studies that examined reliever use showed that SABAs were associated with an increased risk of exacerbations, while four out of 16 studies demonstrated fewer exacerbations with maintenance medication use [19]. Notably, the National Review of Asthma Deaths report published by the Royal College of Physicians in 2015, the first national investigation of asthma deaths in the UK, identified SABA overprescription and insufficient provision of ICS-containing medications as preventable causes of deaths [9]. In addition, high SABA use in those with mild asthma for symptom control rather than early initiation of ICS and/or irregular adherence to ICS-containing regimens may contribute to deteriorating clinical outcomes across the spectrum of disease [20]. Nevertheless, results from a more recent retrospective analysis (2018/2019) of 350 general practitioner (GP) practices in north-west London (UK), in 14 405 children with asthma aged ⩽18 years, did not demonstrate a statistically significant relationship between the number of SABA prescriptions and asthma exacerbations [21].

While the pattern of low ICS use and high SABA use remains a prevailing clinical concern, data on trends in SABA use among children and adolescents with asthma are limited and paediatric phenotypes differ from those of adult populations [18, 22]. Therefore, we aimed to describe the epidemiology and clinical characteristics of asthma, with a focus on SABA prescription volumes, among paediatric residents (aged 1–17 years) of England and the association with exacerbations of varying severity in the previous 10 years.

Methods

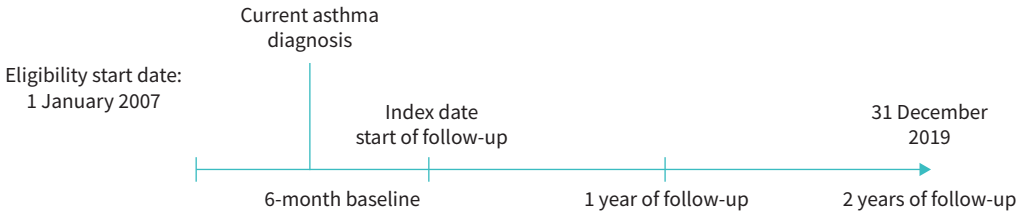
Data sources

This study accessed routinely collected data from GP practices, curated by the Clinical Practice Research Datalink (CPRD) service (available as the CPRD Aurum database) with linked secondary care data spanning accident and emergency (A&E) visits and hospital admissions. The same data source was accessed for the SABA use IN Asthma (SABINA) I UK analysis [18]. Full details of the study methodology are provided in the supplementary material.

Study design and population

This retrospective, longitudinal, open-cohort study (figure 1) explored the association between SABA prescription volumes and asthma exacerbations in an English paediatric population with a GP diagnosis of asthma reflected in their primary care record. We excluded patients with <12-month research-acceptable data prior to the defined index date of 6 months after a recorded asthma diagnosis, or with other chronic lung diseases. An external ethics committee approved this study.

Three age cohorts were categorised as 1–5 years, 6–11 years and 12–17 years, which encompassed the threshold ranges specified by BTS and GINA asthma treatment recommendations. This study design



- Covariates and medication history determined in 6-month baseline period
- Index date 6 months after asthma diagnosis was recorded
- Prior to index date, patients must have 12 months of continuous registration at a CPRD participating GP practice data and meet CPRD "acceptable" data quality criteria
- The study follow-up concludes at the earliest of date of death, transfer out of the database or last date of CPRD data collection in the primary healthcare records, last date of HES data collection, day before birthday that would qualify them for the next cohort or 31 December 2019

FIGURE 1 Study design illustrating entry and exit into the cohort together with baseline and follow-up periods. CPRD: Clinical Practice Research Datalink; GP: general practitioner; HES: Hospital Episode Statistics.

permitted an individual to transition between age cohorts, provided their primary care records indicated persistent asthma prior to the respective index date.

Exposure, outcomes and covariates

A high baseline SABA prescription volume was defined as three or more canisters per year. Patients were categorised into different levels of annual number of SABA prescriptions, defined by using 6 months of prescription data prior to the index date. In a sensitivity analysis, SABA was considered both as a categorical (none, one, two, three to six, seven to 12 and ⩾13 prescriptions) and a continuous variable. The ICS dose was defined according to the BTS/Scottish Intercollegiate Guidelines Network (SIGN) 2019 guidelines [5].

The primary study end-point of asthma exacerbation was defined as symptom worsening, which necessitated a short course of oral corticosteroids (OCS), an A&E visit or hospitalisation. A short course of OCS was defined as a prescription for either oral prednisolone or dexamethasone (below a given threshold dose of 20 mg in the case of prednisolone), not administered on the same day as an annual asthma review.

The following variables were assessed at the individual index date: age, sex, socioeconomic status (as Index of Multiple Deprivation (IMD) 2015 (in quintiles)), body mass index (BMI), history of exacerbations in the 12 months prior to the index date and atopic disease. Prescription data for the baseline period were used to describe patients according to their asthma treatment step (per GINA 2020 recommendations for children (6–11 years) and adolescents (12–17 years)) [23]. Since it was not possible to assign a GINA treatment step to patients who had not been prescribed an asthma medication in the baseline period, these individuals were excluded from further analysis. As GINA does not define a “step 0”, we adopted “0” to define patients not treated with ICS, but who were prescribed SABA during the 6-month baseline period. The proportion of days covered (PDC) was based on the total number of days covered by ICS prescriptions during the same baseline period.

Statistical analysis

Descriptive statistics were computed for all age cohorts. These analysed select demographic variables, measures of disease severity and prescribed baseline medication. In addition, trends in SABA prescriptions during the study period (2008–2018) were described in terms of the number and proportion of patients in each SABA-prescription category and any changes from the prior 12 months.

