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Complications and Health Care Resource Utilization Associated with Systemic Corticosteroids in Children and Adolescents with Persistent Asthma

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Abstract

BACKGROUND: Limited comparative data are available on the impact of systemic corticosteroid (SCS) use in children and adolescents.

OBJECTIVE: To determine if asthmatic children and adolescents treated with SCS have a higher likelihood of developing complications versus those not receiving SCS and to examine health care resource utilization (HCRU) in this population.

METHODS: A retrospective study of data from children and adolescents with persistent asthma retrieved from the MarketScan database, a large US health claims data set, for the period 2000 to 2017 was performed. Propensity score matching was used to pair patients in the SCS and control cohorts. For complications, SCS subgroups (≥4 or 1-3 annual prescriptions) were compared with asthmatic controls without SCS using logistic regression, and for HCRU, cohorts were compared using negative binomial regression.

RESULTS: A total of 67,081 patients were included (SCS: 23,898; control: 43,183). The odds of having a complication were 2.9 (95% confidence interval [CI], 2.5-3.2; $P < .001$) and 1.6 (95% CI, 1.6-1.7; $P < .001$) times higher in the ≥4 and 1 to 3 SCS groups, respectively, in the first year of follow-up versus controls. For asthma-related hospitalizations, the incidence rate ratio (IRR) was 6.9 (95% CI, 5.6-8.6) and 3.1 (95% CI, 2.8-3.4) times greater in the ≥4 SCS and 1 to 3 SCS groups, respectively, versus controls; for asthma-related emergency department visits, IRR was 5.0

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(95% CI, 4.4-5.6) and 2.9 (95% CI, 2.7-3.0) times greater, respectively, versus controls (all $P <$ .01).

CONCLUSION: Children and adolescents receiving SCS for persistent asthma have an increased risk of developing complications and have greater HCRU in the first year of follow-up versus those without SCS exposure.

Keywords

Adolescents; Children; Complications; Health care resource use; Persistent asthma; Systemic corticosteroids

Asthma is a common chronic condition that affects 8.4% of children in the United States.[1] Despite better understanding and treatment options, and the availability of clear guidelines, poor asthma control is widespread, with up to 58.7% of 6- to 17-year-olds in the United States identified as having asthma experiencing an exacerbation in the previous 12 months.[2] An asthma exacerbation is an acute episode of uncontrolled asthma typically requiring systemic corticosteroid (SCS) burst therapy, emergency department (ED) visit, or hospitalization.[3,4] Although SCS may be effective for treating asthma exacerbations, their use is associated with significant adverse events, including increased susceptibility to infections, and metabolic, bone/growth, gastrointestinal, and cardiovascular complications.[5,6] In addition, the findings of the Childhood Asthma Management Program study, which compared the effects of long-term oral corticosteroid use in 5- to 12-year-olds with asthma, showed that multiple bursts over a sustained period can produce a dose-dependent reduction in bone mineral accretion and an increased risk of osteopenia.[7,8] Although precise estimates vary by age and population, use of SCS among children with asthma is common.[9,10] Previous research estimated that in a general US population of children aged 5 to 17 years with asthma, 8.7% received SCS in 2007 to 2008.[11] Among Medicaid recipients in a later US study, 44.2% of children aged 1 to 17 years received SCS during the 2011 to 2015 period.[9] Outside of the United States, a retrospective Dutch database study showed that the probability of a child aged 4 to 12 years with asthma receiving another SCS prescription shortly after their first or second prescription was 38.5% and 47.5%, respectively.[10]

Previous research has shown that ≥4 SCS prescriptions per year can result in significant, long-lasting complications in adults with asthma, including osteoporosis, hypertension, obesity, type 2 diabetes, gastrointestinal ulcers/bleeds, fractures, and cataracts.[12] Receiving 4 or more SCS prescriptions per year (vs <4) has been shown to be associated with increased asthma burden, comorbidities, health care costs,[13] disease exacerbation, and future chronic SCS use,[14] as well as decreased health-related quality of life.[15]

It is unclear if this noted relationship between ≥4 SCS prescriptions and deleterious complications in adults holds true for children; indeed, there are limited studies in general on the association between SCS use and complications among children. Studying complications of SCS use in children is both unique and challenging; many complications (eg, osteoporosis,[16] diabetes[17,18]) have a low prevalence among children and take years of exposure to develop. In a recent systematic literature review, long-term SCS use in

children and adolescents was most commonly related to weight gain, growth retardation, Cushingoid features, behavioral changes, and infection.[19] However, this wide-ranging review consolidated evidence of the association between complications and SCS from disparate sources and covered a number of chronic diseases, only one of which was asthma.

An improved understanding of complications associated with SCS use among asthmatic children and adolescents is needed to optimize patient safety and treatment management. On the basis of previous research documenting increased odds of complications in asthmatic adults receiving ≥4 SCS prescriptions per year,[12] we hypothesized that children and adolescents with persistent asthma receiving ≥4 SCS prescriptions within 1 year would have a higher likelihood of developing SCS-related complications than those with persistent asthma not taking SCS. In this retrospective, comparative cohort study, we also explore health care resource utilization (HCRU) to understand whether SCS-related complications make both asthma and nonasthma treatment more complicated, leading to increased HCRU.

