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Original research article

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Please cite this article as: Morgan A, Maslova E, Kallis C, *et al*. Short-acting β_2-agonists and exacerbations in children with asthma in England: SABINA Junior. *ERJ Open Res* 2023; in press (https://doi.org/10.1183/23120541.00571-2022).

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

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Keywords: asthma, paediatric population, short-acting β_2-agonist, exacerbations

Summary: High SABA prescriptions (≥3 canisters/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.

Word count: 3980/3000

Abstract

Background: Prescription of ≥3 short-acting β_2-agonist (SABA) canisters/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, 6–11, and 12–17 years from the Clinical Practice Research Datalink Aurum database for the period of 1/1/07-31/12/19. Associations between SABA prescriptions (≥3 vs <3 canisters/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 years 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 were prescribed ≥3 SABA canisters/year, respectively. Across all age ranges, the rate of future asthma exacerbations in those prescribed ≥3 vs <3 SABA canisters/year was ≥2-fold higher. More than 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 ≥3 SABA canisters/year to identify children with asthma at risk of exacerbations.

Introduction

Asthma, a chronic heterogenous, 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 2016/17, >75,000 people spanning all age groups experienced an asthma exacerbation, which 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 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 4 of 16 studies demonstrated fewer exacerbations with maintenance medication use [19]. Notably, the National Review of Asthma Deaths (NRAD) report published by the Royal College of Physicians in 2015, which was the first national investigation of asthma deaths in the UK, identified SABA over-prescription and insufficient provision of ICS-containing medications as preventable causes of deaths [20]. 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 [21]. Nevertheless, results from a more recent retrospective analysis (2018/19) 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 [22].

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 [18,23]. We therefore 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 general practitioner (GP) practices, curated by the Clinical Practice Research Datalink (CPRD) service (available as 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 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 permitted an individual to transition between >1 age cohort, 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 ≥3 canisters per year. Patients were categorised into different levels of annual number of SABA prescriptions, defined by using six months of prescription data prior to the index date. In a sensitivity analysis, SABA was considered both as a categorical (0, 1, 2, 3–6, 7–12 and ≥13 prescriptions) and a continuous variable. The ICS dose was defined according to the BTS/SIGN 2019 guidelines [5].

The primary study endpoint of asthma exacerbation was defined as symptom worsening, which necessitated a short course of oral corticosteroids (OCS), an A&E visit, or a 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, socio-economic 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]) [24]. 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. Trends in SABA prescriptions during the study period (2008–2018) were also 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 interval (CI) 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 with 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 [24] 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 over-representation 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 ≥1 atopic disorder(s) increased with age from 48.3% (1–5 years) to 61.7% (12–17 years), characterized largely by an increased prevalence of hay fever. With respect to asthma severity, 15.4%–21.4% of the age cohorts were categorized as GINA treatment step '0', and prescribed SABA monotherapy.

In the 12 months prior to their index date, ≥1 asthma exacerbation(s) were reported in 19.9% of children aged 1–5 years. Most events necessitated hospitalisation. In comparison, ≥1 exacerbation(s) in the 12 months preceding their respective index dates was reported in fewer 6–11- (13.4%) and 12–17-year-olds (13.8%). Events necessitating an A&E visit or hospitalisation were also observed to be lower in the older age cohorts (8.1% and 5.3% in 6–11- and 12–17-year-olds, respectively) vs 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/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 (≥3 canisters/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 3–6 SABA canisters/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) vs 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 ≥2-fold higher in the high- vs low-SABA-prescription group, irrespective of disease severity (Table 2). Among those aged 1–5 years, the unadjusted [IRR (95% CI)], comparing all exacerbation events in high- vs low-SABA-prescription groups, was 2.51 (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 [2.07–2.25]). Consistently high IRRs (>2) were observed for exacerbations which precipitated A&E visits, (adjusted IRRs: 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 [2.37–2.61]). Analysis of SABA prescription categories as an ordinal (0, 1, 2, 3–6, 7–12, ≥13 prescriptions) and continuous variable suggested a dose-response 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 Table S2–S3).

GINA treatment steps and the presence of atopic disease were also 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 vs those with atopic disease (Table 3). A similar differential association of ≥3 SABA prescriptions/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 (≥3 vs <3 SABA canisters/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 also replicated when SABA prescriptions were analysed as a continuous variable.

As expected, males were over-represented across all age cohorts in this study population, with approximately half of all patients exhibiting evidence of atopic disease. High SABA prescription (≥3 canisters/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.

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 [25].