We employed Poisson models with corresponding 95% confidence intervals and p-values to assess exacerbation rates per 10 person-years. Incidence rate ratios (IRRs) for the association between SABA prescription volume and asthma exacerbation events (including multiple episodes for those experiencing frequent exacerbations) were evaluated using multilevel negative binomial models. All regression models used complete-case analysis and were adjusted for age, sex, GINA treatment(s) prescribed, IMD, prior atopic disease, history of asthma exacerbations and quartiles of ICS PDC. Confounders were identified *a*

priori based on historical experience and the published literature [18]. Due to the high proportion of missing data, BMI was not included.

A sensitivity analysis included patients stratified by 2020 GINA treatment(s) prescribed [23] and history of atopic disease, as both were considered *a priori* as possible effect modifiers. The analysis was also repeated in a cohort of children aged 1–5 years with a wheeze code and a combined cohort of children aged 1–5 years with either a wheeze or an asthma code.

Results

Patient characteristics

The analysis included 48 560, 110 091 and 111 891 patients with asthma aged 1–5, 6–11 and 12–17 years, respectively (figure 2). Across all cohorts, most patients were male (table 1), although the proportion of females increased slightly in the older age cohorts. The prevalence of overweight and obesity also increased with increasing age, rising from 7.3% in the 1–5-year cohort to 19.3% in the 12–17-year cohort. IMD data suggested an overrepresentation of socially disadvantaged patients with asthma compared with the national average. In all three age cohorts, eczema was a commonly encountered comorbidity, with ⩾50% of the population manifesting evidence of atopic disease. The proportion of children having one or more atopic disorder(s) increased with age from 48.3% (1–5 years) to 61.7% (12–17 years), characterised largely by an increased prevalence of hay fever. With respect to asthma severity, 15.4–21.4% of the age cohorts were categorised as GINA treatment step "0", and prescribed SABA monotherapy.

In the 12 months prior to their index date, one or more asthma exacerbation(s) were reported in 19.9% of children aged 1–5 years. Most events necessitated hospitalisation. In comparison, one or more exacerbation(s) in the 12 months preceding their respective index dates was reported in fewer 6–11-year-olds (13.4%) and 12–17-year-olds (13.8%). Events necessitating an A&E visit or hospitalisation were also observed to

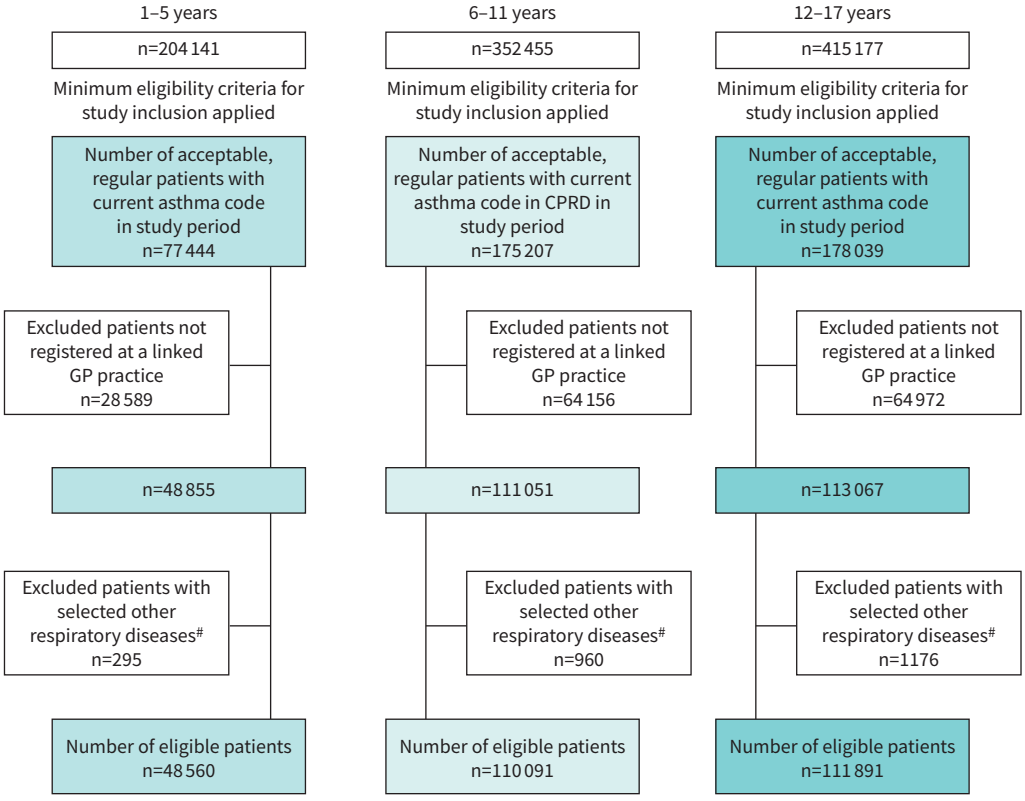


FIGURE 2 Flow chart of study participant inclusion commencing with patients registered in the Clinical Practice Research Datalink CPRD Aurum database with at least one asthma code during the study period and aged 1–17 years. GP: general practitioner. #: respiratory diagnoses include bronchiectasis, bronchopulmonary dysplasia, cystic fibrosis, primary ciliary dyskinesia.

