Received: 29 September 2022 | Revised: 1 November 2022 | Accepted: 2 November 2022

DOI: 10.1111/pai.13885

ORIGINAL ARTICLE

WILEY

Short-acting β_2-agonist use and asthma exacerbations in Swedish children: A SABINA Junior study

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Funding information
AstraZeneca, Grant/Award Number: GPP3

Associate Editor: Ömer Kalayci

Abstract

Background: In adults and adolescents with asthma, use of ≥3 short-acting β_2-agonist (SABA) canisters/year is associated with increased exacerbation risk. Whether this association is present in younger children remains unknown. In this SABA use IN Asthma (SABINA) Junior study, we assessed the association of SABA collection with exacerbation risk in the general Swedish pediatric asthma population.

Methods: This population-based cohort study utilized linked data from the Swedish national healthcare registries involving patients with asthma (<18 years) treated in secondary care between 2006–2015. Exacerbation risk, by baseline SABA collection (0–2 vs. ≥3 canisters, further examined as ordinal/continuous variable) and stratified on comorbid atopic disease (allergic rhinitis, dermatitis and eczema, and food/other allergies), was assessed for 1-year follow-up using negative binomial regression.

Results: Of 219,561 patients assessed, 45.4%, 31.7%, and 26.5% of patients aged 0–5, 6–11, and 12–17 years, respectively, collected ≥3 SABA canisters during the baseline year (high use). Collection of ≥3 SABA canisters (vs. 0–2) was associated with increased exacerbation risk during follow-up (incidence rate ratios [95% confidence interval]: 1.35 [1.29–1.42], 1.22 [1.15–1.29], and 1.26 [1.19–1.34] for 0–5-, 6–11-, and 12–17-year-olds, respectively); the association persisted with SABA as a continuous variable and was stronger among patients without atopic diseases (32%–44% increased risk versus. 14%–21% for those with atopic disease across groups).

Conclusions: High SABA use was associated with increased asthma exacerbation risk in children, particularly in those without comorbid atopic diseases, emphasizing the need for asthma medication reviews and reformative initiatives by caregivers and healthcare providers on SABA use.

KEYWORDS
asthma, children, exacerbations, pediatric, SABINA junior study, short-acting β_2-agonists, Sweden

1 | INTRODUCTION

Asthma is the most common noncommunicable disease in children globally,[1] with a reported prevalence in Sweden of ~7% in children (7–8 years)[2] and 11% in adolescents (14–15 years).[3] Childhood asthma is characterized by multiple phenotypes, and unlike in adults, clinical manifestations of these phenotypes are more likely to change over time, thus hindering diagnosis and treatment, especially among those aged ≤5 years.[4,5] Birth cohorts from the United Kingdom (UK), the Netherlands, and Sweden have identified several phenotypes that optimally characterize the differences in childhood asthma over time.[5,6] Asthma phenotypes emerging in early childhood may be related to temporal patterns of wheeze, where persistent wheeze is strongly associated with atopy and increased airway responsiveness.[7] Among 6–17-year-olds, phenotypes differ and may be based on the presence of other allergic conditions, atopy, or eosinophilia; children with asthma and comorbid atopy and/or eosinophilia are at increased exacerbation risk.[8–11] Thus, similar to adults, children with asthma need to be carefully monitored and may require personalized treatment.

Childhood asthma exerts a persistent burden on patients, caregivers, and healthcare systems,[12] with a considerable proportion of children experiencing ≥1 exacerbation annually,[13] contributing to school absenteeism, reduced activity, disrupted sleep patterns, and associated psychological consequences.[14–16] The burden of childhood asthma may be further compounded by short-acting β_2-agonist (SABA) over-reliance for rapid symptom relief. The SABA use IN Asthma (SABINA) program in adults and adolescents with asthma reported that SABA overuse (≥3 canisters/year) is prevalent in Sweden[17] and associated with poor asthma-related outcomes.[18,19] Few studies have evaluated SABA use in the pediatric population or its impact on clinical outcomes.[20–25] Examining the extent of SABA collection and associated clinical outcomes in children across age groups and asthma phenotypes may provide further insights into reducing asthma morbidity in children. The SABINA Junior study in Sweden describes the pediatric asthma population in secondary care, their treatment regimens, and the association between SABA collection and asthma-related exacerbations.

Key message

This population-based cohort SABINA Junior study assessed the association between short-acting β_2-agonist (SABA) collection and exacerbation risk in a general pediatric population with asthma in Sweden. Our findings revealed that of the 219,561 patients, a considerable proportion across all age groups (45.4%, 31.7%, and 26.5% of patients aged 0–5, 6–11, and 12–17 years, respectively) collected ≥3 SABA canisters during the baseline year (considered high SABA use), which was associated with increased exacerbation risk during follow-up. This association was particularly strong among patients without comorbid atopic diseases.

2 | METHODS

The study protocol was approved by the Stockholm Regional Ethics Committee (registration number: 2017/4:2) and conducted in compliance with the Declaration of Helsinki. In Sweden, patients need not provide consent for use of public register data.[26,27]

2.1 | Study design and population

This population-based, nationwide retrospective cohort study included pediatric Swedish residents with physician-diagnosed asthma (aged 0–17 years) in secondary care utilizing linked data from Swedish national healthcare registries (Appendix S1).

Asthma was identified based on the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes J45 or J46.9 in the Swedish National Patient Register (NPR). Patients were categorized by the number of SABA canisters collected from pharmacies at baseline, that is, the 12-month period between initial asthma diagnosis and the index date, and followed up from index date until study end, death, emigration, or up to 3 years, whichever occurred first (Figure 1). Analytical outcomes were assessed for 1 and 3 years of follow-up. As children can outgrow their asthma, the 1-year follow-up was considered for primary analysis.