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 ≥3 vs <3 SABA canisters/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, particularly in older children and adolescents, the importance of linking data on primary and secondary care to capture all exacerbation events and their associated disease burden. 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 over 40% of the study population experienced an exacerbation [26]. This represented more than 2-fold greater incidence of exacerbations observed in our study, suggesting a potential under-estimation 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 (<18 years) from Sweden (SABINA Jr Sweden study), which reported that collection of ≥3 vs 0–2 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 vs atopic disease across all age groups (0-5, 6–11, and 12–17 years) [27]. Although when stratified by atopic disease, differences in estimated IRR magnitudes were relatively small, non-atopic patients likely 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 [28], thereby affording less clinical benefit from these prescriptions. In addition, the British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) advise that many non-atopic 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 [19,29-34]. A 2015

study investigating SABA prescription fills during a 12-month period found that children who heavily relied on SABA were 5 times more likely to be hospitalised than were low or moderate users [29]. Similarly, a US claims study in children found that prescription of each additional SABA canister was associated with an increased risk of asthma exacerbations [30]. 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 socio-economic 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 [35]. 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 LABA/ICS regimens with SABA reliever [36]; additionally, the efficacy and safety profile of MART in adolescents is consistent with that reported in adults [37]. Moreover, results from a 12-month, double-blind, randomized 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 [38]. 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 [1,19,39].

Our study is not without limitations. Reporting of preschool wheeze may be incomplete, thereby requiring caution when generalizing 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. Also, exposure to tobacco smoke was not included as a covariate in the model, while BMI was excluded as imputation was not possible given the non-random 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 utilizing 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 non-differential 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 socio-economic 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 ≥3 vs <3 SABA canisters/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.

Acknowledgements

We thank Mehmet Berktas (AstraZeneca) and Sofie Arnetorp (AstraZeneca) for input on the study design. Writing and editorial support was provided by Cactus Life Sciences (part of Cactus Communications, Mumbai, India) in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3) and fully funded by AstraZeneca.

Authors and Contributions

JKQ, RV and TT conceptualised the study and all authors contributed to study design. AM, CK and JKQ created code lists for outcomes of interest. AM and CK have 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. JKQ 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 interests

AM and CK have nothing to declare. JKQ 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. JKQ's research group received funding from AstraZeneca for this work. EM, TNT and RJPvdV are employees of AstraZeneca and hold AstraZeneca shares. RJPvdV holds shares in GlaxoSmithKline. GR and IS received consultancy from AstraZeneca to their institutions for this work.

Sources of funding

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

Data sharing statement

This study used existing data from the UK CPRD EHR database, and this data resource is accessible only to researchers with protocols approved by the CPRD's independent scientific advisory committee; therefore, no additional unpublished data are available. All data management and analysis computer codes are available on request. The study protocol and analysis plan are available in the associated supplementary material.

Linked pseudonymised mortality data from the Office for National Statistics (ONS), socioeconomic data from the Index of Multiple Deprivation (IMD) and secondary care data from Hospital Episode Statistics (HES) were provided for this study by CPRD for patients in England. Data is linked by NHS Digital, the statutory trusted third party for linking data, using identifiable data held only by NHS Digital. Select general practices consent to this process at a practice level, with individual patients having the right to opt out. Use of HES and ONS data is Copyright © (2018), re-used with the permission of The Health & Social Care Information Centre, all rights reserved.

Data are available on request from the CPRD. Their provision requires the purchase of a license, and this license 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 license, the code lists have been provided on GitHub. Licenses are available from the CPRD (http://www.cprd.com): The Clinical Practice Research Datalink Group, The

Medicines and Healthcare products Regulatory Agency, 10 South Colonnade, Canary Wharf, London E14 4PU.

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Figure legends

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.

Figure 2: Flow chart of study participant inclusion commencing with patients registered in CPRD Aurum database with at least one asthma code during the study period and aged 1-17 years

[a]Respiratory diagnoses include bronchiectasis, bronchopulmonary dysplasia, cystic fibrosis, primary ciliary dyskinesia
CPRD, Clinical Practice Research Datalink; GP, general practitioner.

Figure 3: Multivariable IRRs of the association between 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
IRR, incidence rate ratio; SABA, short-acting β_2-agonist.

Figure 4: Predictive incidence rates of all exacerbation types in each age group by number of SABA prescriptions stratified by the presence of atopy in a cohort of paediatric patients with asthma in England

IRR, incidence rate ratio; SABA; short-acting β_2-agonist.