TABLE 1 Baseline characteristics of three asthma cohorts of paediatric patients with asthma in England

	1–5 years	6–11 years	12–17 years
Total patients	48 560 (100.0)	110 091 (100.0)	111 891 (100.0)
Follow-up years, median (range)	1.12 (1.21–3.70)	2.19 (1.02–3.54)	2.51 (1.21–3.70)
Demographics			
Sex			
Boys	29 761 (61.3)	66 996 (60.9)	64 705 (57.8)
Girls	18 799 (38.7)	43 095 (39.1)	47 186 (42.2)
BMI			
Underweight	2420 (5.0)	6520 (5.9)	5903 (5.3)
Normal	10 973 (22.6)	40 530 (36.8)	40 326 (36.0)
Overweight	2639 (5.4)	10 618 (9.6)	14 885 (13.3)
Obese	1429 (2.9)	5794 (5.3)	6714 (6.0)
Missing	31 099 (64.0)	46 629 (42.4)	44 028 (39.4)
z-score	0.259±1.633	0.406±1.396	0.636±1.376
Socioeconomic status (IMD)			
1 (least deprived)	9250 (19.1)	22 544 (20.5)	23 624 (21.1)
2	8472 (17.5)	20 107 (18.3)	20 819 (18.6)
3	8545 (17.6)	19 734 (17.9)	20 429 (18.3)
4	9937 (20.5)	21 839 (19.8)	22 014 (19.7)
5 (most deprived)	12 316 (25.4)	25 790 (23.4)	24 905 (22.3)
Missing (not reported)	40 (0.08)	77 (0.07)	100 (0.09)
Comorbidities			
Allergic rhinitis including hay fever	2533 (5.2)	18 999 (17.3)	32 618 (29.2)
Eczema	22 062 (45.4)	57 135 (51.9)	55 256 (49.4)
Food allergy	2533 (5.2)	6957 (6.3)	6205 (5.6)
Atopy:[#] at least one of above	23 473 (48.3)	64 931 (59.0)	69 010 (61.7)
Severity of disease			
GINA treatment steps (2020)[¶]			
0 (SABA only)	7458 (15.4)	18 633 (16.9)	23 955 (21.4)
1	26 945 (55.5)	57 907 (52.6)	49 854 (44.6)
2	6954 (14.3)	6513 (5.9)	3408 (3.1)
3	887 (1.8)	8296 (7.5)	7983 (7.1)
4	214 (0.4)	1615 (1.5)	4849 (4.3)
5[+]	183 (0.4)	455 (0.4)	548 (0.5)
Unassigned (no regular medications)[§]	5919 (12.2)	16 672 (15.1)	21 294 (19.0)
Exacerbation history (in 12 months prior to index date)			
Number of events	0 (0–0)	0 (0–0)	0 (0–0)
Number of events	0.29±0.70	0.18±0.54	0.19±1.60
Any exacerbation	9670 (19.9)	14 731 (13.4)	15 411 (13.8)
Any hospital event	8544 (17.6)	8964 (8.1)	5949 (5.3)
A&E visit	2977 (6.1)	2624 (2.4)	1407 (1.3)
Hospital admission	7015 (14.4)	7627 (6.9)	5082 (4.5)
GP-treated only	1514 (3.1)	6699 (6.0)	10 925 (9.8)
Medication prescription			
ICS			
Dosage level[f]			
None	14 712 (30.3)	36 496 (33.2)	46 009 (41.1)
Very low dose	28 660 (59.0)	51 889 (47.1)	NA
Low dose	4781 (9.9)	19 063 (17.3)	58 852 (52.6)
Medium dose	366 (0.8)	1976 (1.8)	6490 (5.8)
High dose	41 (0.1)	667 (0.6)	540 (0.5)
PDC %	33.95 (16.97–50.92)	33.95 (16.97–46.00)	32.85 (16.97–43.26)
Quartiles			
Lowest (1 month coverage)	12 451 (36.8)	32 223 (43.8)	31 091 (47.2)
Second quartile (⩽2 months of coverage)	10 000 (29.5)	21 001 (28.5)	1935 (2.9)
Third quartile (⩽3 months of coverage)	6277 (18.5)	2068 (2.8)	16 445 (25.0)
Highest (>3 months of coverage)	5120 (15.1)	18 303 (24.9)	16 411 (24.9)
SABA inhaler prescription (12 months)			
0	6021 (12.4)	15 550 (14.1)	19 054 (17.0)
1	10 519 (21.1)	28 167 (25.6)	30 407 (27.2)
2	9597 (19.8)	24 228 (22.0)	22 142 (19.8)

Continued

TABLE 1 Continued

	1–5 years	6–11 years	12–17 years
3–6	17 833 (37.7)	34 502 (31.3)	30 187 (27.0)
7–12	4153 (8.6)	6756 (6.1)	8404 (7.5)
⩾13	437 (0.9)	879 (0.8)	1697 (1.5)
High SABA prescriptions (⩾3 canisters in 12 months prior to index)	22 423 (46.2)	42 137 (38.3)	40 288 (36.0)
LTRA prescription[##]	7555 (15.6)	9883 (9.0)	6446 (5.8)