2.2 | Variables and outcomes

SABA canisters were dichotomized as 0–2 versus. ≥3 based on evidence from studies in adults and adolescents.[18,19] Owing to potential differences in younger children, SABAs were further examined as ordinal (0–2, 3–5, 6–10, and ≥ 11 canister categories) and continuous variables.

Other baseline data comprised demographics; asthma medication, including inhaled corticosteroid (ICS); asthma severity or treatment severity step based on the Global Initiative for Asthma (GINA) 2018 recommendations[19,28] and comorbidities (Table S1) from birth until index date.

The analytical outcome was the incidence of asthma exacerbations during follow-up, defined as hospitalization, emergency room (ER) visit due to asthma, or an oral corticosteroid (OCS) claim for asthma treatment.

2.3 | Statistical analysis

All analyses were stratified by 0–5-, 6–11-, and 12–17-year age groups. Analyses in 0–5-year-olds were exploratory. Baseline SABA canister

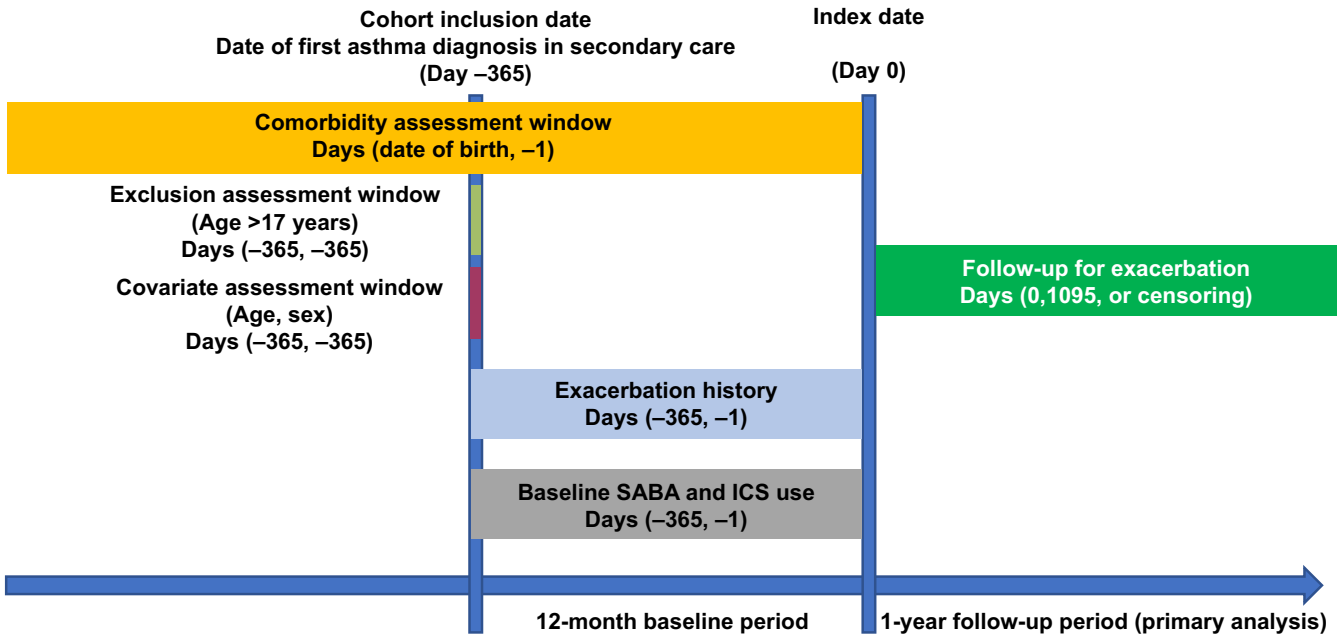

FIGURE 1 Study design ICS, inhaled corticosteroid; SABA, short-acting β_2-agonist.

collection was described by sex and treatment step of patients collecting SABA and the total number of ICS canisters collected by them. The Kruskal-Wallis test assessed statistical significance between groups. The relation between baseline SABA use and individual exacerbation rates during first year of follow-up was modeled using cubic B-splines[29] using the R package ggplot2 (https://cran.r-project.org/web/packages/ggplot2/index.html RRID:SCR_014601).[30]

Negative binomial regression models assessed exacerbation risk (incidence rate ratios [IRRs] with 95% confidence intervals [CIs]) during the first follow-up year and for 3 years of follow-up, based on baseline SABA collection.

The risk of the first observed asthma exacerbation was assessed using Cox proportional hazard models. For this analysis, follow-up for exacerbations started on the index date and ended at the first subsequent exacerbation, adulthood, death, emigration, study end, or 3 years after index, whichever occurred first. All multivariable analyses were adjusted for sex, treatment step, and baseline exacerbation history.

A post hoc analysis evaluated the interaction of SABA and atopic disease on exacerbation risk through model cross-terms (SABA continuous times atopic disease 0/1). The interaction effect was tested through a likelihood-ratio test. The multivariable analyses were stratified on atopic disease.

To visualize the change in exacerbation rate across SABA categories in the stratified groups, predicted exacerbation rate during the first follow-up year for a patient profile stratified on atopic disease was calculated through estimated marginal means using the emmeans R package[31] applied to a negative binomial regression model (Appendix S1).