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

Characteristic	**1–5 years n (%)** [unless otherwise specified]	**6–11 years n (%)** [unless otherwise specified]	**12–17 years n (%)** [unless otherwise specified]
Total	48,560 (100.0%)	110,091 (100.0%)	111,891 (100.0%)
Median (IQR) length of follow-up (years, range)	1.12 (1.21–3.70)	2.19 (1.02–3.54)	2.51 (1.21–3.70)
Demographic			
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%)
Body mass index (kg/m^2)			
Underweight	2,420 (5.0%)	6,520 (5.9%)	5,903 (5.3%)
Normal	10,973 (22.6%)	40,530 (36.8%)	40,326 (36.0%)
Overweight	2,639 (5.4%)	10,618 (9.6%)	14,885 (13.3%)
Obese	1,429 (2.9%)	5,794 (5.3%)	6,714 (6.0%)
Missing	31,099 (64.0%)	46,629 (42.4%)	44,028 (39.4%)
z-score (mean, SD)	0.259 (1.633)	0.406 (1.396)	0.636 (1.376)
Socioeconomic status (IMD)			
1 (least deprived)	9,250 (19.1%)	22,544 (20.5%)	23,624 (21.1%)
2	8,472 (17.5%)	20,107 (18.3%)	20,819 (18.6%)
3	8,545 (17.6%)	19,734 (17.9%)	20,429 (18.3%)
4	9,937 (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			

Characteristic	**1–5 years n (%)** [unless otherwise specified]	**6–11 years n (%)** [unless otherwise specified]	**12–17 years n (%)** [unless otherwise specified]
Allergic rhinitis including hay fever	2,533 (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	2,533 (5.2%)	6,957 (6.3%)	6,205 (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)[a]			
0 (SABA only)	7,458 (15.4%)	18,633 (16.9%)	23,955 (21.4%)
1	26,945 (55.5%)	57,907 (52.6%)	49,854 (44.6%)
2	6,954 (14.3%)	6,513 (5.9%)	3,408 (3.1%)
3	887 (1.8%)	8,296 (7.5%)	7,983 (7.1%)
4	214 (0.4%)	1,615 (1.5%)	4,849 (4.3%)
5[b]	183 (0.4%)	455 (0.4%)	548 (0.5%)
Unassigned (no regular medications)[c]	5,919 (12.2%)	16,672 (15.1%)	21,294 (19.0%)
Exacerbation history (in 12 months prior to index date)			
Median number of events (IQR)	0 (0–0)	0 (0–0)	0 (0–0)
Mean number of events (SD)	0.29 (0.70)	0.18 (0.54)	0.19 (1.60)
Any exacerbation	9,670 (19.9%)	14,731 (13.4%)	15,411 (13.8%)
Any hospital event	8,544 (17.6%)	8,964 (8.1%)	5,949 (5.3%)
A&E visit	2,977 (6.1%)	2,624 (2.4%)	1,407 (1.3%)
Hospital admission	7,015 (14.4%)	7,627 (6.9%)	5,082 (4.5%)
GP-treated only	1,514 (3.1%)	6,699 (6.0%)	10,925 (9.8%)
Medication prescription			

Characteristic	**1–5 years n (%)** [unless otherwise specified]	**6–11 years n (%)** [unless otherwise specified]	**12–17 years n (%)** [unless otherwise specified]
Inhaled corticosteroids			
Dosage level[d]			
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	4,781 (9.9%)	19,063 (17.3%)	58,852 (52.6%)
Medium dose	366 (0.8%)	1,976 (1.8%)	6,490 (5.8%)
High dose	41 (0.1%)	667 (0.6%)	540 (0.5%)
PDC (expressed as a percentage)			
Median (IQR)	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 (up to 2 months of coverage)	10,000 (29.5%)	21,001 (28.5%)	1,935 (2.9%)
Third quartile (up to 3 months of coverage)	6,277 (18.5%)	2,068 (2.8%)	16,445 (25.0%)
Highest (more than 3 months of coverage)	5,120 (15.1%)	18,303 (24.9%)	16,411 (24.9%)
SABA inhaler prescription (12 months)			
0	6,021 (12.4%)	15,550 (14.1%)	19,054 (17.0%)
1	10,519 (21.1%)	28,167 (25.6%)	30,407 (27.2%)
2	9,597 (19.8%)	24,228 (22.0%)	22,142 (19.8%)
3–6	17,833 (37.7%)	34,502 (31.3%)	30,187 (27.0%)
7–12	4,153 (8.6%)	6,756 (6.1%)	8,404 (7.5%)