Data are presented as n (%) or median (interquartile range) or mean±SD, unless otherwise stated. BMI: body mass index; IMD: Index of Multiple Deprivation; GINA: Global Initiative for Asthma; SABA: short-acting β_2-agonist; A&E: accident and emergency; GP: general practitioner; ICS: inhaled corticosteroids; PDC: proportion of days covered; LTRA: leukotriene receptor antagonist; NA: not assessed. [#]: defined as the presence of food allergy, hay fever, allergic rhinitis or eczema/atopic dermatitis at any time prior to the index date; [¶]: for children aged 1–5 years and children and adolescents aged 6–11 years: GINA step 0, SABA only; GINA step 1, low-dose ICS (as needed); GINA step 2, low-dose ICS daily; GINA step 3, low-dose ICS plus long-acting β_2-agonist (LABA) or medium-dose ICS only; GINA step 4, medium-dose ICS plus LABA; GINA step 5, medium-dose ICS plus LABA and/or added therapies. For children and adolescents aged 12–17 years: GINA step 0, SABA only; GINA step 1, low-dose ICS as needed; GINA step 2, low-dose ICS daily; GINA step 3, low-dose ICS plus LABA; GINA step 4, medium-dose ICS plus LABA; GINA step 5, high-dose ICS plus LABA and/or added therapies [23]; [+]: includes patients on maintenance oral corticosteroids (OCS). Patients are classified as being on maintenance OCS if they have had five or more OCS prescriptions in the 6-month baseline period; [§]: includes patients who have received a short course of OCS only, as well as patients who were not prescribed any regular asthma medications during the baseline period; [f]: ICS dose was defined according to British Thoracic Society/Scottish Intercollegiate Guidelines Network 2019 guidelines; [##]: includes both patients prescribed LTRA only or as an add-on therapy during the 6-month baseline period.

be lower in the older age cohorts (8.1% and 5.3% in 6–11-year-olds and 12–17-year-olds, respectively) *versus* the youngest cohort (17.6% in 1–5-year-olds).

SABA and ICS inhaler prescriptions

During the baseline period, 30.3% of children aged 1–5 years were not prescribed ICS-containing inhalers, with this proportion increasing to 41.1% in the cohort aged 12–17 years (table 1). Among those who were prescribed an ICS-containing inhaler, primarily at very low dose, median PDC was ∼33% across all cohorts (∼2-month coverage per year). During the baseline period, ∼25% of children had PDC >50% for ICS-containing medications, although some evidence suggested that coverage was slightly higher in the older age cohorts. Additionally, between 30.3% and 41.1% of patients across all age cohorts did not receive any prescriptions for ICS-containing medications.

High-volume SABA prescriptions (three or more canisters per year) were prevalent in all age groups (36.0–46.2%) and were especially notable in the youngest cohort (46.2%). Slightly more than 30% of study participants were prescribed between three and six SABA canisters per year. There was no evidence to suggest that this prescribing pattern had varied substantially over the 10-year study interval (2008–2018; supplementary figure S1). Across all age cohorts, the proportion of children for whom SABA canister prescriptions had increased, decreased or remained the same relative to the prior 12 months was also remarkably consistent over time, although the proportion of children who received fewer SABA prescriptions relative to the preceding 12 months was consistently higher than the proportion of those prescribed a larger quantity of canisters relative to the previous 12 months (supplementary figure S2).

SABA inhaler prescriptions and exacerbations

Asthma exacerbation event rates were highest in the youngest cohort (5.22 per 10 person-years) *versus* older cohorts (2.28 and 1.68 per 10 person-years in 6–11- and 12–17-year-olds, respectively) (supplementary table S1). Across all age cohorts, GP-managed exacerbations were the most common. However, the rate of asthma exacerbations was at least two-fold higher in the high- *versus* low-SABA-prescription group, irrespective of disease severity (table 2). Among those aged 1–5 years, the unadjusted IRR, comparing all exacerbation events in high- *versus* low-SABA-prescription groups, was 2.51 (95% CI 2.42–2.61). The association of high-volume SABA prescriptions with asthma exacerbations was slightly attenuated in the adjusted analysis (adjusted IRR 2.16, 95% CI 2.07–2.25). Consistently high IRRs (>2) were observed for exacerbations which precipitated A&E visits (adjusted IRR, 95% CI 2.36, 2.10–2.65; 2.14, 1.96–2.35; 2.95, 2.60–3.34) among children aged 1–5, 6–11 and 12–17 years, respectively.

The highest adjusted IRR was observed for GP-managed exacerbations, *i.e.* milder events, in children aged 1–5 years (2.49, 95% CI 2.37–2.61). Analysis of SABA prescription categories as an ordinal (none, one, two, three to six, seven to 12 and ⩾13 prescriptions) and continuous variable suggested a dose–response

TABLE 2 Association between at least three short-acting β_2-agonist prescriptions and asthma exacerbation incidence in a cohort of paediatric patients with asthma in England

	Patients n	Unadjusted effect estimates		Patients n	Adjusted[#] effect estimates	
		IRR (95% CI)	p-value		IRR (95% CI)	p-value
Age 1–5 years						
GP-managed	43 137	2.68 (2.56–2.80)	<0.001	42 604	2.49 (2.37–2.61)	<0.001
A&E	43 137	2.53 (2.27–2.82)	<0.001	42 604	2.36 (2.10–2.65)	<0.001
Hospitalisation	43 137	2.35 (2.21–2.50)	<0.001	42 604	1.92 (1.79–2.05)	<0.001
Hospitalisation and A&E	43 137	2.31 (2.18–2.45)	<0.001	42 604	1.88 (1.77–1.99)	<0.001
All exacerbations	43 137	2.51 (2.42–2.61)	<0.001	42 604	2.16 (2.07–2.25)	<0.001
Age 6–11 years						
GP-managed	93 961	2.86 (2.76–2.96)	<0.001	93 358	2.19 (2.11–2.27)	<0.001
A&E	93 961	2.75 (2.52–2.99)	<0.001	93 358	2.14 (1.96–2.35)	<0.001
Hospitalisation	93 961	2.18 (2.08–2.29)	<0.001	93 358	1.62 (1.54–1.70)	<0.001
Hospitalisation and A&E	93 961	2.16 (2.07–2.26)	<0.001	93 358	1.63 (1.56–1.71)	<0.001
All exacerbations	93 961	2.55 (2.47–2.62)	<0.001	93 358	1.90 (1.84–1.95)	<0.001
Age 12–17 years						
GP-managed	91 029	3.34 (3.19–3.49)	<0.001	90 518	2.11 (2.01–2.21)	<0.001
A&E	91 029	4.62 (4.12–5.19)	<0.001	90 518	2.95 (2.60–3.34)	<0.001
Hospitalisation	91 029	2.19 (2.09–2.30)	<0.001	90 518	1.53 (1.46–1.62)	<0.001
Hospitalisation and A&E	91 029	2.23 (2.13–2.34)	<0.001	90 518	1.59 (1.51–1.67)	<0.001
All exacerbations	91 029	2.71 (2.62–2.81)	<0.001	90 518	1.78 (1.72–1.84)	<0.001

