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

Online supplementary material

Methods

Data sources

This study accessed routinely collected primary care data from general practitioner (GP) practices using the EMIS Web software, i.e., data which are curated by the UK Clinical Practice Research Datalink (CPRD) service and furnished to researchers as the CPRD Aurum database. This was the identical data source used for the SABA use IN Asthma (SABINA) I UK analysis [1]. As of October 2020, CPRD Aurum had archived longitudinal health data for nearly 12 million living patients, representing approximately 18.0 % of the UK population. Aurum data have been shown to be representative of the national demographic, including age and sex [2]. Data in CPRD Aurum contain information on clinical diagnoses, healthcare consultations, prescribed medications by primary care providers (PCPs), laboratory tests and referrals to medical specialists. Linked socioeconomic data from the Index of Multiple Deprivation (IMD) and secondary care data spanning accident and emergency (A&E) visits and admissions from Hospital Episode Statistics (HES) were provided for this study by CPRD. Approximately 75% of CPRD practices in England are eligible for linkage [2].

Study design and population

This retrospective, longitudinal, open-cohort study explored the association between use of SABA inhalers and rate of asthma exacerbations in an English paediatric population. Children and adolescents with a GP diagnosis of asthma entered into their primary care record were included. The definition of asthma in this study has been validated previously for adults comparing the CPRD GOLD database against a reference standard of physician reviewed patient notes and exhibits a high positive predictive value (PPV>86%) [3]. The index date for each patient was defined as 6 months after an asthma code was recorded in the clinical notes (Figure 1). We excluded patients with <12-month research-acceptable data prior to the index date or with other chronic respiratory diseases, such as cystic fibrosis, bronchiectasis or primary ciliary dyskinesia, chronic upper airway cough syndrome or bronchopulmonary dysplasia. Codes are available at https://github.com/NHLI-Respiratory-Epi/SABINAJr.

Three, separate, age cohorts of 1–5 years, 6–11 years and 12–17 years were defined, reflecting the age thresholds specified by both BTS and GINA asthma treatment recommendations. For the 1–5-year-old cohort, the initiation of follow-up was defined as the latest of index date (01/01/2007), initial date of current GP registration plus 1 year, commencement of HES data collection (01/04/2007) and date of first birthday (6th and 12th birthday for the 6–11- and 12–17-year-old cohorts, respectively). The conclusion of follow-up for the 1–5-year-old cohort was defined as the earliest of the study end date (31/12/2019), completion of GP registration, close of HES data collection (01/05/2019), last date of data collection (practice level), death and last day before the 6th birthday (12th or 18th birthday in the case of the 6–11 and 12–17 age cohorts, respectively). With this study design, an individual could transition to older age cohorts, provided their primary care record indicated the presence of persistent asthma, i.e., a current SNOMED CT asthma code 6 months prior to the index date in order to enter each age-specific cohort.

Exposure, outcomes and covariates

The main exposure was the total number of SABA prescriptions issued during the baseline period and each prescription served as a surrogate for actual inhaler use. A high number of SABA prescriptions was defined as three or more (≥3) per year. In a sensitivity analysis, SABA was considered both a categorical variable based on the distribution of prescription data (0, 1, 2, 3–6, 7–12, ≥13 canisters) and a continuous variable. Patients were categorised into different levels of annual SABA prescriptions, defined by using six months of prescription data prior to the index date.

In this study, the primary outcome of interest was the number of asthma exacerbations. We included both GP-managed exacerbations defined as symptomatic worsening necessitating a short course of oral corticosteroids (OCS), an A&E department visit or a hospital admission. 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. Hospital admissions for asthma as a primary diagnosis were identified by ICD-10 codes (J45 and J46) and Accident and Emergency visits were identified by a diagnostic code highly suggestive of an A&E attendance for asthma (251). Events dated 14 days apart were assumed to represent ongoing treatment for the same event rather than sequential, new events. Where this occurred, the event was categorised based on its highest level of urgency (in the order of hospital admission, A&E visit and GP visit).

The following variables were assessed at each individual index date: age, sex, socioeconomic status (as an index of multiple deprivation [IMD] 2015 [in quintiles]); body mass index (BMI), categorised as underweight, normal weight, overweight or obese, according to UK standard growth curves and internationally recognised BMI thresholds; history of exacerbations in the 12 months prior to the index date and atopic disease, defined as the presence of food allergy, hay fever, allergic rhinitis or eczema/atopic dermatitis at any time prior to the index date. Baseline prescription data were used to describe patients according to their asthma treatment level, i.e., GINA treatment step 1, 2, 3, 4 and 5 as defined by the GINA 2020 recommendations for children [6–11 years] and adolescents [12–17 years]) [4].