Characteristic	**1–5 years n (%)** [unless otherwise specified]	**6–11 years n (%)** [unless otherwise specified]	**12–17 years n (%)** [unless otherwise specified]
≥13	437 (0.9%)	879 (0.8%)	1,697 (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[e]	7,555 (15.6%)	9,883 (9.0%)	6,446 (5.8%)

[a]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 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. See https://ginasthma.org/wp-content/uploads/2020/04/GINA-2020-full-report_-final-_wms.pdf, accessed 12 November 2021).
[b]Includes patients on maintenance OCS. Patients are classified as being on maintenance OCS if they have had ≥5 OCS prescriptions in the 6-month baseline period.
[c]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.
[d]ICS dose was defined according to BTS/SIGN 2019 guidelines.
[e]Includes both patients prescribed LTRA only or as an add-on therapy during the 6-month baseline period.
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; GINA: Global Initiative for Asthma; GP: general practitioner; ICS: inhaled corticosteroids; IMD: Index of Multiple Deprivation; IQR: interquartile range; LABA: long-acting β_2-agonist; LTRA: leukotriene receptor antagonist; NA, not assessed; OCS: oral corticosteroids; PDC: proportion of days covered; SABA: short-acting β_2-agonist; SD: standard deviation.

Table 2. Association between at least three SABA prescriptions and asthma exacerbation incidence in a cohort of paediatric patients with asthma in England

Definitions of exacerbation by patient care type		Unadjusted effect estimates				Adjusted* effect estimates		
Age 1–5 years	**n**	**IRR**	**95% CI**	**p-value**	**n**	**IRR**	**95% CI**	**p-value**
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

*Adjusted for age, sex, GINA treatment steps, 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.

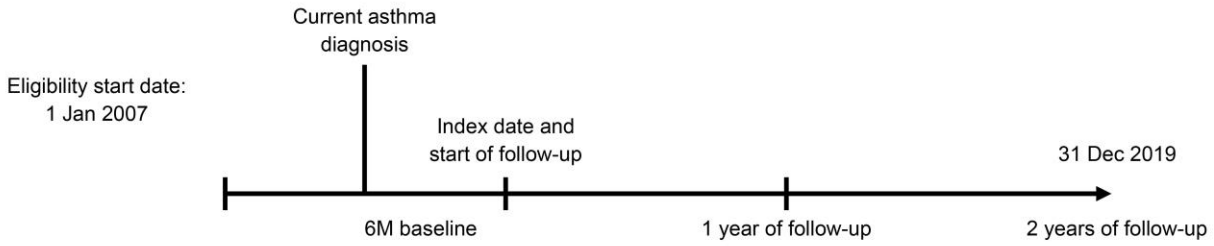
Table 3. Stratified and interaction analysis by atopy for the association of ≥3 SABA prescriptions (binary exposure) with incidence of acute exacerbations (GP and all hospital data) in a cohort of paediatric patients with asthma in England

Multilevel negative binomial model		**Effect estimates by stratified analysis**			**Effect estimates by interaction analysis**		
Age cohort	**N**	**IRR**	**95% CI**	**p-value**	**IRR**	**95% CI**	**p-value**
Age 1–5 years (n=42,604)							
Atopy (No/Yes)							
Interaction term					p=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 (n=93,358)							
Atopy (No/Yes)							
Interaction term					p=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 (n=90,518)							
Atopy (No/Yes)							
Interaction term					p=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