IRR: incidence rate ratio; GP: general practitioner; A&E: accident and emergency. [#]: adjusted for age, sex, Global Initiative for Asthma treatment steps, Index of Multiple Deprivation, prior atopy, asthma exacerbations during previous 12 months and quartiles of inhaled corticosteroids proportion of days covered. Random effect estimated to adjust for clustering of patients within GP practices. Atopy defined as the presence of food allergy, hay fever, allergic rhinitis or eczema/atopic dermatitis at any time prior to the index date.

relationship between SABA prescription volume and exacerbation rate, with an increase in IRRs observed with a higher number of SABA canisters prescribed (figure 3 and supplementary tables S2 and S3).

GINA treatment steps and the presence of atopic disease were investigated as effect modifiers of the association between SABA prescription volume and exacerbation risk. While SABA prescription counts remained significantly associated with asthma exacerbations, the IRRs of exacerbations decreased as GINA treatment steps advanced (supplementary table S4). Evidence of effect modification by the presence of atopic disease was also observed in children aged 1–5 years (p=0.019) and 12–17 years (p=0.012), such that the effect estimates for a higher, annual number of SABA prescriptions were greater in those with nonatopic asthma *versus* those with atopic disease (table 3). A similar differential association of three or more SABA prescriptions per year with exacerbation risk between atopic and nonatopic patients with asthma was also evident when the number of SABA prescriptions were modelled as a continuous variable (figure 4).

An association between SABA prescriptions and asthma exacerbations was observed in both the wheeze and wheeze or asthma cohorts (supplementary table S5) as was an association of socioeconomic status with asthma exacerbation rates (supplementary table S6).

Discussion

In this retrospective, longitudinal, open-cohort study, higher SABA prescriptions (three or more *versus* fewer than three SABA canisters per year) was associated with increased future exacerbation event rates across three different age cohorts of a paediatric asthma population in England, emphasising the need for careful monitoring of symptoms and reliever use to identify children at risk of deteriorating disease control. These findings were replicated when SABA prescriptions were analysed as a continuous variable.

As expected, males were overrepresented across all age cohorts in this study population, with approximately half of all patients exhibiting evidence of atopic disease. High SABA prescription (three or more canisters per year) commonly occurred across all cohorts. Additionally, the proportion of patients in each SABA category remained stable over time, with limited fluctuations in SABA prescription volume from one year to the next.

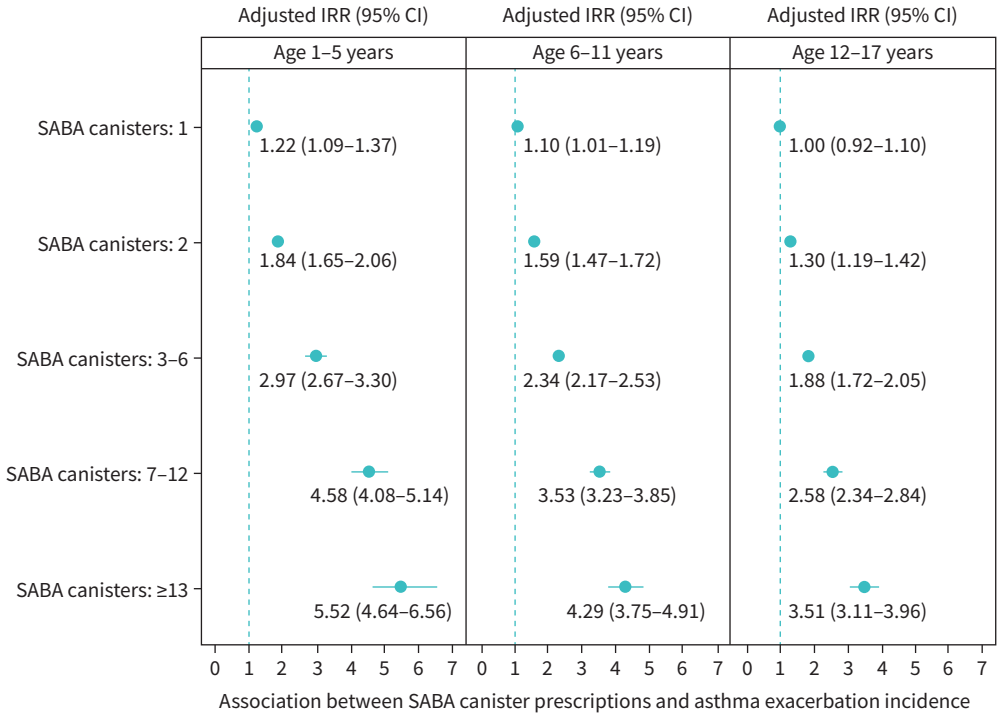


FIGURE 3 Multivariable incidence rate ratios (IRRs) of the association between short-acting β_2-agonist (SABA) prescription volume and incidence of asthma exacerbation by age group in a cohort of paediatric patients with asthma in England. Reference point is zero SABA prescriptions.