3 | RESULTS

3.1 | Study population

Of the 219,561 patients analyzed (Figure 2), 52.1%, 26.5%, and 21.4% were aged 0–5, 6–11, 12–17 years, respectively. Patients with longer-term follow-up and frequent hospital contacts could be included in more than one age-specific cohort, that is, a patient with a visit at age 4, 8, and 14 years was included in all three cohorts (Figure S1). Overall, 40.2% of patients were female (Table 1) and 21.9%, 49.1%, and 58.5% of patients aged 0–5, 6–11, and 12–17 years, respectively, had comorbid atopic disease (Results and Table S2).

Most patients collected 0–2 ICS-containing canisters at baseline (65.7%, 72.8%, and 73.5% of 0–5-, 6–11-, and 12–17-year-olds, respectively), with 23.3%, 27.7%, and 30.9% collecting zero canisters (Table 1). Baseline exacerbation rate was highest in 0–5-year-olds (rate per 100 person-years [95% CI]: 16.52 [16.29–16.76]), followed by 12–17-year-olds (16.09 [15.73–16.45]) and 6–11-year-olds (12.19 [11.91–12.48]; Table 1). Across age groups, exacerbations requiring OCS were most common (rates per 100 person-years: 7.2–15.7).

3.2 | SABA collection during the baseline year

Overall, 45.4%, 31.7%, and 26.5% of 0–5-, 6–11-, and 12–17-year-olds, respectively, claimed ≥3 SABA canisters in the baseline year (Table 1). SABA collection increased with the number of ICS canisters and treatment step at baseline across age groups (Table S3).

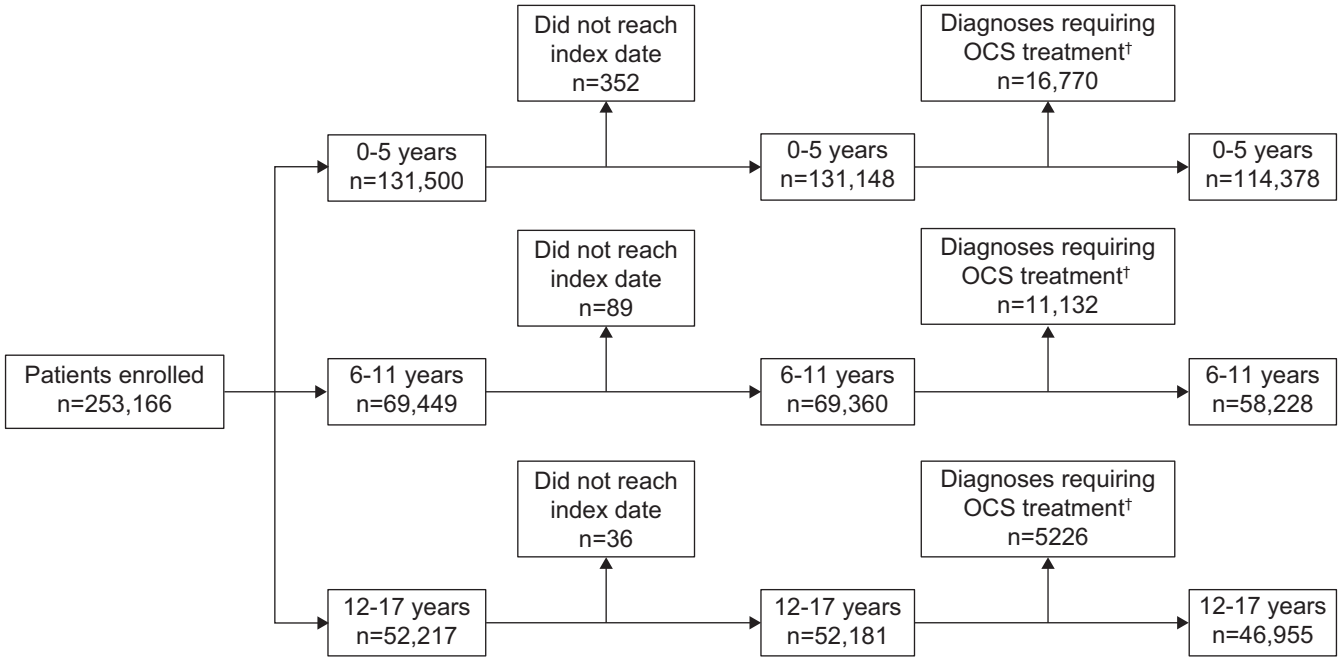

FIGURE 2 Patient disposition and study population stratified by age groups among pediatric patients with asthma. BPD, bronchopulmonary dysplasia; OCS, oral corticosteroid. †Diagnoses include cystic fibrosis, bronchiectasis, BPD originating in the perinatal period, and chronic lung disease following BPD/prematurity, croup, Crohn's disease, ulcerative colitis, juvenile arthritis, and anaphylaxis.

3.3 | Exacerbations at follow-up

The unadjusted exacerbation rate during 1-year follow-up increased with baseline SABA collection across all age groups and was highest for 12–17-year-olds and lowest for 0–5-year-olds (Figure 3). In an adjusted multivariable analysis, across age groups, ≥3 versus 0–2 SABA collection at baseline was associated with an increased exacerbation rate during 1-year follow-up (IRRs [95% CI]: 1.35 [1.29–1.42], 1.22 [1.15–1.29], and 1.26 [1.19–1.34] for 0–5-, 6–11-, and 12–17-year-olds, respectively; Table 2). A "dose–response" relation was noted when SABA was examined as an ordinal and continuous variable (Table 2). Similar results were observed during 3 years of follow-up (Table S4).