METHODS

Study design

This was a retrospective, comparative cohort analysis of data retrieved from a large US health claims data set, MarketScan Claims Database, which included commercial claims. The study period spanned January 1, 2000, to December 31, 2017 (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). Study population selection criteria, including age range (≥2 and <18 years at index date), are provided in Table I. MarketScan is a publicly available database that can be purchased for approved health research. It is not nationally representative, but it has been shown to broadly reflect the commercially insured population in the United States.

Cohort assignment and determination of index date

Patients were assigned to 2 main cohorts according to any SCS use or no SCS use (control cohort). In the SCS cohort, the index date was defined as the first prescription for SCS in the study period. The study period spanned January 1, 2000, to December 31, 2017, with the index date selected from January 1, 2001, to December 31, 2015. Patients in the SCS cohort were required to meet the Healthcare Effectiveness Data and Information Set (HEDIS) criteria 1 year before and 1 year after their index date, and could not have any prescriptions for SCS for at least 1 year before the index date. In the control cohort, index date was defined as the first HEDIS event in HEDIS year 2; a HEDIS event was considered any visit or dispensing event as detailed in the above inclusion criteria. The index date for the control cohort was selected from January 1, 2001, to December 31, 2015. Although the data set spanned 15 years, each individual patient was only required to have a minimum of 2 years of data capture. Control patients were required to have no SCS prescriptions in any data captured for them regardless of their individual length of follow-up.

Data collection

Complications presumed to have a clinical association with SCS among the patients studied, based on the consensus of the physician authors, were analyzed. See Table E1 (available

in this article's Online Repository at www.jaci-inpractice.org) for the full list, including International Classification of Disease codes (ICD-9 and ICD-10). The baseline period was defined as the 1-year period before the index date and follow-up period defined as the 1-year period after the index date. Characteristics evaluated at baseline included age, gender, region of the United States, health insurance type, years of follow-up, number of chronic conditions, and use (<7 or ≥7 canisters) of short-acting β-agonists (SABA) per patient. In addition, HCRU, such as asthma-related and all-cause (ED, inpatient [IP], and outpatient [OP]) visits, and number of prescriptions were assessed. The number of chronic conditions for each patient was calculated as the total number of ICD-9 or ICD-10 codes (excluding asthma and the conditions in Table E2, available in this article's Online Repository at www.jaci-inpractice.org) reported in the claims data in the baseline year. SCS use was categorized into 3 cohorts: ≥4 annual prescriptions, 1 to 3 annual prescriptions, and no prescriptions (control cohort).

Outcomes

The odds of occurrence of any complication in children and adolescents with persistent asthma treated with SCS during the follow-up period were determined. Incidence rate ratios (IRRs) for asthma-related and all-cause ED, IP, and OP visits during the follow-up period were also assessed.

Statistical analysis

Patients with asthma who take SCS may be more likely to have severe or ill-controlled asthma than those with asthma not taking such medication.[22] If patients' disease is more severe, they may experience greater disease exacerbation and, as a result, use more SCS and be at a greater risk of experiencing complications.[14,22] In recognition of this, and with the aim of achieving internal validity and minimizing selection bias, propensity score matching was employed. By matching baseline clinical and demographic variables, patients in the SCS cohort were paired with patients in the control cohort. Variables used for matching included age, gender, Charlson Comorbidity Index (excluding asthma), β-agonist use during baseline (<7 or ≥7 canisters in 1 year), calendar index year (to control for potential variations in treatment or epidemiology over time), duration (years) of follow-up, and the following indicator variables: asthma-related ED visit or hospitalization during baseline (any ED or IP visit with ICD diagnosis of asthma during baseline) and quartiles of total health care expenditures.

The study implemented k-nearest-neighbor matching, using a logit model to estimate propensity scores. The number of neighbors (k) used to calculate the matched outcome was set to 100, and the frequency with which the observation was used as a match was saved into a weight variable. With this approach each patient in the SCS cohort had a normalized weight equal to 1 and patients in the control cohort were assigned weights based on the frequencies of being used in the matching. Calculated weights ranged from 0.01 to 7.64, and the weighted number of control patients was the same as the number of patients in the SCS cohort. A higher weight was associated with a higher frequency of being used as a match, indicating greater "similarity" of control to patients in the SCS cohort. In the analysis reported here, weights generated from k-nearest-neighbor matching were used as probability

weights, and corresponding methods and techniques of weighted analysis were used for all unadjusted and adjusted results.

For the incidence of any complications (as detailed above), a random-effects logistic regression model (with fixed-time effects) was used to compare the SCS subgroups (≥4 or 1-3 annual SCS prescriptions) with the control cohort, controlling for the number of chronic conditions (noncomplications), age, gender, region, urban Metropolitan Statistical Area (MSA), type of health insurance, and years of follow-up. For HCRU, random-effects (fixed-time effects) analysis using negative binomial regression was employed. Random-effects regression was used to compare incidence rate of event for the SCS subgroups (≥4 or 1-3 annual prescriptions) with the control cohort, controlling for the number of chronic conditions (noncomplications), age, gender, region, urban MSA, type of health insurance, and years of follow-up. Odds ratios (ORs), IRRs, and 95% confidence intervals (CIs) are reported. Statistical analysis was conducted using STATA/MP 15.1 (StataCorp LLC, College Station, Texas). Propensity matching was carried out using the "PSMATCH2" Stata module.[23]

RESULTS

Study population

Data for 54,510,816 individual patients were obtained from the MarketScan database for the 2000 to 2017 period. After applying inclusion and exclusion criteria, 67,081 individuals were included in the study. After cohort assignment, there were 23,898 in the SCS cohort and 43,183 in the control cohort (see Figure E2 in this article's Online Repository at http://www.jaci-inpractice.org/). Unadjusted baseline demographic data for the study population in the 1-year baseline period and data for the control group postmatching are presented in Table II. The weighted cohort was used in the full analysis. As intended after weighted adjustment, there was no statistically significant difference between the SCS and control cohorts in age, gender, total duration of follow-up, and some types of insurance (Table II). In both cohorts, approximately two-thirds of patients were male, mean age was 7.7 years, mean total duration of follow-up was 4 years, and over a fifth of patients had 3 years' follow-up. There were statistically significant differences between the SCS and control cohorts in geographic region, MSA, some types of insurance, and some years of follow-up after the weighted adjustment.