TABLE 3 Stratified and interaction analysis by atopy for the association of three or more short-acting β_2-agonist prescriptions (binary exposure) with incidence of acute exacerbations (general practitioner (GP) and all hospital data) in a cohort of paediatric patients with asthma in England

	Patients n	Effect estimates by stratified analysis		Effect estimates by interaction analysis	
		IRR (95% CI)	p-value	IRR (95% CI)	p-value
Age 1–5 years	42 604				
Atopy (no/yes)					
Interaction term					0.019
No atopy (reference category)	21 672	2.22 (2.09–2.36)	<0.001	2.26 (2.14–2.39)	<0.001
Atopy	20 932	2.10 (1.99– 2.23)	<0.001	2.06 (1.95–2.18)	<0.001
Age 6–11 years	93 358				
Atopy (no/yes)					
Interaction term					0.067
No atopy (reference category)	37 544	1.96 (1.86–2.07)	<0.001	1.96 (1.87–2.06)	<0.001
Atopy	55 814	1.86 (1.79–1.93)	<0.001	1.86 (1.79–1.93)	<0.001
Age 12–17 years	90 518				
Atopy (no/yes)					
Interaction term					0.012
No atopy (reference category)	33 926	1.92 (1.81–2.04)	<0.001	1.88 (1.78–1.98)	<0.001
Atopy	56 592	1.71 (1.63–1.78)	<0.001	1.73 (1.66–1.80)	<0.001

Multilevel negative binomial model covariates included age, sex, Global Initiative for Asthma treatment steps (step 1 used as reference category), Index of Multiple Deprivation, prior atopy, asthma exacerbations during previous 12 months and quartiles of inhaled corticosteroids proportion of days covered. Random effect estimated to adjust for clustering of patients within GP practices. Atopy defined as the presence of food allergy, hay fever, allergic rhinitis or eczema/atopic dermatitis at any time prior to the index date. IRR: incidence rate ratio.

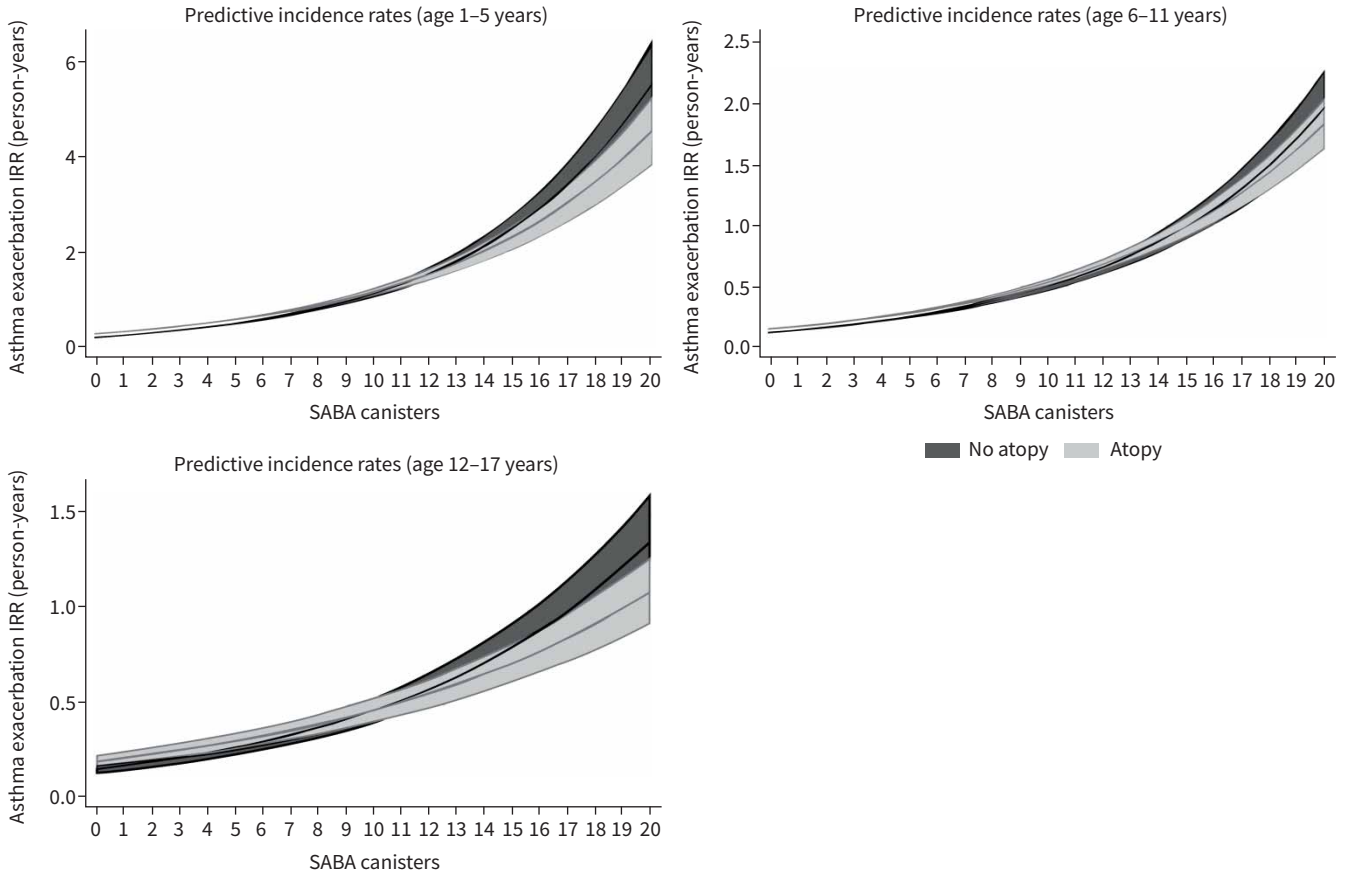


FIGURE 4 Predictive incidence rates of all exacerbation types in each age group by number of short-acting β_2-agonist (SABA) prescriptions stratified by the presence of atopy in a cohort of paediatric patients with asthma in England. IRR: incidence rate ratio.