The following treatment steps applied to 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 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. Treatment steps for children and adolescents aged 12–17 years were similarly categorized with the exception of GINA step 5: *high-dose ICS* plus LABA and/or added therapies. See https://ginasthma.org/wp-content/uploads/2020/04/GINA-2020-full-report_-final-_wms.pdf, accessed 12 November 2021).

Since it was not possible to assign a GINA treatment step classification to patients who had not been prescribed an asthma medication by their GP in the baseline period, these individuals were excluded from further analysis. Note that the GINA recommendations do not

define a ‘step 0’. In this analysis, we adopted ‘0’ to define patients not treated with ICS, but who were prescribed SABA during the 6-month baseline interval. 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 each of our three age cohorts. These addressed select demographic variables, measures of disease severity and prescribed medications at baseline. We also described trends in SABA prescriptions during the study period of 2008–2018, in terms of the number and proportion of patients in each category of SABA prescribed as well as any departures in quantity from the previous year.

We employed Poisson models, with a corresponding 95% confidence interval (CI) and p-values, to estimate exacerbation rates per 10 person-years. Multilevel, negative binomial models were implemented to estimate incidence rate ratios (IRRs) for the association between the volume of SABA prescriptions and the frequency of asthma exacerbation (including multiple episodes for those experiencing frequent exacerbations). This type of statistical model accounted for any overdispersion of the outcome variables and/or clustering of patients within GP practices. All available patient follow-up was applied to the estimation of IRRs. All regression models used complete-case analysis and were adjusted for age, sex, prescribed GINA treatment step, 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 [1]. Due to the high proportion of missing data, BMI was not included. All analyses were performed with STATA statistical software, version 17 (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC.).

In a sensitivity analysis, the study population was stratified by 2020 GINA treatment steps [4] prescribed and a history of atopic disease, since 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 15 years with either a wheeze or an asthma code.