When stratified by presence of atopic disease, the association between baseline SABA collection and risk of asthma exacerbations was significant for both groups, but the association was stronger among patients without versus those with comorbid atopic disease ($p < .001$; Table S5). Collection of ≥3 versus 0–2 SABA canisters at baseline was associated with a greater risk of any asthma exacerbation during 1-year follow-up among patients with nonatopic versus atopic disease (IRRs [95% CI]: 1.44 [1.35–1.54] versus 1.21 [1.12–1.31], 1.32 [1.17–1.49] versus 1.14 [1.07–1.22], and 1.44 [1.27–1.64] versus 1.20 [1.12–1.28] for 0–5-, 6–11-, and 12–17-year-olds, respectively; Figure 4 and Table 2). This relation persisted during 3 years of follow-up (Table S4). Similar results were observed for the risk of the first exacerbation, in the overall analysis and when stratified on atopic disease, regardless of the follow-up period (Table S6 and Figures S2 and S3).

When stratified by presence of atopic disease, the predicted rate of any exacerbation type during 1-year follow-up increased with higher baseline SABA canister collection (Figure S4). Despite a lower exacerbation rate with collection of zero SABA canisters in patients with nonatopic versus atopic disease, a steeper increase in the exacerbation rate with a high SABA canister collection was observed in the nonatopic group.

4 | DISCUSSION

Overall, 45%, 32%, and 27% of patients with asthma aged 0–5, 6–11, and 12–17 years, respectively, collected ≥3 SABA canisters during the baseline year (considered overuse). SABA overuse was associated with an increased exacerbation risk by 35%, 22%, and 26% for 0–5-, 6–11-, and 12–17-year-olds, respectively. While this association was observed irrespective of atopic status at baseline, it was stronger among patients without comorbid atopic diseases.

SABAs have long been recommended for symptom relief in the management of childhood asthma. However, GINA no longer recommends as-needed SABA monotherapy for patients ≥6 years, although monotherapy continues to be recommended for those under 5 years owing to lack of clinical data on an alternative reliever.[5] Instead, GINA recommends ICS-formoterol as the preferred reliever for adolescents with mild asthma and for those with moderate-to-severe asthma prescribed ICS-formoterol as maintenance and reliever therapy (MART).[4] In 6–11-year-olds, SABA is the only reliever option, except for those on MART, with

TABLE 1 Baseline demographics, disease characteristics, and medications among pediatric patients with asthma in Sweden

	0–5 years (n = 114,378)	6–11 years (n = 58,228)	12–17 years (n = 46,955)
Female, *n* (%)	43,994 (38.5)	22,988 (39.5)	21,286 (45.3)
Index age, years			
Mean (SD)	1.7 (1.5)	7.8 (1.8)	13.7 (1.7)
Atopic disease, *n* (%)	25,098 (21.9)	28,601 (49.1)	27,492 (58.5)
Treatment step, *n* (%)			
0	16,624 (14.5)	9482 (16.3)	8218 (17.5)
1	6990 (6.1)	4961 (8.5)	4438 (9.5)
2	44,407 (38.8)	21,295 (36.6)	11,104 (23.6)
3	46,357 (40.5)	12,566 (21.6)	10,661 (22.7)
4	0 (0.0)	4354 (7.5)	6611 (14.1)
5	0 (0.0)	5570 (9.6)	5923 (12.6)
SABA canisters			
Mean (SD)	2.7 (2.5)	2.1 (2.2)	1.8 (2.3)
Number of SABA canisters, *n* (%)			
0	26,000 (22.7)	18,264 (31.4)	18,966 (40.4)
1	786 (0.7)	2772 (4.8)	2951 (6.3)
2	35,641 (31.2)	18,751 (32.2)	12,574 (26.8)
3–5	36,694 (32.1)	14,007 (24.1)	9417 (20.1)
6–10	13,471 (11.8)	3911 (6.7)	2590 (5.5)
≥11	1786 (1.6)	523 (0.9)	457 (1.0)
Number of ICS canisters, *n* (%)			
0	26,658 (23.3)	16,136 (27.7)	14,520 (30.9)
1	26,978 (23.6)	15,828 (27.2)	11,859 (25.3)
2	21,531 (18.8)	10,408 (17.9)	8147 (17.4)
3–5	28,063 (24.5)	12,223 (21.0)	9610 (20.5)
6–10	9434 (8.2)	3051 (5.2)	2428 (5.2)
≥11	1714 (1.5)	582 (1.0)	391 (0.8)
Daily dose of ICS, μg[a]			
Mean (SD)	117.1 (111.2)	175.7 (147.5)	221.6 (186.9)
Baseline exacerbation rate, per 100 person-years (95% CI)			
Hospitalization	6.14 (6.00–6.29)	0.69 (0.62–0.76)	0.40 (0.34–0.45)
ER visit	3.59 (3.48–3.70)	0.06 (0.04–0.08)	0.09 (0.06–0.11)
OCS	7.15 (6.99–7.30)	11.52 (11.24–11.79)	15.73 (15.37–16.08)
Any	16.52 (16.29–16.76)	12.19 (11.91–12.48)	16.09 (15.73–16.45)
Medications, *n* (%)			
SABA	86,184 (75.4)	24,433 (42.0)	12,389 (26.4)
Any ICS	87,720 (76.7)	42,092 (72.3)	32,435 (69.1)
ICS monotherapy	86,968 (76.0)	35,598 (61.1)	18,346 (39.1)
LABA	185 (0.2)	1638 (2.8)	2705 (5.8)
ICS/LABA	2031 (1.8)	9104 (15.6)	16,829 (35.8)
LTRA	18,954 (16.6)	7895 (13.6)	7699 (16.4)
OCS	7284 (6.4)	5567 (9.6)	5903 (12.6)
Antibiotics	15,231 (13.3)	1878 (3.2)	2935 (6.3)
Cough and cold medications	26,185 (22.9)	7423 (12.7)	4531 (9.6)
Antihistamines	42,990 (37.6)	43,282 (74.3)	40,746 (86.8)