Baseline HCRU

Unadjusted baseline HCRU results in the 1-year baseline period are presented for both cohorts in Table III, along with propensity-weighted data for the control group. HCRU was similar across the SCS and weighted control groups, but some differences persisted. Both groups were mostly balanced based on the variables used in the propensity score adjustment. The SCS and weighted control group were not statistically significantly different across asthma-related ED or IP visits (combined), number of chronic comorbidities, and quartiles of total health care expenditures. The proportion of patients receiving ≥7 canisters of SABA was statistically significantly different between the 2 groups (5.7% vs 5.2%; $P = .01$), but the magnitude was similar. The proportion of patients with all-cause ED visits was significantly

higher in the SCS group compared with the preweighted control group (22.9% vs 12.2%; $P < .001$).

SCS-associated complications during the first year of follow-up

Patients with ≥4 SCS or 1 to 3 SCS prescriptions per year were more likely to experience a complication compared with those with no SCS exposure. The proportion of patients experiencing any complication in the first year of follow-up was 62.7% and 42.8% in the ≥4 and 1 to 3 SCS prescription groups, respectively, versus 32.8% for the control group ($P < .001$ for both comparisons). Patients with ≥4 SCS annual prescriptions had 2.9 (95% CI, 2.5-3.2; $P < .001$) and those with 1 to 3 SCS annual prescriptions had 1.6 (95% CI, 1.6-1.7; $P < .001$) times higher odds of developing a complication in the first year of follow-up compared with patients with no SCS exposure (Figure 1; Table E3, available in this article's Online Repository at www.jaci-inpractice.org). For each year of SCS exposure before the year in which the complication occurred, the odds of developing a complication in the current year were slightly, but significantly, elevated (OR, 1.04; 95% CI, 1.0-1.1; $P < .001$) in patients with SCS use versus controls.

Persistent asthma treated with SCS associated with high HCRU during the first year of follow-up

Asthma-related HCRU was greater in patients with ≥4 SCS and 1 to 3 SCS annual prescriptions versus those with no SCS prescriptions. The percentage of patients with ≥1 asthma-related IP admission in the first year of follow-up was 9.8% and 2.4% in patients with ≥4 SCS and 1 to 3 SCS annual prescriptions, respectively, compared with 1.5% in patients with no SCS prescription ($P < .001$ for both comparisons, Table IV). In the ≥4 SCS and 1 to 3 SCS groups, 26.1% and 12.2% of patients had an asthma-related ED visit, respectively, compared with 6.2% in the control group ($P < .001$ for both). A greater percentage of patients in both SCS groups had an all-cause ED visit compared with controls (38.5% and 23.3% in the ≥4 SCS and 1-3 SCS groups, respectively, vs 15.2% in the control group; $P < .001$ for both comparisons). Regression analysis (Figure 2; Table E4, available in this article's Online Repository at www.jaci-inpractice.org) of HCRU data showed that the number of asthma-related IP admissions was 6.9 (95% CI, 5.6-8.6) times and 3.1 (95% CI, 2.8-3.4) times greater for patients in the ≥4 SCS and 1 to 3 SCS groups, respectively, compared with the number of admissions for patients with no SCS exposure ($P < .01$ for both); the estimated IRR of having an asthma-related ED visit was 5.0 (95% CI, 4.4-5.6) and 2.9 (95% CI, 2.7-3.0) times greater, respectively, compared with no SCS use ($P < .01$ for both).

DISCUSSION

Persistent asthma treated with SCS associated with complications

Data analyzed from more than 65,000 children and adolescents with persistent asthma show that SCS exposure was associated with higher odds of developing a complication in the first year of follow-up, with children and adolescents having 2.9 or 1.6 times higher the odds of developing a complication if receiving ≥4 or 1 to 3 SCS prescriptions per year, respectively. The results demonstrate that even a few annual SCS prescriptions significantly

increase risk of complication development and show that SCS exposure in previous years is associated with a small but statistically significant (OR, 1.04; $P < .001$) increase in the odds of incurring a complication. The results also show that the number of asthma-related hospitalizations and asthma-related ED visits were 6.9 and 5.0 times greater, respectively, in patients with persistent asthma receiving ≥4 annual prescriptions than in those with no SCS exposure.