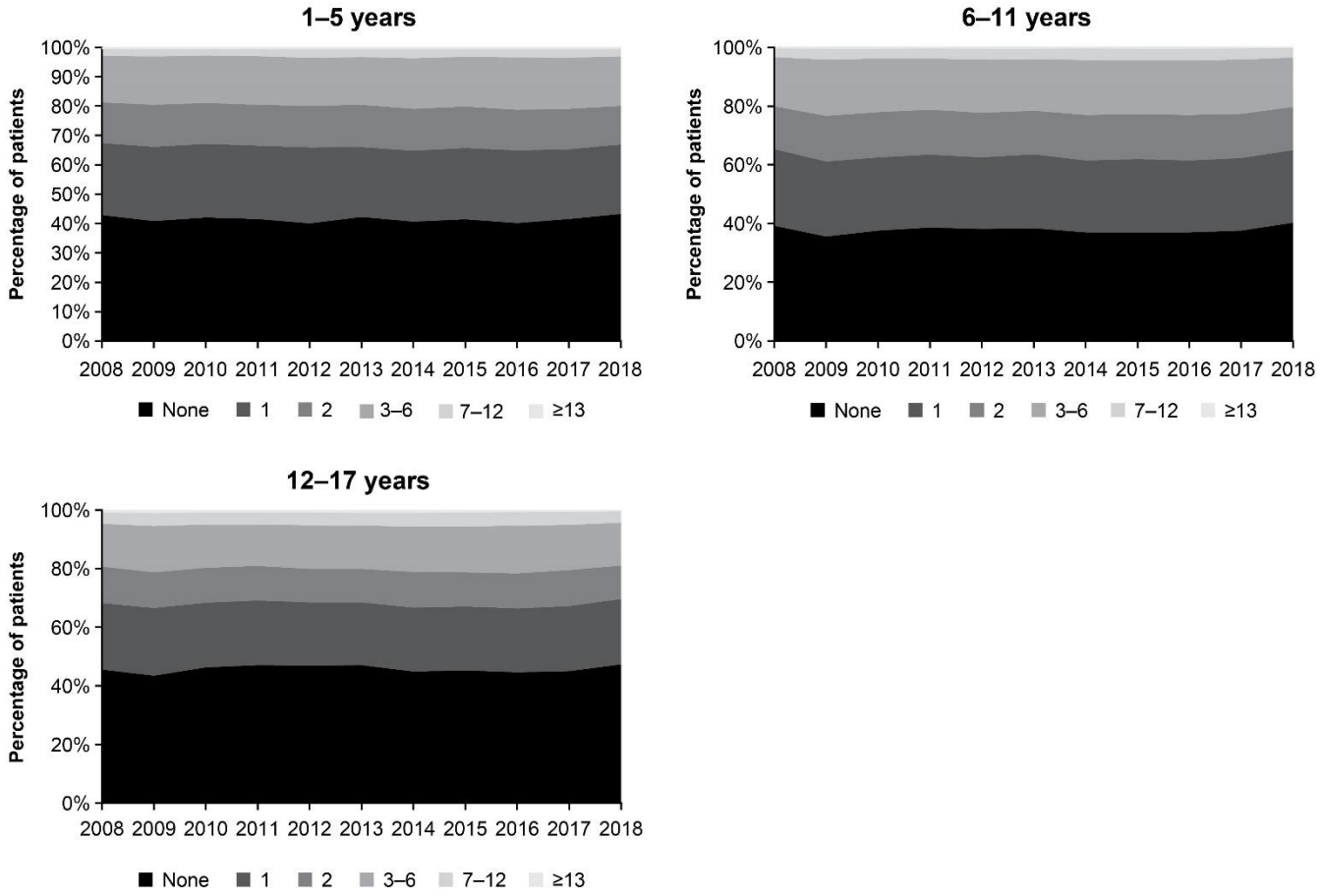
Ethical Approval

The protocol for this research was approved by an external review committee for the research data governance group (RDG); for the Medicines and Healthcare products Regulatory Agency (MHRA) Database Research (protocol number 20_000084), and the approved protocol was available to the journal editors and reviewers during the peer review process. Generic ethical approval for observational research using CPRD with approval from RDG was granted by a Health Research Authority (HRA) Research Ethics Committee (East Midlands Derby, REC reference number 05/MRE04/87). Linked pseudonymised data were provided for this study by CPRD. Datasets were linked by National Health Service (NHS) Digital, the statutory trusted third party for linking data, using identifiable data proprietary to NHS Digital. Select practices consented to this process, with individual patients afforded the right to opt out.

Role of the funding source

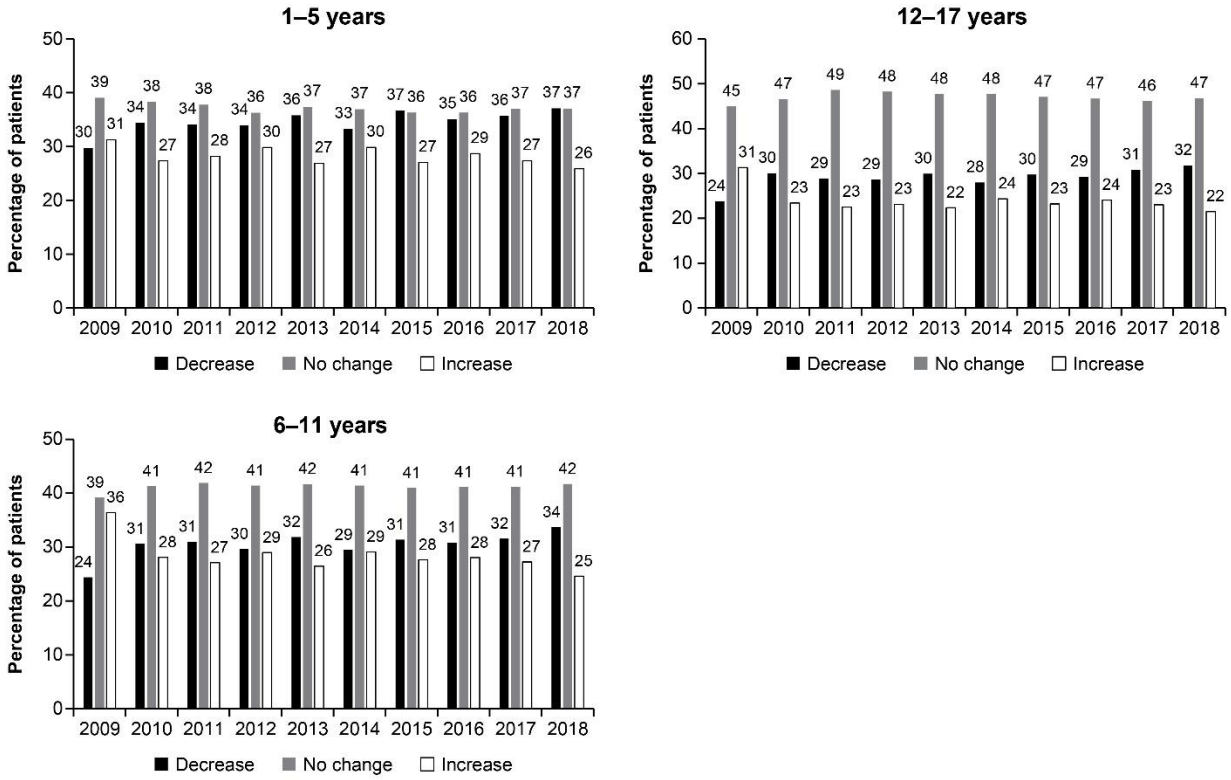
AstraZeneca funded the SABINA studies and was involved in designing the program, developing the study protocol and conducting the studies.