Across all age cohorts, >30% of patients were not prescribed ICS, with a considerable proportion (15.4–21.4%) prescribed SABA monotherapy. With respect to ICS, the median reported PDC was only 33%, suggesting a suboptimal number of annual ICS prescriptions. This is in line with the results from a systematic literature review that reported widespread low adherence to ICS-containing medications, with the majority of high-quality studies consistently reporting an association between low adherence and higher risk of severe asthma exacerbations, both in adults and children [24].

The proportion of children with a history of prior exacerbation(s), which may be considered a proxy measure of poor asthma control, was lower in older age groups (19.9%, 13.4% and 13.8% of patients aged 1–5, 6–11 and 12–17 years, respectively). Although <20% of patients experienced any exacerbation in the baseline period, prescription of three or more *versus* fewer than three SABA canisters per year was associated with higher future exacerbation event rates across all age cohorts and exacerbation severities. The highest IRRs were observed for GP-managed exacerbation events, particularly among those aged 1–5 years. Analysis of SABA both as a categorical and a continuous variable replicated the stepwise association across age cohorts and exacerbation severities. Across all exacerbation types, IRRs were highest in the youngest age group, suggesting that this cohort risks a greater frequency and severity of events than older age groups with higher SABA prescription counts. These data also emphasise the importance of linking data on primary and secondary care to capture all exacerbation events and their associated disease burden, particularly in older children and adolescents. Notably, findings from the Preventing and Lessening Exacerbations of Asthma in School-age children Associated with a New Term (PLEASANT) study, a cluster randomised trial conducted in children aged 4–16 years in the UK which searched individual patient records in the primary care setting, revealed that >40% of the study population experienced an exacerbation [25]. This represented more than two-fold greater incidence of exacerbations observed in our study, suggesting a potential underestimation of exacerbation rates in this cohort of paediatric patients, and further underscoring the need to implement public health initiatives to improve the accurate recording of asthma exacerbations in primary care in the UK.

Atopic disease appeared to be an effect modifier of the relationship between SABA prescription volume and asthma exacerbation, with the association more pronounced in the nonatopic disease group. Overall, our results are consistent with those from a population-based cohort study involving 219 561 children with asthma (aged <18 years) from Sweden (SABINA Jr Sweden study), which reported that collection of three or more *versus* zero to two SABA canisters at baseline was associated with a greater risk of any exacerbation (requiring OCS burst therapy, emergency department visits or hospital admission) among patients with nonatopic *versus* atopic disease across all age groups (0–5, 6–11 and 12–17 years) [26]. Although when stratified by atopic disease, differences in estimated IRR magnitudes were relatively small, nonatopic patients probably used more SABA for rapid, symptomatic relief and consequently sought healthcare consultations for exacerbation episodes. However, this finding may also be explained, in part, by a lower therapeutic response to ICS in the nonatopic disease group [27], thereby affording less clinical benefit from these prescriptions. In addition, the BTS/SIGN advise that many nonatopic children aged <5 years with recurrent episodes of viral-induced wheezing do not go on to develop chronic atopic asthma, with the majority not requiring treatment with ICS [5]; therefore, this may also explain the high SABA prescription patterns observed in this study.

The few studies that have considered paediatric populations have reported an association between increased SABA prescriptions and poor asthma-related outcomes [19, 28–33]. A 2015 study investigating SABA prescription fills during a 12-month period found that children who heavily relied on SABA were five times more likely to be hospitalised than were low or moderate users [28]. Similarly, a claims study in children in the United States of America found that prescription of each additional SABA canister was associated with an increased risk of asthma exacerbations [29]. Compared with the SABINA I study, which included adults and adolescents with asthma [18], our study demonstrates that high proportions of SABA prescriptions occur more commonly within a paediatric population, with a lower proportion of children prescribed any ICS. These findings indicate the value of adopting a lower SABA prescription threshold in this age group, tracking GP visits for asthma exacerbations and ensuring treatment optimisation if annual SABA prescription volume exceeds its established threshold. Furthermore, evidence of an association between social deprivation and increased exacerbation risk, as observed in our study, suggests a need to closely monitor asthma symptoms, diagnoses, optimal management and rate of exacerbation events among children from lower socioeconomic strata.

On the basis that increased SABA use is a marker of poor asthma control [1], it is possible that this group of paediatric patients who may suffer more frequent and severe exacerbations have exacerbation-prone phenotypes [34]. Current asthma treatment and prevention strategies increasingly emphasise the need to improve asthma control. GINA suggests that exacerbation risk may be reduced by prescribing ICS and avoiding SABA monotherapy in paediatric populations [1]. ICS–formoterol as MART in a single inhaler offers an effective treatment option for patients with asthma that is associated with consistently lower rates of exacerbations compared with fixed-dose long-acting β_2-agonist/ICS regimens with SABA reliever [35]; additionally, the efficacy and safety profile of MART in adolescents is consistent with that reported in adults [36]. Moreover, results from a 12-month, double-blind, randomised study in 341 children with asthma aged 4–11 years reported that treatment with once-daily ICS–formoterol plus additional as-needed doses (MART) was associated with a prolonged time to first exacerbation, compared with once-daily maintenance dosing with ICS-formoterol or high-dose ICS [37]. However, current evidence supporting the treatment of children with asthma aged <12 years with MART is limited. Additionally, treatment with MART is not yet approved for children with asthma aged <12 years in the UK. Therefore, to further reduce the exacerbation burden in children and adolescents with asthma, it is important to focus on other aspects of asthma management, such as regular scheduling of asthma reviews, the education of parents, caregivers and children on effective inhaler use and the importance of treatment adherence, the treatment of comorbidities, and addressing the effects of allergens and tobacco smoke [1, 19, 38].