(Continues)

TABLE 1 (Continued)

	0–5 years (n = 114,378)	6–11 years (n = 58,228)	12–17 years (n = 46,955)
Nasal corticosteroids	4232 (3.7)	16,663 (28.6)	23,113 (49.2)
Antidepressants	<5[b]	108 (0.2)	966 (2.1)
Commonly used oral antibiotics	46,557 (40.7)	10,326 (17.7)	5715 (12.2)
Amoxicillin	15,171 (13.3)	1459 (2.5)	718 (1.5)
Phenoxymethylpenicillin	39,721 (34.7)	9370 (16.1)	5198 (11.1)
Antibiotics for systemic use	21,495 (18.8)	21,641 (37.2)	20,373 (43.4)

Abbreviations: CI, confidence interval; ER, emergency room; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; SABA, short-acting β_2-agonist; SD, standard deviation.

[a] Computed among patients using ICS.

[b] The number of patients was too low to report.

a recommendation to use low-dose ICS with as-needed SABA at step 1. Adoption of updated GINA recommendations in clinical practice may reduce future SABA overuse. However, globally, discordance between local clinical recommendations and those of GINA may hinder progress.

High SABA use may also be ascribed to the reluctance of parents/caregivers of pediatric patients to use ICS,[16] likely due to safety concerns associated with ICS use in children.[32] Approximately three-quarters of 6–11- and 12-17-year-olds collected ICS-containing medication at baseline. Although most patients were at treatment step 2 or 3, 66%–74% of patients across age groups collected only 0–2 canisters annually, indicating considerable ICS underuse. High SABA use may also be a consequence of poor response to ICS medications, particularly among patients with nonatopic disease. Children with eosinophilic airway inflammation, characteristic of atopic asthma, respond better to ICS treatment but not to leukotriene receptor antagonists (LTRAs), while nonatopic children demonstrate a varied response to ICS or LTRA treatment.[33,34]

Our findings align with other studies that have shown an association between SABA overuse and exacerbations in children and adolescents.[23] The SABINA Junior UK study (*manuscript submitted*) also reported that prescriptions of ≥3 SABA canisters/year (vs. 0–2) were associated with higher exacerbation event rates across the three pediatric age groups. A study from the United States (US) demonstrated that children with commercial insurance and those with Medicaid using ≥3 SABA canisters/year (vs. 1–2) were at a greater risk of asthma-related exacerbations requiring hospitalization, ER visits, or OCS treatment.[23] Although the study adopted the same SABA collection threshold, which is typically considered overuse in adults,[18,19] it is unclear what threshold is clinically most relevant for childhood asthma. Notably, stockpiling of SABA canisters at kindergarten/school and at home may be commonly practiced by caregivers of children with asthma. This practice is recommended in the US[35] and UK[36] and is likely common in Sweden. There was some variation in the overuse threshold based on the severity of asthma exacerbations, as well as across age groups, when SABA was examined as a continuous variable. Our findings indicate that for severe exacerbations necessitating hospitalization or ER visits, a higher SABA overuse threshold may be more clinically relevant.

No other studies besides ours and SABINA Junior UK, conducted in parallel, have evaluated the interaction of atopic disease and SABA use on exacerbation risk in children. We observed that although comorbid atopic disease per se puts patients at a greater initial risk of exacerbations in our prediction model, increased SABA canister collection was associated with a greater rate of risk increase in nonatopic (vs. atopic) patients with asthma. Pediatric cohorts have established a link between allergic comorbidity and asthma exacerbations,[8,37] with our findings suggesting that exacerbation risk by SABA collection varies based on atopic phenotype. We hypothesize that pediatric patients with asthma and atopic disease may be monitored carefully by healthcare providers due to a more persistent and overt phenotype.[8,37] Thus, after an asthma exacerbation, they may receive appropriate treatment and remain at lower risk of recurrent episodes. This may be coupled with a poorer response to ICS among children with nonatopic disease.[33,34] Indeed, certain nonatopic asthma phenotypes (e.g., asthma with childhood obesity[38–40]) are often resistant to anti-inflammatory therapies, such as ICS.[41] These patients may therefore receive less anti-inflammatory protection against an exacerbation and may also be more likely to rely on their SABA inhalers, further compounding the problem.

Reducing SABA overuse in children requires the medical community to address the underlying factors contributing to such behavior and provide alternative reliever options to patients.[42] Proper communication, education, and training on correct inhaler technique, and medication adherence are essential to gain the most benefit from maintenance therapies. Studies on anti-inflammatory reliever therapy in pediatric patients with mild asthma, such as the Children's Anti-inflammatory REliever study,[43] are limited. Clinical trials, especially those that investigate the impact of asthma phenotypes such as presence of atopy on treatment and outcomes, are needed to bridge the evidence gap for asthma management in children across age groups and asthma severities.