Figure S1: Trends in SABA inhaler use, 2008–2018. Number of prescriptions for SABA in three paediatric age cohorts, 2008–2018 (percentage of patients prescribed 0, 1, 2, 3–6, 7–12 or ≥13 SABA canisters per given year)



SABA: short-acting β_2-agonist.

Figure S2: Change in SABA use during previous 12 months in three paediatric age cohorts, 2009–2018



Percentage of patients for whom the number of prescribed SABA canisters has increased, decreased or remained the same relative to the prior 12 months.

SABA: short-acting β_2-agonist.

Table S1: Asthma exacerbation incidence rates per 10 person-years in three age cohorts of paediatric patients with asthma in England

Age cohort and patient care type	n	Events	Person-years	Rate/100,000 person-years	95% CI
Age 1–5 years					
GP-managed	43,137	19,565	55,210.28	3.54	3.53–3.56
A&E	43,137	2,979	55,210.28	0.54	0.53–0.55
Hospitalisation	43,137	9,467	55,210.28	1.71	1.70–1.73
Hospitalisation and A&E	43,137	10,406	55,210.28	1.88	1.87–1.90
All exacerbations	43,137	28,811	55,210.28	5.22	5.20–5.24
Age 6–11 years					
GP-managed	93,961	33,251	212,734.40	1.56	1.56–1.57
A&E	93,961	4,384	212,734.40	0.21	0.20–0.21
Hospitalisation	93,961	15,994	212,734.40	0.75	0.75–0.76
Hospitalisation and A&E	93,961	16,994	212,734.40	0.80	0.80–0.80
All exacerbations	93,961	48,519	212,734.40	2.28	2.27–2.29
Age 12–17 years					
GP-managed	91,029	22,847	224,578.30	1.02	1.01–1.02
A&E	91,029	2,814	224,578.30	0.13	0.12–0.13
Hospitalisation	91,029	16,380	224,578.30	0.73	0.73–0.73
Hospitalisation and A&E	91,029	16,212	224,578.30	0.72	0.72–0.73
All exacerbations	91,029	37,753	224,578.30	1.68	1.68–1.69

A&E, accident and emergency; CI, confidence interval; GP, general practitioner.

Table S2. Multivariable association between quantity of SABA prescriptions as a categorical variable and asthma exacerbations in three age cohorts of a paediatric patients with asthma in England