Previous research has shown that SCS use is associated with complications in adults,[24,25] but few studies exist in children. On the basis of 2 systematic literature reviews, Aljebab et al[6,19] found evidence of complications associated with short- and long-term use of SCS among children. However, these 2 studies were literature reviews of disparate publications across a number of diseases (eg, renal failure and leukemia), and many of the included studies were designed to examine a specific type of complication (eg, hypothalamic-pituitary-adrenal axis suppression or growth).[6,19]

Analysis of SCS exposure

Our study adds to the literature on complications associated with SCS use among children and adolescents in several novel ways. The analysis measured SCS exposure as the total number of SCS prescriptions within the year, enabling comparison of complications in patients who received as few as 1 to 3 or ≥4 prescriptions per year with patients with no SCS exposure. The justification for using ≥4 SCS prescriptions per year as the principal measure of exposure was based on previously published evidence in asthmatic adults.[12] Because SCS prescription dosages are adjusted for weight and age, it was hypothesized that using the number of SCS prescriptions within 1 year as the measure of exposure would still be a relevant measure of exposure for children. This measure of SCS exposure could reflect short-term burst therapy for patients with exacerbations. It is common to focus on long-term and chronic SCS exposure because it is associated with the highest odds of complications.[26–28] However, examining 1 to 3 and ≥4 prescriptions per year may be more consistent with actual prescribing patterns for many children and adolescents with asthma. There are numerous other ways to measure SCS exposure that may provide meaningful results and would be beneficial in future studies. For example, the average SCS daily dose, cumulative annual SCS dose, and number of days of exposure could all provide further insight. These alternatives are beyond the scope of this article and were not considered in the analytic approach.

Other novel aspects of our study are the inclusion of only children and adolescents with HEDIS-defined persistent asthma, and the assessment of the association between SCS use and complications within the same year. Our findings suggest that children and adolescents exposed to as few as 1 to 3 SCS annual prescriptions experience complications within the current year; this outcome is particularly problematic for this age group considering the potential number of years of future SCS exposure over their lifetimes.

Given the large proportion of children with asthma who experience exacerbations and the prevalence of SCS use to treat them,[2,9,10,29] studies designed to assess potential complications associated with SCS exposure are urgently needed. SCS use is commonly measured as an outcome of treatment that suggests inadequate control and greater disease

severity. For example, the UK's National Institute for Clinical and Health Research requires receipt of 4 SCS prescriptions within 1 year before authorization for certain asthma biologic medications for patients more than 6 years of age.[30] Our results provide one approach to studying the potential complications of using SCS with a specific measure of exposure (number of prescriptions in the current year, with particular focus on ≥4). Future studies of other measures of SCS exposure (eg, cumulative annual dose) and durations of exposure (eg, several years of cumulative exposure) are needed to augment our understanding.

Persistent asthma treated with SCS associated with high HCRU

A secondary objective of our study was to examine HCRU among children and adolescents with asthma receiving SCS, based on the hypothesis that SCS-related complications make both asthma and nonasthma treatment more complicated, resulting in increased HCRU. For example, if a child is persistently vomiting because of SCS use (a common adverse drug reaction[6]), it is possible that this episode would require a physician visit, antiemetic medication, and potentially an ED visit to manage dehydration. In addition, if the child was treated with SCS for an asthma exacerbation, the inability to tolerate the SCS may complicate treatment of the exacerbation. All of these factors may contribute to increased HCRU.

Previous research has found that patients with significant exposure to SCS who developed possible SCS-related side effects were more likely to use health care services than those without such side effects.[31] Barry et al[32] showed that patients ≥12 years old with asthma who received SCS incurred significantly higher health care expenditures attributable to steroid-induced morbidity compared with patients with no steroid exposure. Our results are consistent with this hypothesis and previous literature showing a significant increase in both asthma-related and all-cause OP, IP, and ED visits as well as prescriptions.[5,26,27,31] However, an important caveat is that children and adolescents with asthma who need SCS are by definition in greater need of HCRU than those who do not need SCS. Our study design attempted to mitigate these differences across study groups through using weighted propensity score matching. Despite potential mitigation of this bias by the study design, it is not certain how much of the increase in HCRU is driven by SCS-associated complications versus inherent differences in the cohorts.

Study limitations

Although it would be intractable to conduct a randomized controlled trial to test the current hypothesis, our study design is not without limitations. The biggest challenge in conducting an observational study is that patients with asthma who take SCS may be inherently different from those who do not take any. In addition, those who take ≥4 SCS prescriptions may have inherent differences compared with those who take 1 to 3 SCS. For example, patients receiving SCS are more likely to have severe or ill-controlled asthma than those with asthma who do not receive SCS.[14,22] If patients' disease is more severe, they may experience greater disease exacerbation and, as a result, use more SCS and be at greater risk of experiencing complications.[5,24–28,33,34] Furthermore, patients with more severe asthma may be sicker or have more comorbidities associated with SCS-related complications. To control for this potential difference, we used measures that reflect asthma control and severity as well as

general health to match the SCS cohort with the control cohort through the propensity score matching. As is clear from the lack of baseline differences between groups, this method may have mitigated the observed differences between groups; however, there is potential for unobserved differences that may persist. It is possible that these differences were not completely eradicated and that some or all of the results reflect inherent differences between the cohorts rather than direct exposure to SCS. In addition, the propensity score weighting did not attempt to mitigate differences between treatment groups within the SCS cohort. As a result, the conclusions drawn with respect to differences between the group taking ≥4 SCS prescriptions and the group taking 1 to 3 SCS prescriptions may be limited. The overall approach to mitigating the potential selection bias in the analysis is only 1 of many possible methods. Other methods or sensitivity analyses could have been undertaken to examine the extent of the sensitivity of the conclusions to the propensity score weighting approach. This is a further limitation of our research, and results should be interpreted with appropriate caution. In addition, as discussed above, there are other means of measuring exposure that were not considered in this research (eg, continuous exposure, cumulative annual dose, etc.). Furthermore, there could be time-dependent relationships that we did not explore in this research.