Our study adds to the limited data on the extent of SABA use, its association with exacerbations, and influence of atopic comorbidities among children with asthma. Owing to the presence of transient phenotypes, results were presented for 1-year follow-up; however, long-term results for 3 years of follow-up demonstrated similar trends. The nationwide reach of this study

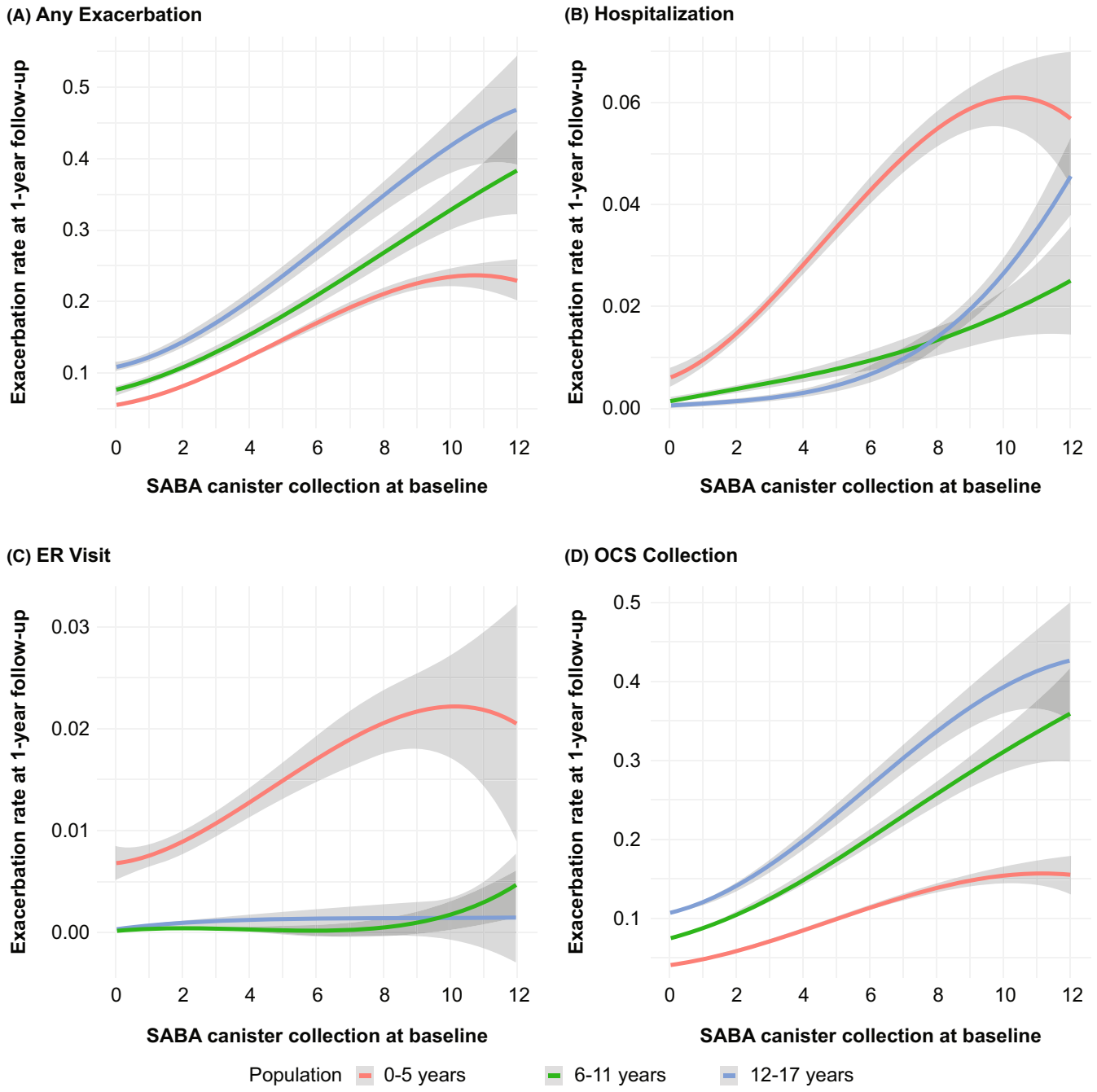

FIGURE 3 Unadjusted exacerbation rate during the first follow-up year by baseline SABA use† among pediatric patients with asthma Smoothed curves derived using cubic B-splines. The scale on the y-axis is different in the four panels. The gray band denotes 95% confidence intervals. ER, emergency room; OCS, oral corticosteroid; SABA, short-acting β_2-agonist. †Continuous variable.

reduces potential selection bias and ensures generalizability of results. Moreover, the validity of the Swedish NPR and Prescribed Drug Register is high for ICD-10 and Anatomical Therapeutic Chemical (ATC) asthma codes.[44]

This study has some limitations. The analysis for children aged 0–5 years was exploratory due to possible misclassification of asthma diagnoses in these children. Further, registry-based data reporting pharmacy collections may not reflect actual medication use, and stockpiling of canisters is a possibility, contributing to potential overestimation of actual SABA use in children. As registers lack clinical data on objective asthma severity measures or lung function, influence from such factors cannot be discounted. Other potential confounders include inhaler technique, second-hand smoke, obesity, and pollutants. The association analysis was not adjusted for ICS medication adherence, which may differ from SABA reliance. However, analyses were adjusted for disease severity using treatment step and prior exacerbations. Atopy was defined solely by the presence of comorbid atopic diseases without using any standardized measures of allergic sensitization to classify atopic and nonatopic asthma. Additionally, only patients in secondary care (with ≥1

TABLE 2 Association of SABA[a] with exacerbations during the first follow-up year among pediatric patients with asthma