Multilevel negative binomial model		Unadjusted effects				Adjusted* effects		
Age cohort and patient care type	**n**	**IRR**	**95% CI**	**p-value**	**n**	**IRR**	**95% CI**	**p-value**
Age 1–5 years								
GP-managed	43,137				42,604			
0 (reference)		Ref.	Ref.	Ref.		Ref.	Ref.	Ref.
1		1.11	0.98–1.26	0.092		1.29	1.12–1.48	<0.001
2		1.74	1.54–1.97	<0.001		2.09	1.82–2.39	<0.001
3–6		3.10	2.76–3.48	<0.001		3.64	3.19–4.16	<0.001
7–12		5.55	4.90–6.28	<0.001		6.16	5.34–7.10	<0.001
≥13		9.06	7.50–10.95	<0.001		8.74	7.12–10.74	<0.001
A&E	43,137				42,604			
0 (reference)		Ref.	Ref.	Ref.		Ref.	Ref.	Ref.
1		1.34	0.98–1.85	0.069		1.46	1.02–2.08	0.04
2		1.75	1.28–2.39	<0.001		1.87	1.32–2.65	0.001
3–6		3.25	2.42–4.37	<0.001		3.46	2.47–4.83	<0.001
7–12		5.41	3.95–7.40	<0.001		5.58	3.91–7.97	<0.001
≥13		7.36	4.65–11.65	<0.001		7.24	4.44–11.81	<0.001
Hospitalisation	43,137				42,604			
0 (reference)		Ref.	Ref.	Ref.		Ref.	Ref.	Ref.
1		1.05	0.88–1.24	0.604		1.16	0.96–1.39	0.1
2		1.56	1.32–1.85	<0.001		1.66	1.39–1.98	<0.001
3–6		2.58	2.21–3.02	<0.001		2.45	2.07–2.91	<0.001
7–12		4.33	3.66–5.13	<0.001		3.63	3.01–4.37	<0.001
≥13		5.74	4.38–7.51	<0.001		3.64	2.75–4.81	<0.001
Hospitalisation and A&E	43,137				42,604			
0 (reference)		Ref.	Ref.	Ref.		Ref.	Ref.	Ref.
1		1.06	0.91–1.24	0.468		1.16	0.98–1.37	0.015
2		1.52	1.31–1.77	<0.001		1.58	1.34–1.87	<0.001
3–6		2.54	2.20–2.94	<0.001		2.36	1.34–1.87	<0.001
7–12		4.08	3.49–4.77	<0.001		3.37	2.84–4.00	<0.001
≥13		5.63	4.42–7.19	<0.001		3.77	2.94–4.85	<0.001
All exacerbations	43,137			<0.001	42,604			<0.001
0 (reference)		Ref.	Ref.	Ref.		Ref.	Ref.	Ref.
1		1.09	0.98–1.20	0.122		1.22	1.09–1.37	<0.001
2		1.63	1.48–1.81	<0.001		1.84	1.65–2.06	<0.001
3–6		2.83	2.57–3.11	<0.001		2.97	2.67–3.30	<0.001
7–12		4.83	4.35–5.36	<0.001		4.58	4.08–5.14	<0.001
≥13		7.41	6.29–8.74	<0.001		5.52	4.64–6.56	<0.001
Age 6–11 years								
GP-managed	93,961				93,358			
0 (reference)		Ref.	Ref.	Ref.		Ref.	Ref.	Ref.
1		0.91	0.83–1.01	0.071		1.14	1.03–1.27	0.001
2		1.54	1.40–1.69	<0.001		1.84	1.66–2.03	<0.001
3–6		2.79	2.54–3.06	<0.001		2.92	2.65–3.22	<0.001
7–12		5.96	5.38–6.60	<0.001		4.83	4.33–5.39	<0.001
≥13		10.93	9.31–12.83	<0.001		6.72	5.71–7.90	<0.001
A&E	93,961				93,358			
0 (reference)		Ref.	Ref.	Ref.		Ref.	Ref.	Ref.
1		0.95	0.75–1.20	0.658		1.11	0.86–1.43	0.42
2		1.18	0.93–1.50	0.162		1.34	1.05–1.71	0.02
3–6		2.32	1.85–2.90	<0.001		2.34	1.84–2.97	<0.001
7–12		5.32	4.17–6.78	<0.001		4.28	3.30–5.56	<0.001
≥13		7.87	5.50–11.28	<0.001		5.15	3.55–7.46	<0.001
Hospitalisation	93,961				93,358			
0 (reference)		Ref.	Ref.	Ref.		Ref.	Ref.	Ref.
1		0.9	0.79–1.02	0.099		1.07	0.94–1.22	0.191
2		1.24	1.10–1.41	0.001		1.36	1.20–1.54	<0.001
3–6		1.92	1.71–2.17	<0.001		1.83	1.62–2.06	<0.001
7–12		4.00	3.50–4.56	<0.001		2.76	2.41–3.16	<0.001
≥13		5.59	4.51–6.93	<0.001		2.64	2.12–3.28	<0.001
Hospitalisation and A&E	93,961				93,358			
0 (reference)		Ref.	Ref.	Ref.		Ref.	Ref.	Ref.
1		0.89	0.79–0.99	0.040		1.05	0.93–1.17	0.3
2		1.2	1.07–1.34	0.001		1.31	1.17–1.47	<0.001