Additional potential limitations should be considered when interpreting the reported results. Sample size limitations among children and adolescents precluded more comprehensive analyses of specific conditions or groupings. It is challenging to find a large enough sample to observe SCS use over time among children. In addition, many of the complications may take years or even decades to develop. For example, there were only 3 individuals with a diagnostic code for obesity who met the criteria of having ≥4 SCS prescriptions in the follow-up (and only n = 1 with dyslipidemia). The inability to have sufficient sample power to analyze individual conditions or groups of conditions is a limitation of our research. However, when combined as a single endpoint including all complications, there was adequate sample size for the main analysis. Likewise, the OR of 1.04 for previous years' SCS exposure may be statistically significant but may not be clinically relevant. The study design attempted to ensure that the control group had no exposure to SCS, and eligibility criteria dictated that patients in the SCS groups were not permitted to have received any prescriptions for SCS for at least 1 year before the index date. It is, however, possible that patients in the control group had exposure to SCS before the baseline year and that those in the SCS groups had SCS exposure before the 1-year preindex period.

As the study was based on insurance claims data, adherence to prescribed treatments was not known. It is possible that a patient received 4 prescriptions in the year but only took 2. The effect of this bias would be to reduce the odds of complications associated with SCS compared with reality. In addition, the reporting of SCS-associated complications may vary within the age range studied. For example, a 2-year-old child may be taken to the physician or ED by a concerned parent on the same day that symptoms develop, but a 17-year-old teenager may be less likely to communicate his or her symptoms or promptly seek care. The study did not assess asthma disease severity as this was not available from the claims data, although asthma-related hospitalization or ED visit, which may be seen as a proxy for disease severity, was included in the propensity score calculation. As a study of patients in the United States with commercial insurance, treatment use for patients with government

insurance, such as Medicaid, is not represented and study findings may not reflect patterns in other countries or alternative health care systems. It is also acknowledged that individuals with state or no insurance may show different trends in health care access, quality of care, disease severity, and prescription uptake[35–37]; such characteristics would not have been captured in our study.

CONCLUSION

The results reported here show that children and adolescents who are exposed to even a few SCS prescriptions within a year have an increased risk of developing complications, with deleterious effects seen even with short-term use. This study highlights the need to be considerate of adverse effects of SCS prescriptions, as well as the greater HCRU in children and adolescents with persistent asthma treated with SCS. The study also demonstrates the need to optimize disease management of asthma, through both seeking the causes of inadequate disease control and reducing the need for SCS use by exploring SCS—sparing treatment approaches.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of interest:

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Abbreviations used

CI	Confidence interval
ED	Emergency department
HCRU	Health care resource utilization
HEDIS	Healthcare Effectiveness Data and Information Set

ICD	International Classification of Disease
IP	Inpatient
IRR	Incidence rate ratio
MSA	Metropolitan statistical area
OP	Outpatient
OR	Odds ratio
SABA	Short-acting β-agonist
SCS	Systemic corticosteroid

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What is already known about this topic?

A clear association exists between systemic corticosteroid use and complications in individuals with asthma ≥18 years of age, but this association in asthmatic children and adolescents under 18 years is less well explored.

What does the article add to our knowledge?

Children and adolescents who receive as few as 1 to 3 systemic corticosteroid prescriptions per year have an increased risk of developing corticosteroid-related complications.

How does this study impact current management guidelines?

Optimal management of persistent asthma in children and adolescents should aim to reduce the need for systemic corticosteroids, in recognition of the associated potential for complications.