	0–5 years (n = 114,378)			6–11 years (n = 58,228)			12–17 years (n = 46,955)		
Baseline SABA canisters	**Number of patients**	**Number of events**	**IRR (95% CI)**	**Number of patients**	**Number of events**	**IRR (95% CI)**	**Number of patients**	**Number of events**	**IRR (95% CI)**
Overall									
0–2	62,427	3750	1.00 (ref)	39,787	3254	1.00 (ref)	34,491	3852	1.00 (ref)
3–5	36,694	3759	1.24 (1.18–1.31)	14,007	1790	1.16 (1.08–1.23)	9417	1657	1.16 (1.08–1.24)
6–10	13,471	2172	1.57 (1.47–1.67)	3911	742	1.31 (1.19–1.43)	2590	707	1.44 (1.30–1.60)
≥11	1786	504	1.86 (1.64–2.12)	523	210	1.89 (1.57–2.26)	457	264	1.98 (1.65–2.38)
0–2	62,427	3750	1.00 (ref)	39,787	3254	1.00 (ref)	34,491	3852	1.00 (ref)
≥3	51,951	6435	1.35 (1.29–1.42)	18,441	2742	1.22 (1.15–1.29)	12,464	2628	1.26 (1.19–1.34)
Continuous	114,378	10,185	1.06 (1.05–1.07)	58,228	5996	1.05 (1.04–1.06)	46,955	6480	1.04 (1.03–1.06)
Atopic									
0–2	12,728	1401	1.00 (ref)	18,573	2414	1.00 (ref)	19,707	2958	1.00 (ref)
3–5	8526	1437	1.17 (1.07–1.27)	7432	1336	1.09 (1.01–1.17)	5780	1266	1.10 (1.02–1.19)
6–10	3383	770	1.24 (1.12–1.38)	2262	580	1.23 (1.11–1.36)	1698	538	1.37 (1.22–1.53)
≥11	461	193	1.72 (1.41–2.09)	334	148	1.52 (1.25–1.85)	307	193	1.83 (1.49–2.23)
0–2	12,728	1401	1.00 (ref)	18,573	2414	1.00 (ref)	19,707	2958	1.00 (ref)
≥3	12,370	2400	1.21 (1.12–1.31)	10,028	2064	1.14 (1.07–1.22)	7785	1997	1.20 (1.12–1.28)
Continuous	25,098	3801	1.04 (1.02–1.05)	28,601	4478	1.03 (1.02–1.05)	27,492	4955	1.04 (1.03–1.05)
Nonatopic									
0–2	49,699	2349	1.00 (ref)	21,214	840	1.00 (ref)	14,784	894	1.00 (ref)
3–5	28,168	2322	1.29 (1.20–1.38)	6575	454	1.24 (1.09–1.42)	3637	391	1.33 (1.15–1.54)
6–10	10,088	1402	1.78 (1.64–1.94)	1649	162	1.39 (1.13–1.70)	892	169	1.60 (1.28–2.00)
≥11	1325	311	1.97 (1.67–2.32)	189	62	2.88 (1.93–4.25)	150	71	2.47 (1.65–3.67)
0–2	49,699	2349	1.00 (ref)	21,214	840	1.00 (ref)	14,784	894	1.00 (ref)
≥3	39,581	4035	1.44 (1.35–1.54)	8413	678	1.32 (1.17–1.49)	4679	631	1.44 (1.27–1.64)
Continuous	89,280	6384	1.07 (1.06–1.08)	29,627	1518	1.07 (1.05–1.09)	19,463	1525	1.06 (1.04–1.08)

Note: Negative binomial regression models were used; all analyses were adjusted for sex, treatment steps, and baseline exacerbation history (any type and categorized as 0, 1, and ≥2 exacerbations).Atopic diseases comprised vasomotor and allergic rhinitis, dermatitis and eczema, and allergies, including those of food and substances other than drugs and biological substances, as classified by respective ICD codes. Nonatopic disease was defined as the absence of atopic diseases.

Abbreviations: CI, confidence interval; ICD, International Statistical Classification of Diseases and Related Health Problems; IRR, incidence rate ratio; ref, reference; SABA, short-acting β_2-agonist.

[a]≥3 canisters versus 0–2 canisters.

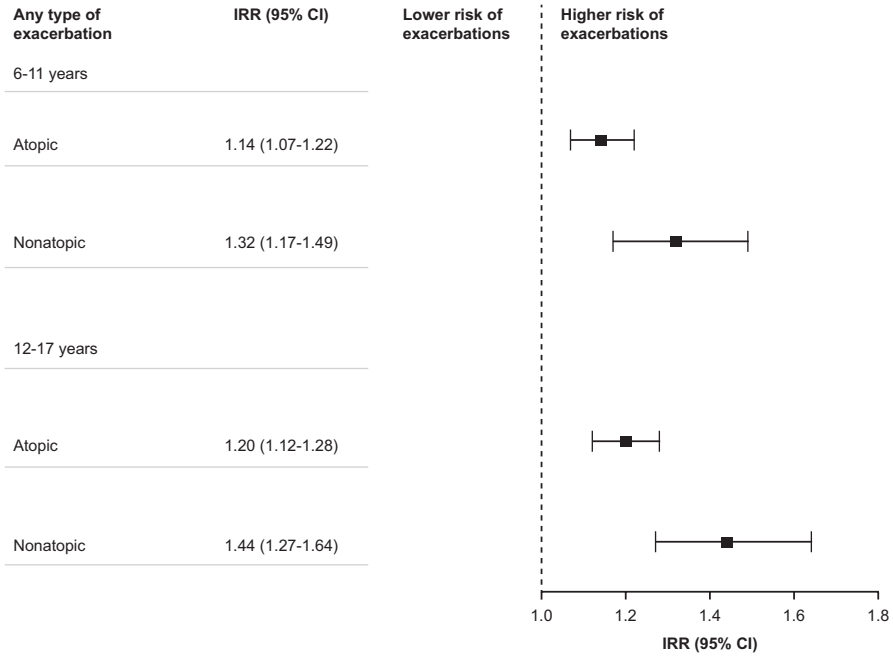

FIGURE 4 Multivariable associations of SABA† with exacerbation rates during the first follow-up year stratified by atopic disease and age group. Negative binomial regression models were used; all analyses were adjusted for sex, treatment steps, and baseline exacerbation history (any type and categorized as 0, 1, and ≥2 exacerbations). Atopic diseases comprised allergic rhinitis, dermatitis and eczema, and allergies, including those of food and substances other than drugs and biological substances, as classified by respective ICD codes. Nonatopic disease was defined as the absence of atopic diseases. CI, confidence interval; ICD, International Statistical Classification of Diseases and Related Health Problems; IRR, incidence rate ratio; SABA short-acting β_2-agonist. † ≥ 3 canisters versus 0–2 canisters.

hospital visit) were included, although prescriptions dispensed from primary care were included.