3–6		1.9	1.71–2.11	<0.001		1.80	1.62–2.01	<0.001
7–12		3.72	3.30–4.19	<0.001		2.62	2.32–2.97	<0.001
≥13		4.75	3.92–5.76	<0.001		2.56	2.10–3.11	<0.001
All exacerbations	93,961				93,358			
0 (reference)		Ref.	Ref.	Ref.		Ref.	Ref.	Ref.
1		0.91	0.84–0.98	0.014		1.10	1.01–1.19	0.003
2		1.40	1.30–1.51	<0.001		1.59	1.47–1.72	<0.001
3–6		2.39	2.22–2.58	<0.001		2.34	2.17–2.53	<0.001
7–12		4.88	4.48–5.30	<0.001		3.53	3.23–3.85	<0.001
≥13		7.99	6.98–9.14	<0.001		4.29	3.75–4.91	<0.001
Age 12–17								
GP-managed	91,029				90,518			
0 (reference)		Ref.	Ref.	Ref.		Ref.	Ref.	Ref.
1		0.71	0.63–0.80	<0.001		1.08	0.95–1.23	0.2
2		1.12	0.99–1.27	0.061		1.56	1.38–1.78	<0.001
3–6		2.12	1.89–2.39	<0.001		2.47	2.19–2.80	<0.001
7–12		4.77	4.21–5.41	<0.001		3.72	3.26–4.25	<0.001
≥13		11.04	9.42–12.95	<0.001		5.38	4.58–6.32	<0.001
A&E	91,029				90,518			
0 (reference)		Ref.	Ref.	Ref.		Ref.	Ref.	Ref.
1		0.97	0.66–1.41	0.862		1.21	0.82–1.79	0.3
2		1.40	0.97–2.03	0.075		1.55	1.06–2.29	0.03
3–6		3.37	2.36–4.82	<0.001		3.30	2.27–4.79	<0.001
7–12		8.14	5.64–11.74	<0.001		6.27	4.25–9.24	<0.001
≥13		27.12	18.07–40.70	<0.001		13.91	9.13–21.20	<0.001
Hospitalisation	91,029				90,518			
0 (reference)		Ref.	Ref.	Ref.		Ref.	Ref.	Ref.
1		0.74	0.65–0.85	<0.001		0.94	0.82–1.07	0.32
2		0.92	0.80–1.04	0.181		1.09	0.96–1.24	0.2
3–6		1.41	1.24–1.59	<0.001		1.45	1.28–1.64	<0.001
7–12		2.68	2.34–3.07	<0.001		1.94	1.69–2.22	<0.001
≥13		5.62	4.69–6.72	<0.001		2.66	2.22–3.18	<0.001
Hospitalisation and A&E	91,029				90,518			
0 (reference)		Ref.	Ref.	Ref.		Ref.	Ref.	Ref.
1		0.77	0.69–0.87	<0.001		0.96	0.85–1.08	0.5
2		0.96	0.85–1.09	0.550		1.12	0.99–1.27	0.07
3–6		1.51	1.34–1.70	<0.001		1.53	1.36–1.71	<0.001
7–12		2.78	2.45–3.14	<0.001		2.07	1.82–2.36	<0.001
≥13		5.76	4.91–6.76	<0.001		2.91	2.48–3.42	<0.001
All exacerbations	91,029				90,518			
0 (reference)		Ref.	Ref.	Ref.		Ref.	Ref.	Ref.
1		0.73	0.66–0.80	<0.001		1.00	0.92–1.10	0.9
2		1.03	0.94–1.12	0.575		1.30	1.19–1.42	<0.001
3–6		1.76	1.62–1.92	<0.001		1.88	1.72–2.05	<0.001
7–12		3.54	3.22–3.89	<0.001		2.58	2.34–2.84	<0.001
≥13		7.69	6.81–8.68	<0.001		3.51	3.11–3.96	<0.001

*Adjusted for age, sex, GINA treatment step, IMD, prior atopy, asthma exacerbations during previous 12 months and quartiles of ICS 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.

A&E, accident and emergency; CI, confidence interval; GINA, Global Initiative for Asthma; GP, general practitioner; ICS, inhaled corticosteroids; IMD, Index of Multiple Deprivation; IRR, incidence rate ratio; SABA, short-acting β_2-agonist.

Table S3. Multivariable association between quantity of SABA prescriptions as a continuous variable and asthma exacerbations in three age cohorts of a paediatric patients with asthma in England

Multilevel negative binomial model		Unadjusted effects				Adjusted* effects		
Age cohort and patient care type	**n**	**IRR**	**95% CI**	**p-value**	**n**	**IRR**	**95% CI**	**p-value**
Age 1–5 years								
GP-managed	43,137	120	1.19–1.21	<0.001	42,604	1.19	1.18–1.20	<0.001
A&E	43,137	1.17	1.15–1.19	<0.001	42,604	1.16	1.14–1.19	<0.001
Hospitalisation	43,137	1.17	1.15–1.18	<0.001	42,604	1.12	1.11–1.14	<0.001
Hospitalisation and A&E	43,137	1.16	1.15–1.17	<0.001	42,604	1.12	1.10–1.13	<0.001
All exacerbations	43,137	1.18	1.18–1.19	<0.001	42,604	1.16	1.15–1.17	<0.001
Age 6–11 years								
GP-managed	93,961	1.23	1.23–1.24	<0.001	93,358	1.17	1.16–1.18	<0.001
A&E	93,961	1.21	1.19–1.23	<0.001	93,358	1.16	1.14–1.18	<0.001
Hospitalisation	93,961	1.18	1.17–1.19	<0.001	93,358	1.11	1.10–1.12	<0.001
Hospitalisation and A&E	93,961	1.17	1.16–1.18	<0.001	93,358	1.10	1.09–1.11	<0.001
All exacerbations	93,961	1.21	1.20–1.22	<0.001	93,358	1.14	1.13–1.14	<0.001
Age 12–17 years								
GP-managed	91,029	1.21	1.21–1.22	<0.001	90,518	1.10	1.11–1.13	<0.001
A&E	91,029	1.24	1.23–1.26	<0.001	90,518	1.17	1.15–1.19	<0.001
Hospitalisation	91,029	1.15	1.14–1.16	<0.001	90,518	1.08	1.07–1.08	<0.001
Hospitalisation and A&E	91,029	1.15	1.14–1.15	<0.001	90,518	1.08	1.07–1.09	<0.001
All exacerbations	91,029	1.18	1.17–1.19	<0.001	90,518	1.09	1.09–1.10	<0.001

*Adjusted for age, sex, GINA treatment step, IMD, prior atopy, asthma exacerbations during previous 12 months and quartiles of ICS 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.