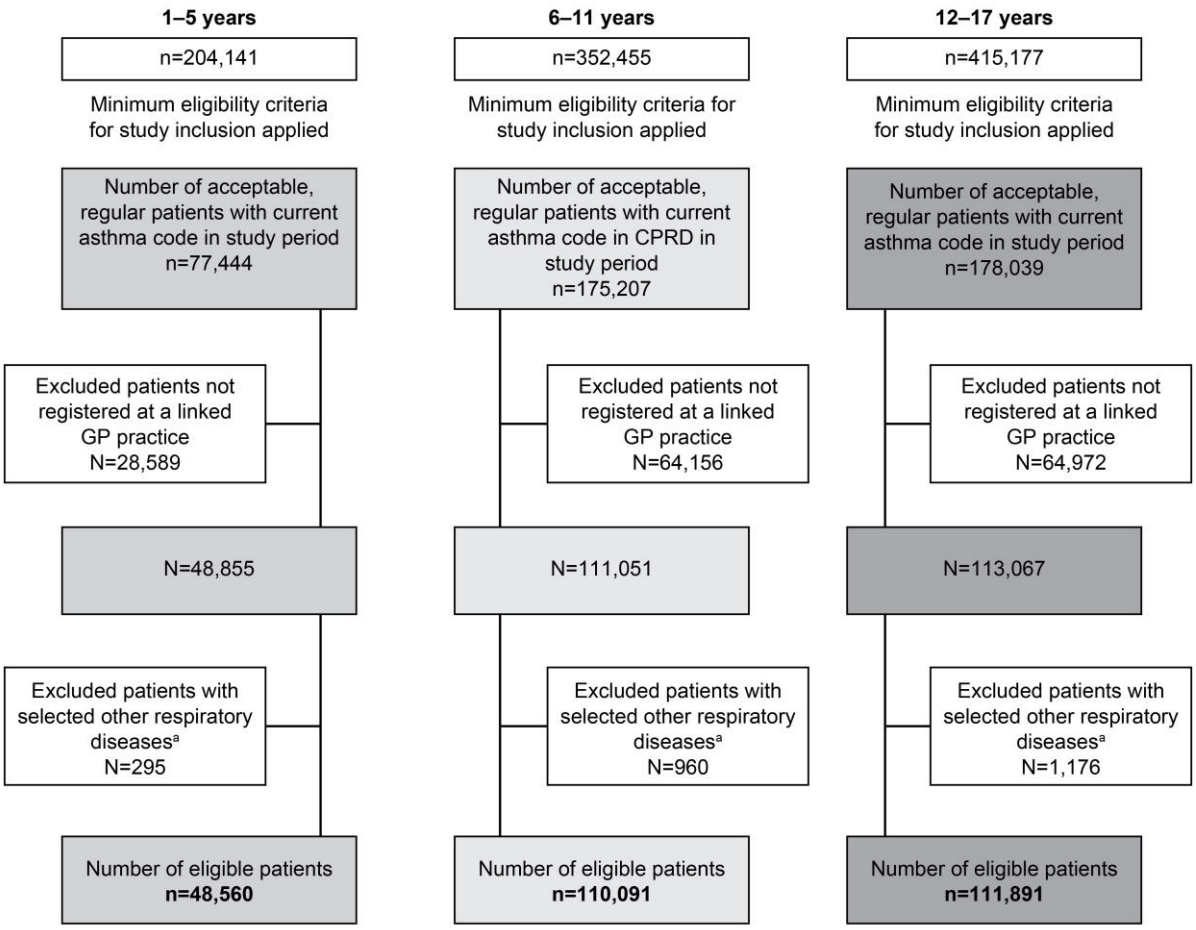
Covariates included: age, sex, GINA treatment steps (step 1 used as reference category), IMD, prior atopy, asthma exacerbations during previous 12 months and quartiles of ICS proportion of days covered. Random effect estimated to adjust for clustering of patients within GP practices.

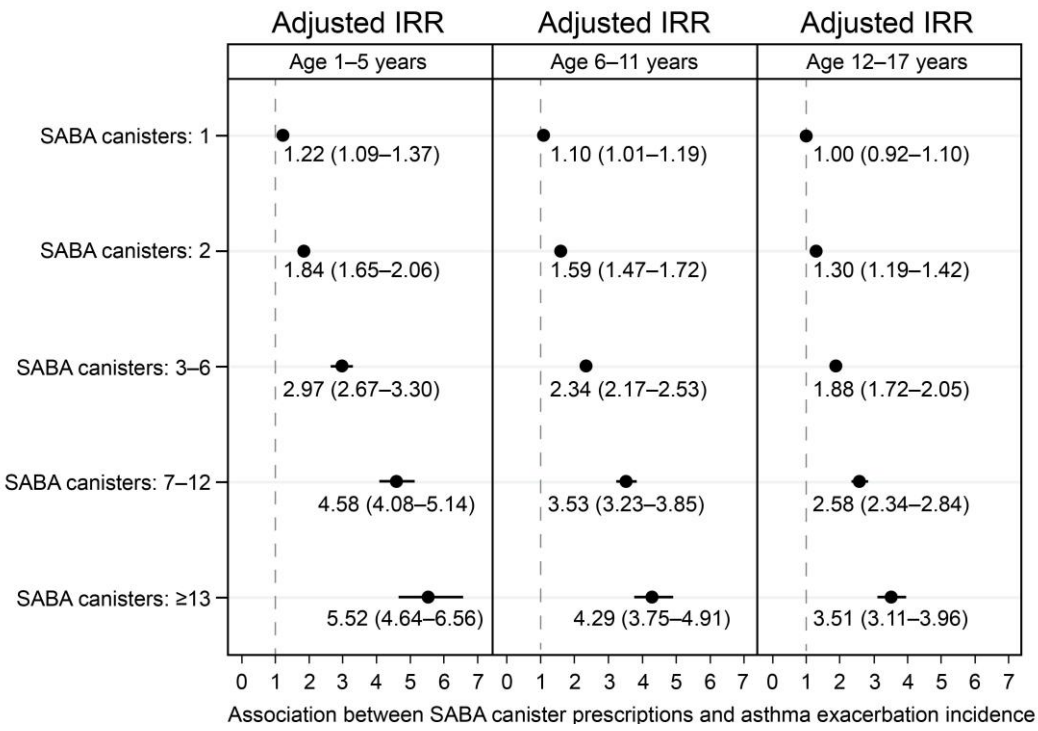
Atopy defined as the presence of food allergy, hay fever, allergic rhinitis or eczema/atopic dermatitis at any time prior to the index date.