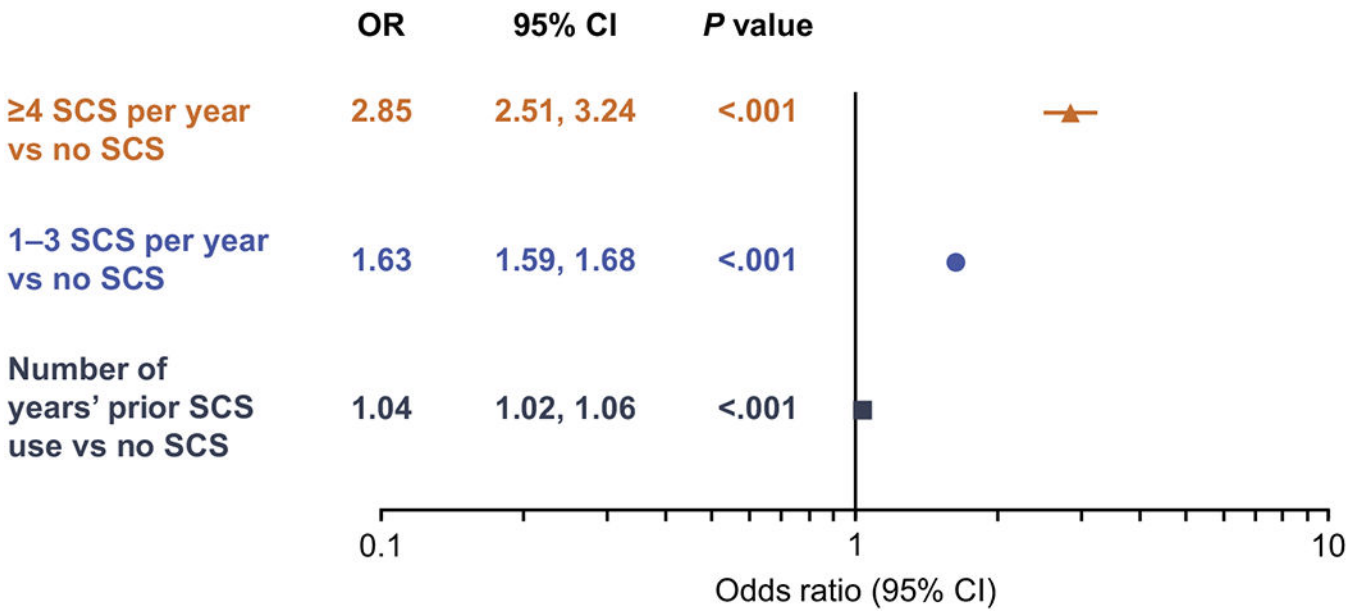

FIGURE 1.

Odds ratios of complications associated with SCS use in children and adolescents with persistent asthma. Data presented based on random-effects (fixed-time effects) regression controlled for the number of chronic conditions (noncomplications) age, gender, region, type of health insurance, urban Metropolitan Statistical Area, and years of follow-up. *CI*, Confidence interval; *OR*, odds ratio; *SCS*, systemic corticosteroids.

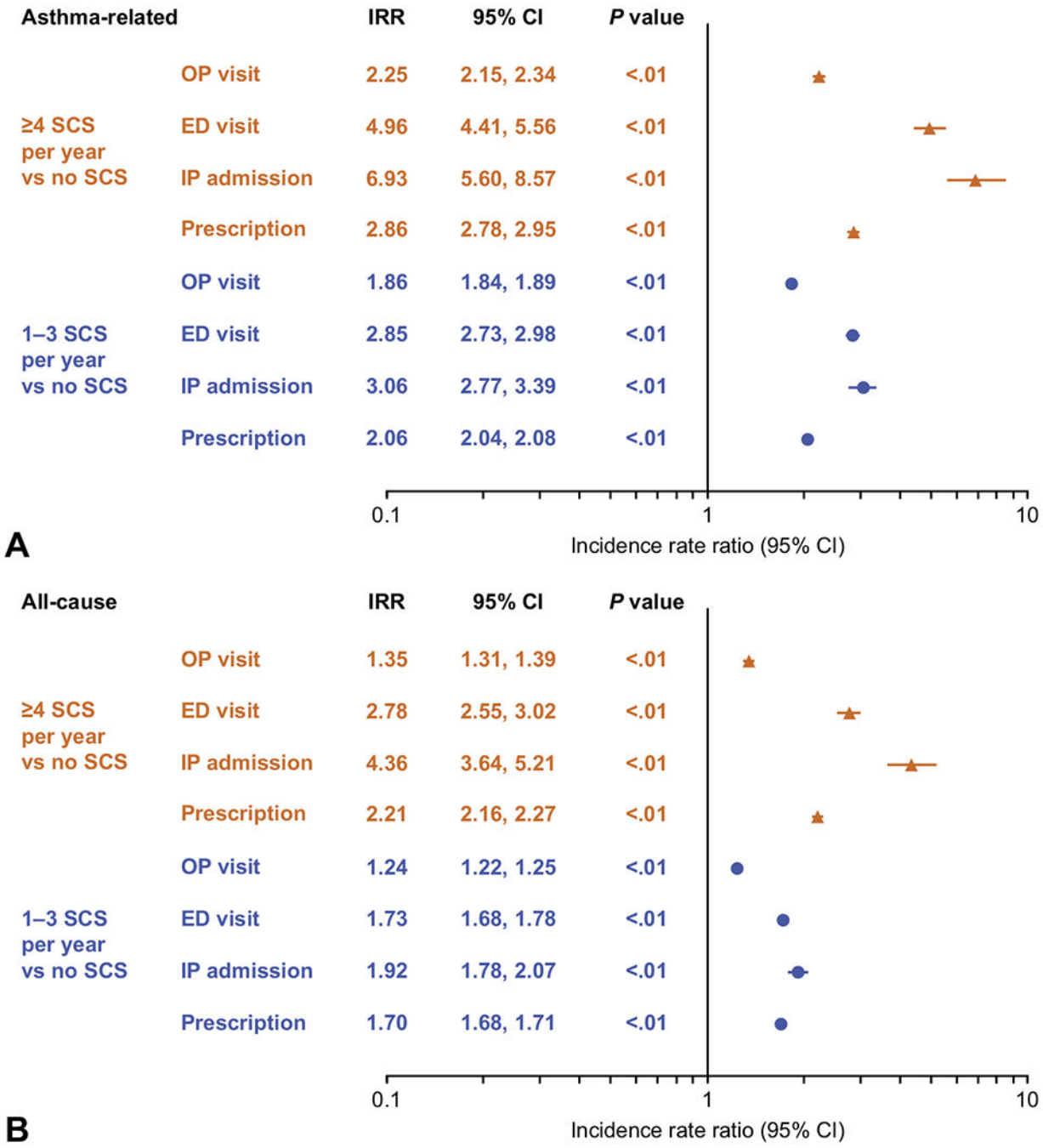

FIGURE 2.