A&E, accident and emergency; CI, confidence interval; GINA, Global Initiative for Asthma; GP, general practitioner; ICS, inhaled corticosteroids; IMD, Index of Multiple Deprivation; IRR, incidence rate ratio; SABA, short-acting β_2-agonist.

Table S4. Stratified and interaction analysis by GINA treatment step for the association of ≥3 SABA canister prescriptions (binary exposure) with incidence of asthma acute exacerbations (GP and all hospital data) in a cohort of paediatric patients with asthma in England

Multilevel negative binomial model		Effect estimates by stratified analysis				Effect estimates by interaction analysis		
Age cohort	**n**	**IRR**	**95% CI**	**p-value**	**n**	**IRR**	**95% CI**	**p-value**
Age 1–5 years								
GINA (0–5)								
Significant interaction term					33,814	Yes (at least one p-value<0.05)		
0	N/A*	N/A*	N/A*	N/A*		1.20	0.90–1.59	0.217
1 (reference category)	26,926	1.18	1.17–1.19	<0.001		1.18	1.17–1.19	<0.001
2	5,598	1.11	1.10–1.13	<0.001		1.12	1.10–1.13	<0.001
3	886	1.14	1.10–1.18	<0.001		1.14	1.10–1.18	<0.001
4	N/A*	N/A*	N/A*	N/A*		1.09	1.02–1.16	0.012
5	171	1.06	1.03–1.10	0.001		1.04	0.99–1.09	0.089
Age 6–11 years								
GINA (0–5)								
Significant interaction term					73,544	Yes (at least one p-value<0.05)		
0	N/A*	N/A*	N/A*	N/A*		1.14	0.95–1.37	0.155
1 (reference category)	57,870	1.15	1.14–1.16	<0.001		1.14	1.13–1.15	<0.001
2	5,302	1.10	1.09–1.12	<0.001		1.11	1.09–1.12	<0.001
3	8,290	1.11	1.09–1.12	<0.001		1.11	1.10–1.13	<0.001
4	1,613	1.11	1.08–1.14	<0.001		1.12	1.09–1.15	<0.001
5	452	1.10	1.08–1.14	<0.001		1.08	1.05–1.11	<0.001
Age 12–17 years								
GINA (0–5)								
Significant interaction term					65,821	Yes (at least one p-value<0.05)		
0	N/A*	N/A*	N/A*	N/A*		1.39	0.70–2.77	0.349
1 (reference category)	49,803	1.11	1.10–1.12	<0.001		1.11	1.10–1.11	<0.001
2	2,657	1.07	1.04–1.09	<0.001		1.07	1.05–1.09	<0.001
3	7,979	1.07	1.06–1.08	<0.001		1.07	1.06–1.09	<0.001
4	4,846	1.07	1.06–1.09	<0.001		1.07	1.06–1.08	<0.001
5	530	1.05	1.03–1.07	<0.001		1.02	1.00–1.04	0.110

Covariates included age, sex, GINA treatment steps (step 1 used as reference category), IMD, prior atopy, asthma exacerbations during previous 12 months and quartiles of ICS 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.

*Due to lack of convergence

CI, confidence interval; GINA, Global Initiative for Asthma; GP, general practitioner; ICS, inhaled corticosteroids; IMD, Index of Multiple Deprivation; IRR, incidence rate ratio; SABA, short-acting β_2-agonist.

Table S5: Association between ≥3 SABA prescriptions and asthma exacerbations in a cohort of paediatric patients in England aged 1-5 years determined by a wheeze code only or a wheeze or asthma code