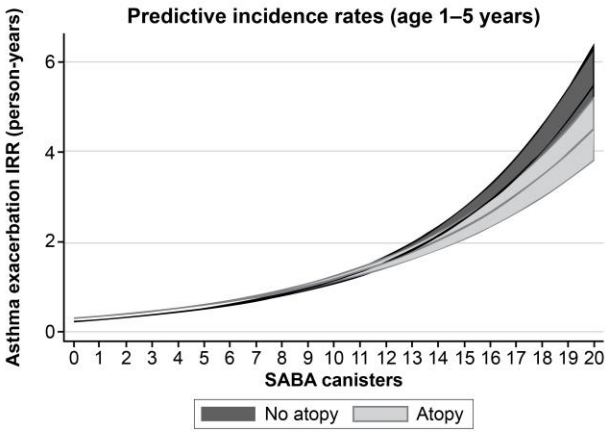
GINA, Global Initiative for Asthma; GP, general practitioner; ICS, inhaled corticosteroids; IMD, Index of Multiple Deprivation; IRR, incidence rate ratio; SABA, short-acting β_2-agonist.

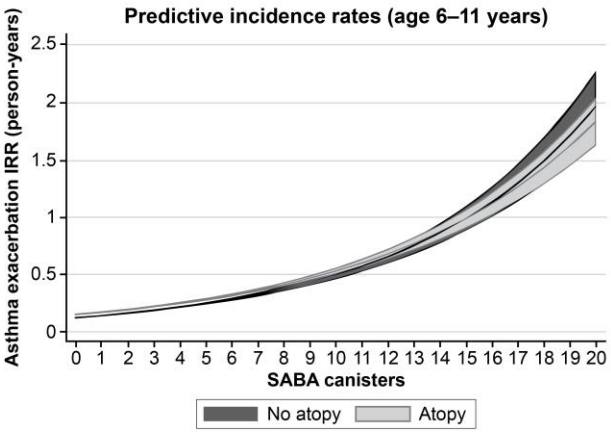


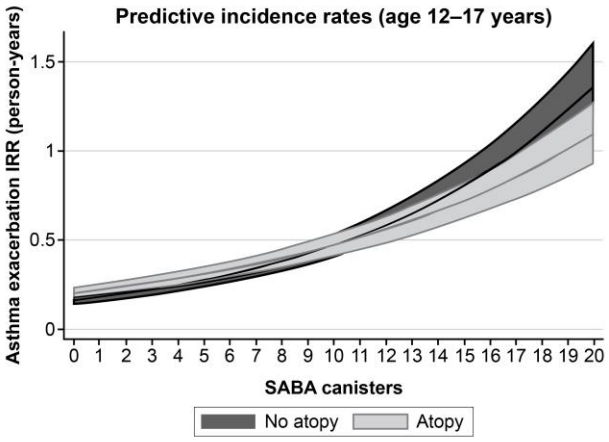
- Covariates and medication history determined in 6-month baseline period
- Index date 6 months after asthma diagnosis was recorded
- Prior to index date, patients must have 12 months of continuous registration at a CPRD participating GP practice data and meet CPRD 'acceptable' data quality criteria
- 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 Dec 2019