Our study is not without limitations. Reporting of preschool wheeze may be incomplete, thereby requiring caution when generalising the results. In addition, there may be possible nondifferential misclassification of wheeze and asthma diagnosis in preschool children, leading to a potential underestimation of the true association between SABA use and asthma outcomes. The use of prescription data may not always reflect actual dispensing and/or medication use and does not provide information on medication adherence. Nevertheless, the use of routinely collected healthcare record data from a large paediatric asthma population, including children aged 1–5 years provides a comprehensive assessment of prescribing patterns of asthma medication in children in the UK. Due to the retrospective nature of this study and the lack of data on additional reasons for SABA overuse and ICS underuse, it was not possible to stratify patients with high SABA use into individualised risk categories, which may have aided healthcare providers in identifying those at risk of exacerbations. Moreover, inaccessibility to immunoglobulin E concentrations

and skin prick test results restricted our definition of atopic disease to patient record entries. In addition, exposure to tobacco smoke was not included as a covariate in the model, while BMI was excluded as imputation was not possible given the nonrandom nature of the missing data. We were unable to investigate those asthma exacerbations managed at home by increasing SABA dosing frequency, and these unrecorded episodes might have proven to be additional contributors to subsequent exacerbation events. In addition, as with all studies utilising secondary databases, the identification of asthma-related events, such as exacerbations, was dependent on the quality and accuracy of data recording. Some misclassification of GINA treatment steps may have occurred, given the lack of dosage data and the challenges to differentiating as-needed SABA from regular use based on prescription data alone, lack of objective, asthma control measures and the surrogacy of prescriptions for actual medication use. Children may have been simultaneously prescribed multiple reliever inhalers for use at home or school or to be kept by caregivers, which may have potentially contributed to an overestimation of SABA use; however, since this potential exposure misclassification is most likely to be nondifferential with regard to the risk of future exacerbations, leading to a bias toward the null, the observed association between higher SABA prescriptions at baseline and increased future exacerbation rates is likely to be conservative. Finally, although data from the IMD was collected, this study did not examine the impact of a range of factors (including the socioeconomic status of patients, GP knowledge of asthma and their level of training, and perceptions and beliefs of patients and/or caregivers on asthma and its treatment) on prescribing patterns of SABA and ICS; however, it is envisaged that these important areas will be the subject of future research. Crucially, additional important areas of further research would be the improved identification of asthma phenotypes in children and an evaluation of the association between SABA and health outcomes across wheeze phenotypes.

Conclusions

Across all three paediatric asthma cohorts, prescription of three or more *versus* fewer than three SABA canisters per year was associated with higher exacerbation event rates, irrespective of exacerbation severity or patient age. In this retrospective, longitudinal, open-cohort study, >30% of children were not prescribed ICS and the median PDC was only 33%, suggesting inadequate prescribing of ICS. Our findings underscore the need to align clinical practices with latest evidence-based treatment recommendations and regularly monitor both disease control and SABA use in the paediatric asthma population to ensure earlier identification of those at risk of deteriorating clinical outcomes.

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Data sharing/availability statement: This study used existing data from the UK Clinical Practice Research Datalink (CPRD) Electronic Health Record database. All data management and analysis computer codes are available on request.. The study protocol and analysis plan are available in the associated supplementary material. Access to CPRD data is subject to protocol approval via CPRD's Research Data Governance (RDG) Process. Their provision requires the purchase of a licence, and this licence does not permit the authors to make them publicly available to all. This work used data from the version collected in October 2020 and has clearly specified the data selected in the Methods section. To allow identical data to be obtained by others, via the purchase of a licence, the code lists have been provided on GitHub. Licenses are available from the CPRD (www.cprd.com): The Clinical Practice Research Datalink Group, The Medicines and Healthcare Products Regulatory Agency, 10 South Colonnade, Canary Wharf, London E14 4PU, UK.

Author contributions: J.K. Quint, R.J.P. van der Valk and T.N. Tran conceptualised the study and all authors contributed to study design. A. Morgan, C. Kallis and J.K. Quint created code lists for outcomes of interest. A. Morgan and C. Kallis verified the underlying data, prepared the data and performed statistical analyses. All authors contributed to interpretation of results. All authors had full access to all the data in the study and accept responsibility to submit for publication. J.K. Quint wrote the first draft of the manuscript, with critical

revision of the manuscript by all authors. All authors approved the final manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. The corresponding author is also the guarantor for this manuscript and accepts full responsibility for the work, had access to all the data and was responsible for the decision to publish.

Conflict of interest: A. Morgan and C. Kallis have nothing to declare. E. Maslova, T.N. Tran and R.J.P. van der Valk are employees of AstraZeneca and hold AstraZeneca shares. R.J.P. van der Valk holds shares in GlaxoSmithKline. G. Roberts and I. Sinha received consultancy from AstraZeneca to their institutions for this work. J.K. Quint reports grants from AUK-BLF and The Health Foundation; grants and personal fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline and Bayer; and grants from Chiesi, outside the submitted work. J.K. Quint's research group received funding from AstraZeneca for this work.

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