Incidence rate ratios of (**A**) asthma-related and (**B**) all-cause HCRU associated with SCS use in children and adolescents with persistent asthma. Data presented based on random-effects (fixed-time effects) negative binomial regression controlled for the number of chronic conditions (noncomplications), age, gender, region, urban Metropolitan Statistical Area, type of health insurance, and years of follow-up. *CI*, Confidence interval; *ED*, emergency

department; *HCRU*, health care resource utilization; *IP*, inpatient; *IRR*, incidence rate ratio; *OP*, outpatient; *SCS*, systemic corticosteroids.

TABLE I.

Study population selection criteria

Inclusion criteria
• Age ≥2 and <18 years at index date
• Children and adolescents with diagnosis of "persistent" asthma defined by HEDIS[20,21]
– For those aged 5 to <18 years, at least 1 of the following during both the measurement year and the year before (ie, 2 consecutive years):
○ ≥1 emergency department visit with asthma as the principal diagnosis, or
○ ≥1 inpatient visit (hospitalization) for asthma as the principal diagnosis, or
○ ≥4 outpatient asthma-related visits with asthma as 1 of the listed diagnoses, and ≥2 asthma medication dispensing events,[*] or
○ ≥4 asthma medication dispensing events[*]
– For those aged ≥2 to <5 years, the above HEDIS criteria had to be met but a diagnosis of asthma or "wheeze" was permitted
• Continuous enrollment for 3 years minimum, to allow ≥1 year before and ≥2 years after index date
Exclusion criteria
• Any diagnosis of COPD, chronic bronchitis, emphysema, or cystic fibrosis at any time
• Crohn's disease, ulcerative colitis, autoimmune hepatitis, rheumatoid arthritis, or any of the diseases[†] for which SCS are used in the 1-year preindex (baseline) period[‡]

COPD, Chronic obstructive pulmonary disease; *HEDIS*, Healthcare Effectiveness Data and Information Set; *SCS*, systemic corticosteroids.

[*] Examples of individual dispensing events include a supply of asthma medication for ≤30 days, inhalers of the same medication dispensed on the same day, or an injection of asthma medication.

[†] Full list of diseases excluded are listed in Table E2 (available in this article's Online Repository at www.jaci-inpractice.org).

[‡] To avoid including patients using SCS for other conditions (not asthma).

TABLE II.

Patient demographics in the 1-year preindex (baseline) period

	Pre-weighted							Weighted			
Demographics	**≥4 SCS* N = 986**	***P* value vs controls**	**1-3 SCS† N = 22,912**	***P* value vs controls**	**All SCS users N = 23,898**	**All controls N = 43,183**	***P* value**	**All controls N = 23,898**	***P* value vs all SCS users**	***P* value ≥4 SCS vs controls**	***P* value 1-3 SCS vs controls**
Age											
Age (y), mean ± SD	6.8 ± 4.3	<.001	7.8 ± 4.2	<.001	7.7 ± 4.2	8.5 ± 4.2	<.001	7.7 ± 4.2	>.99	<.001	.24
Age 2-11 y, n (%)	818 (83.0)	<.001	17,792 (77.7)	<.001	18,610 (77.9)	31,651 (73.3)	<.001	18,824 (78.8)	.005	<.001	.001
Age 12 to <18 y, n(%)	168 (17.0)	<.001	5120 (22.3)	<.001	5288 (22.1)	11,532 (26.7)	<.001	5074 (21.2)	.005	<.001	.001
Sex, n (%)											
Male	576 (58.4)	.80	14,030 (61.2)	<.001	14,606 (61.1)	25,399 (58.8)	<.001	14,661 (61.3)	.54	.01	.76
Female	410 (41.6)	.80	8882 (38.8)	<.001	9292 (38.9)	17,784 (41.2)	<.001	9237 (38.7)	.54	.01	.76
Geographic region, n (%)											
Northeast	136 (13.8)	<.001	3572 (15.6)	<.001	3708 (15.5)	8228 (19.1)	<.001	4713 (19.7)	<.001	<.001	<.001
North Central	248 (25.2)	.11	5415 (23.6)	.05	5663 (23.7)	9916 (23.0)	.03	5321 (22.3)	<.001	.01	<.001
South	455 (46.1)	<.001	9636 (42.1)	<.001	10,091 (42.2)	15,275 (35.4)	<.001	8522 (35.7)	<.001	<.001	<.001
West	130 (13.2)	<.001	3966 (17.3)	<.001	4096 (17.1)	9042 (20.9)	<.001	4940 (20.7)	<.001	<.001	<.001
Unknown	17 (1.7)	.90	323 (1.4)	.01	340 (1.4)	722 (1.7)	.01	402 (1.7)	.006	.90	.004
Rural residence indicator, n (%)											
MSA	835 (84.7)	.25	19,395 (84.6)	<.001	20,230 (84.7)	37,127 (86.0)	<.001	20,578 (86.1)	<.001	.09	<.001
Non-MSA	134 (13.6)	.19	3176 (13.9)	<.001	3310 (13.9)	5277 (12.2)	<.001	2898 (12.1)	<.001	.07	<.001
Unknown	17 (1.7)	.85	341 (1.5)	.003	358 (1.5)	779 (1.8)	.003	422 (1.8)	.006	.90	.01
Chronic conditions											