1–5 years
n=204,141
Minimum eligibility criteria for study inclusion applied
Number of acceptable, regular patients with current asthma code in study period n=77,444
Excluded patients not registered at a linked GP practice N=28,589
N=48,855
Excluded patients with selected other respiratory diseases[a] N=295
Number of eligible patients n=48,560
6–11 years
n=352,455
Minimum eligibility criteria for study inclusion applied
Number of acceptable, regular patients with current asthma code in CPRD in study period n=175,207
Excluded patients not registered at a linked GP practice N=64,156
N=111,051
Excluded patients with selected other respiratory diseases[a] N=960
Number of eligible patients n=110,091
12–17 years
n=415,177
Minimum eligibility criteria for study inclusion applied
Number of acceptable, regular patients with current asthma code in study period n=178,039
Excluded patients not registered at a linked GP practice N=64,972
N=113,067
Excluded patients with selected other respiratory diseases[a] N=1,176
Number of eligible patients n=111,891


Adjusted IRR
Adjusted IRR
Adjusted IRR
Age 1–5 years
Age 6–11 years
Age 12–17 years
SABA canisters: 1
SABA canisters: 2
SABA canisters: 3–6
SABA canisters: 7–12
SABA canisters: ≥13
1.22 (1.09–1.37)
1.10 (1.01–1.19)
1.00 (0.92–1.10)
1.84 (1.65–2.06)
1.59 (1.47–1.72)
1.30 (1.19–1.42)
2.97 (2.67–3.30)
2.34 (2.17–2.53)
1.88 (1.72–2.05)
4.58 (4.08–5.14)
3.53 (3.23–3.85)
2.58 (2.34–2.84)
5.52 (4.64–6.56)
4.29 (3.75–4.91)
3.51 (3.11–3.96)
0 1 2 3 4 5 6 7
Association between SABA canister prescriptions and asthma exacerbation incidence


Predictive incidence rates (age 1–5 years)
Asthma exacerbation IRR (person-years)
0
2
4
6
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
SABA canisters
No atopy
Atopy


Predictive incidence rates (age 6–11 years)
Asthma exacerbation IRR (person-years)
0
0.5
1
1.5
2
2.5
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
SABA canisters
No atopy
Atopy


Predictive incidence rates (age 12–17 years)
Asthma exacerbation IRR (person-years)
0
0.5
1
1.5
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
SABA canisters
No atopy
Atopy

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.