In conclusion, a large proportion of Swedish children with asthma aged 0–17 years collected ≥3 SABA canisters/year, which was associated with a significant risk of exacerbations and was stronger in children without atopic diseases. These results emphasize the need for educational initiatives targeted at pediatric patients, parents/caregivers, and clinicians, with a principal focus on aligning treatment of childhood asthma with updated global evidence-based treatment recommendations.

AUTHOR CONTRIBUTIONS

Erik Melén: Conceptualization (equal); Formal analysis (supporting); Investigation (lead); Methodology (equal); Resources (equal); Supervision (equal); Visualization (equal); Writing - original draft (equal); Writing - review and editing. **Bright I. Nwaru:** Conceptualization (equal); Investigation (equal); Methodology (equal); Resources (equal); Supervision (equal); Visualization (equal); Writing - original draft (equal); Writing - review and editing. **Fredrik Wiklund:** Conceptualization (equal); Data curation (lead); Formal analysis (lead); Investigation (equal); Methodology (equal); Resources (equal); Software (lead); Supervision (equal); Validation (equal); Visualization (equal); Writing - original draft (equal); Writing - review and editing. **Sofie de Fine Licht:** Conceptualization (equal); Investigation (equal); Methodology (equal); Project Administration (supporting); Resources (equal); Supervision (equal); Validation (equal); Visualization (equal); Writing - original draft (equal); Writing - review and editing. **Gunilla Telg:** Conceptualization (equal); Data curation (lead); Formal analysis (supporting); Funding acquisition (lead); Investigation (equal); Methodology (equal); Project Administration (lead); Resources (equal); Supervision (equal); Validation (equal); Visualization (equal); Writing - original draft (equal); Writing - review and editing. **Ekaterina Maslova:** Conceptualization (equal); Investigation (equal); Methodology (equal); Resources (equal); Supervision (equal); Visualization (equal); Writing - original draft (equal); Writing - review and editing. **Ralf J. P. van der Valk:** Conceptualization (equal); Investigation (equal); Methodology (equal); Resources (equal); Supervision (equal); Visualization (equal); Writing - original draft (equal); Writing - review and editing. **Trung N. Tran:** Conceptualization (equal); Investigation (equal); Methodology (equal); Resources (equal); Supervision (equal); Visualization (equal); Writing - original draft (equal); Writing - review and editing. **Magnus Ekström:** Conceptualization (equal); Investigation (equal); Methodology (equal); Resources (equal); Supervision (equal); Visualization (equal); Writing - original draft (equal); Writing - review and editing. **Christer Janson:** Conceptualization (equal); Investigation (equal); Methodology (equal); Resources (equal); Supervision (equal); Visualization (equal); Writing - original draft (equal); Writing - review and editing.

ACKNOWLEDGEMENTS

Medical writing and editorial support were provided by Michelle Rebello, PhD, and Tejaswini Subbannayya, PhD, of Cactus Life

Sciences (part of Cactus Communications), Mumbai, India, in accordance with the Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3) and funded by AstraZeneca.

FUNDING INFORMATION

This study was funded by AstraZeneca. Dr. Melén is supported by grants from the Swedish Research Council, the Swedish Heart-Lung Foundation, and Region Stockholm (ALF). AstraZeneca funded the SABINA studies and was involved in designing the program, developing the study protocol, conducting the studies, and performing the analyses. AstraZeneca was given the opportunity to review the manuscript before submission.

CONFLICT OF INTEREST

Dr. de Fine Licht, Mrs. Telg, Dr Maslova, Dr. van der Valk, and Dr. Tran are full-time employees of AstraZeneca. Mrs. Telg and Dr. Maslova own shares in AstraZeneca. Dr. van der Valk owns shares in AstraZeneca and GlaxoSmithKline. Dr. Melén has received personal fees from AstraZeneca, Chiesi, Novartis, and Sanofi outside the submitted work. Drs. Nwaru and Ekström report no conflicts of interest relevant to this work. Dr. Janson has received personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline PLC, Novartis, and Teva outside the submitted work. Dr. Wiklund is an employee of Statisticon, of which AstraZeneca is a client. The authors have no other conflicts of interests to declare.

DATA AVALIBILITY STATEMENT

The dataset is still subject to further analyses but will continue to be held and managed by the Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden. Relevant anonymized patient-level data are available on reasonable request from the authors.

ETHICAL APPROVAL

The study protocol was approved by the Stockholm Regional Ethics Committee (registration number: 2017/4:2) and conducted in compliance with the Declaration of Helsinki. In Sweden, patients need not provide consent for use of public register data.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/pai.13885.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Melén E, Nwaru BI, Wiklund F, et al. Short-acting β_2-agonist use and asthma exacerbations in Swedish children: A SABINA Junior study. *Pediatr Allergy Immunol*. 2022;33:e13885. doi: 10.1111/pai.13885