Definitions of exacerbation by patient care type		Unadjusted effect estimates				Adjusted* effect estimates		
Age 1–5 years wheeze cohort	**n**	**IRR**	**95% CI**	**p-value**	**n**	**IRR**	**95% CI**	**p-value**
GP	43,412	3.90	3.72–4.09	<0.001	16,668	2.31	2.15–2.48	<0.001
A&E attendance	43,412	4.10	3.65–4.59	<0.001	16,668	2.38	1.99–2.85	<0.001
Hospital admission	43,412	4.78	4.43–5.17	<0.001	16,668	2.25	2.02–2.51	<0.001
A&E and admission	43,412	4.44	4.15–4.76	<0.001	16,668	2.18	1.98–2.41	<0.001
Hospital and GP	43,412	3.97	3.80–4.14	<0.001	16,668	2.16	2.03–2.29	<0.001
Age 1–5 years wheeze or asthma cohort	**n**	**IRR**	**95% CI**	**p-value**	**n**	**IRR**	**95% CI**	**p-value**
GP	34,707	2.67	2.54–2.82	<0.001	34,278	2.51	2.37–2.66	<0.001
A&E attendance	34,675	2.64	2.33–2.99	<0.001	34,249	2.50	2.19–2.86	<0.001
Hospital admission	34,686	2.37	2.20–2.54	<0.001	34,257	1.97	1.82–2.12	<0.001
A&E and admission	34,682	2.33	2.18–2.48	<0.001	34,255	1.91	1.78–2.05	<0.001
Hospital and GP	34,691	2.49	2.38–2.60	<0.001	34,263	2.17	2.07–2.28	<0.001

*Adjusted for age, sex, GINA treatment steps, IMD, prior atopy, prior events and quartiles of ICS 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.

A&E, accident and emergency; CI, confidence interval; GINA, Global Initiative for Asthma; GP, general practitioner; ICS, inhaled corticosteroids; IMD, Index of Multiple Deprivation; IRR, incidence rate ratio; SABA, short-acting β_2-agonist.

Table S6: Adjusted IRRs* for risk factors of asthma exacerbations across all severities in three age cohorts of a paediatric asthma population in England

	1–5 years			6–11 years			12–17 years		
	IRR	**95% CI**	**p-value**	**IRR**	**95% CI**	**p-value**	**IRR**	**95% CI**	**p-value**
SABA prescriptions									
<3	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
≥ 3	2.16	2.07–2.25	<0.001	1.9	1.84–1.95	<0.001	1.78	1.72–1.84	<0.001
Age	0.88	0.86–0.90	<0.001	0.89	0.88–0.9	<0.001	0.96	0.94–0.97	<0.001
Sex									
Males	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Females	0.87	0.84–0.90	<0.001	0.88	0.86–0.91	<0.001	1.32	1.28–1.37	<0.001
GINA									
0	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
1	0.92	0.82–1.03	0.168	1.06	0.93–1.20	0.393	1.2	1.01–1.43	0.037
2	1.38	1.24–1.53	<0.001	1.68	1.49–1.89	<0.001	1.78	1.53–2.08	<0.001
3	1.51	1.29–1.78	<0.001	1.90	1.67–2.17	<0.001	1.72	1.44–2.05	<0.001
4	1.45	1.13–1.85	0.003	2.40	2.06–2.8	<0.001	2.29	1.92–2.74	<0.001
5	2.91	2.33–3.64	<0.001	4.24	3.51–5.12	<0.001	1.90	1.52–2.39	<0.001
IMD 2015									
1 (least)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
2	1.06	1.00–1.13	0.050	0.01	0.96–1.06	0.676	1.02	0.97–1.07	0.483
3	1.07	1.00–1.14	0.051	1.08	1.02–1.13	0.004	1.06	1.00–1.11	0.043
4	1.15	1.08–1.22	<0.001	1.12	1.06–1.17	<0.001	1.10	1.05–1.16	<0.001
5 (most)	1.17	1.09–1.24	<0.001	1.16	1.10–1.22	<0.001	1.16	1.10–1.23	<0.001
Atopy									
No	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Yes	1.18	1.14–1.22	<0.001	1.18	1.4–1.21	<0.001	1.15	1.11–1.19	<0.001
Exacerbation history (in previous 12 months)									
No	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Yes	1.52	1.48–1.55	<0.001	1.75	1.72–1.79	<0.001	1.86	1.82–1.9	<0.001
PDC quintiles									
0	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
1	1.17	1.05–1.3	0.004	1.13	1.00–1.28	0.052	1.05	0.89–1.25	0.556
2	1.16	1.04–1.29	0.009	1.11	0.98–1.26	0.093	1.01	0.83–1.22	0.947
3	1.11	0.99–1.24	0.066	1.16	1.00–1.34	0.051	1.04	0.88–1.24	0.615
4	1.13	1.01–1.26	0.033	1.14	1.01–1.29	0.039	1.11	0.94–1.32	0.209

*Adjusted for age, sex, GINA treatment steps, IMD, prior atopy, prior events and quartiles of ICS 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.

CI, confidence interval; GINA: Global Initiative for Asthma; GP, general practitioner; ICS, inhaled corticosteroids; IMD, Index of Multiple Deprivation; IRR, incidence rate ratio; PDC, proportion of days covered; SABA, short-acting β_2-agonist.

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