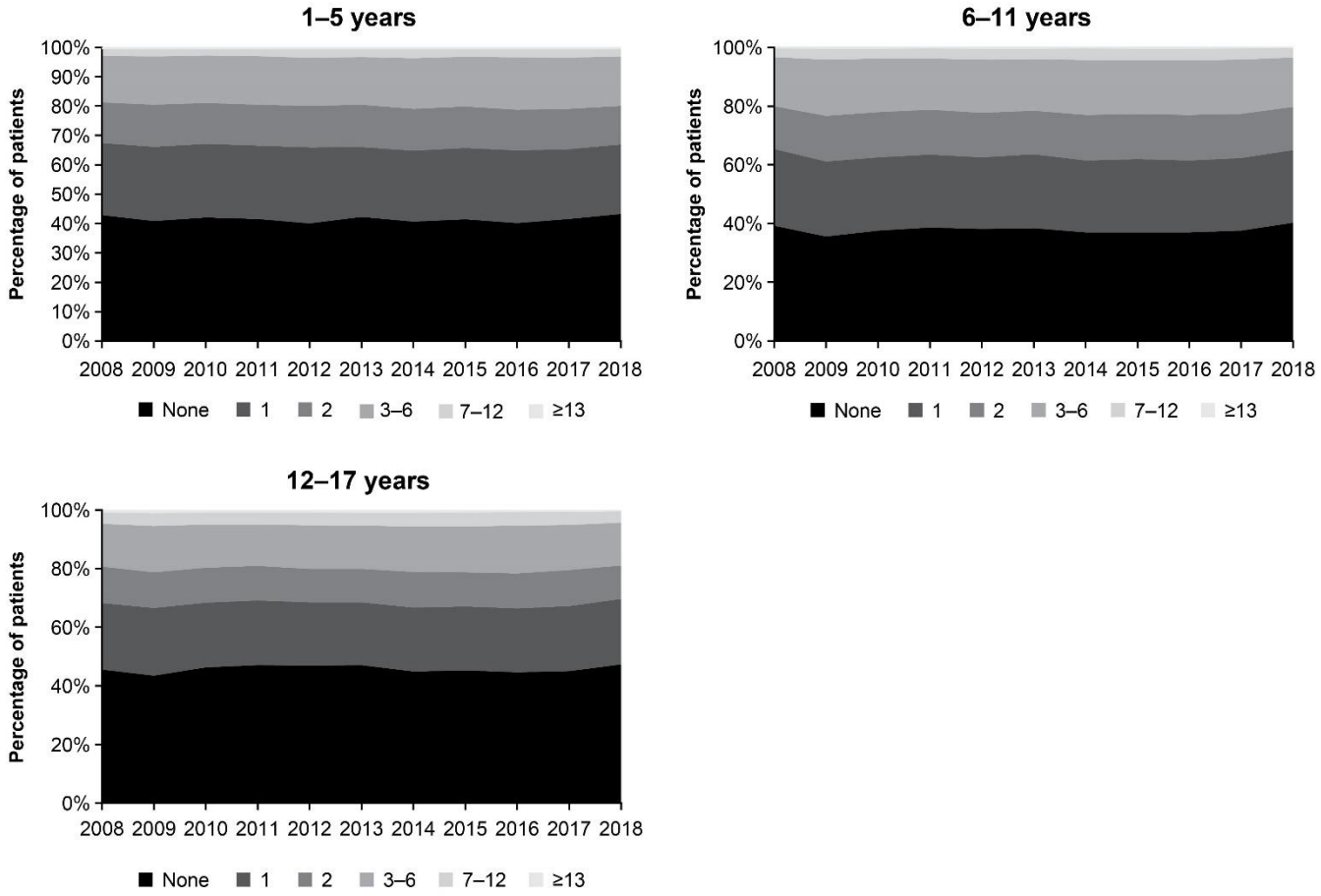
Ethical Approval

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

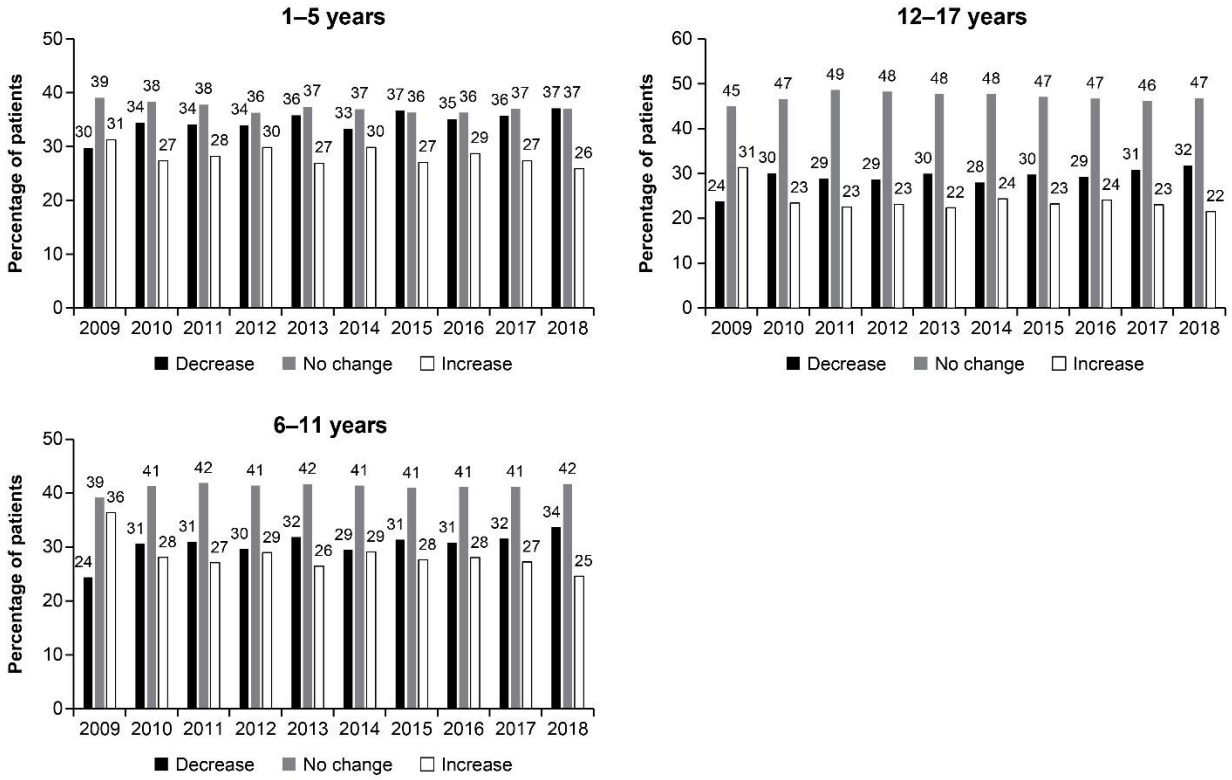
AstraZeneca funded the SABINA studies and was involved in designing the program, developing the study protocol and conducting the studies.

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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