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Demographics	Pre-weighted							Weighted			
	≥4 SCS* N = 986	*P* value vs controls	1-3 SCS† N = 22,912	*P* value vs controls	All SCS users N = 23,898	All controls N = 43,183	*P* value	All controls N = 23,898	*P* value vs all SCS users	*P* value ≥4 SCS vs controls	*P* value 1-3 SCS vs controls
Total number of chronic conditions, mean ± SD	2.1 ± 1.9	<.001	1.6 ± 1.6	<.001	1.7 ± 1.7	1.4 ± 1.5	<.001	1.7 ± 1.7	.63	<.001	.36
Insurance plan type, n (%)											
Health Maintenance Organization	144 (14.6)	.007	4253 (18.6)	.04	4397 (18.4)	7737 (17.9)	.12	4130 (17.3)	<.001	.004	<.001
Preferred Provider Organization	582 (59.0)	.50	13,214 (57.7)	.48	13,796 (57.7)	25,028 (58.0)	.56	14,011 (58.6)	.02	.74	.013
Other plan types‡	260 (26.4)	.10	5445 (23.8)	.30	5705 (23.9)	10,418 (24.1)	.46	5757 (24.1)	.51	.03	.33
Years of follow-up, n(%)											
2	366 (37.1)	.57	7595 (33.1)	<.001	7961 (33.3)	15,646 (36.2)	<.001	8196 (34.3)	.007	.02	.002
3	204 (20.7)	.18	5054 (22.1)	.19	5258 (22.0)	9719 (22.5)	.13	5129 (21.5)	.09	.44	.06
4	131 (13.3)	.94	3208 (14.0)	.02	3339 (14.0)	5774 (13.4)	.03	3205 (13.4)	.03	.88	.03
5	108 (11.0)	.83	2468 (10.8)	.88	2576 (10.8)	4635 (10.7)	.85	2711 (11.3)	.02	.61	.02
6	49 (5.0)	.80	1290 (5.6)	.01	1339 (5.6)	2224 (5.2)	.01	1281 (5.4)	.17	.47	.13
7	32 (3.2)	.31	915 (4.0)	.46	947 (4.0)	1674 (3.9	.58	1052 (4.4)	.004	.02	.01
8	25 (2.5)	.80	797 (3.5)	<.001	822 (3.4)	1151 (2.7)	<.001	700 (2.9)	<.001	.34	<.001
9	26 (2.6)	.14	543 (2.4)	<.001	569 (2.4)	850 (2.0)	<.001	564 (2.4)	.87	.46	.94
10	19 (1.9)	.09	378 (1.6)	<.001	397 (1.7)	561 (1.3)	<.001	368 (1.5)	.21	.20	.26
11	9 (0.9)	.67	295 (1.3)	.01	304 (1.3)	455 (1.1)	.01	317 (1.3)	.53	.14	.66
Duration of follow-up											

Demographics	Pre-weighted							Weighted			
	≥4 SCS* N = 986	*P* value vs controls	1-3 SCS† N = 22,912	*P* value vs controls	All SCS users N = 23,898	All controls N = 43,183	*P* value	All controls N = 23,898	*P* value vs all SCS users	*P* value ≥4 SCS vs controls	*P* value 1-3 SCS vs controls
Total duration of follow-up (y), mean ± SD	3.9 ± 2.4	.22	4.0 ± 2.4	<.001	4.0 ± 2.4	3.8 ± 2.3	<.001	4.0 ± 2.4	.09	.14	.05

MSA, Metropolitan statistical area; *SCS*, systemic corticosteroids; *SD*, standard deviation.

*Patient demographics in the 1-year preindex (baseline) period reported for patients with ≥4 SCS prescriptions during year 1.

†Patient demographics in the 1-year preindex (baseline) period reported for patients with 1-3 SCS prescriptions during year 1.

‡Includes Consumer-driven Health Plan, Exclusive Provider Organization, High-deductible Health Plan, and Point-of-Service.

J Allergy Clin Immunol Pract. Author manuscript; available in PMC 2022 April 01.

TABLE III.

Health care resource utilization in the 1-year pre-index (baseline) period

	Pre-weighted			Weighted	
Health care resource	**All SCS users N = 23,898**	**All controls N = 43,183**	***P* value**	**All controls N = 23,898**	***P* value**
≥1 asthma-related IP or ED visit, n (%)	4079 (17.1)	1789 (4.1)	<.001	4061 (17.0)	.80
≥1 non–asthma-related IP or ED visit, n (%)	3279 (13.7)	4314 (10.0)	<.001	3247 (13.6)	.62
≥1 all-cause IP admission, n (%)	1376 (5.8)	635 (1.5)	<.001	1084 (4.5)	<.001
≥1 asthma-related IP admission, n (%)	1142 (4.8)	289 (0.7)	<.001	799 (3.3)	<.001
≥1 non–asthma-related IP admission, n (%)	279 (1.2)	368 (0.9)	<.001	342 (1.4)	.002
All-cause IP admissions, mean ± SD	0.07 ± 0.45	0.02 ± 0.20	<.001	0.06 ± 0.35	<.001
Asthma-related IP admissions, mean ± SD	0.05 ± 0.26	0.01 ± 0.12	<.001	0.04 ± 0.27	<.001
Non–asthma-related IP admissions, mean ± SD	0.02 ± 0.37	0.01 ± 0.16	0.006	0.02 ± 0.21	.334
Length of stay per all-cause admission (d), mean ± SD	0.13 ± 0.74	0.04 ± 0.55	<.001	0.11 ± 0.81	<.001
Length of stay per asthma-related admission (d), mean ± SD	0.05 ± 0.21	0.01 ± 0.08	<.001	0.03 ± 0.18	<.001
Length of stay per non–asthma-related admission (d), mean ± SD	0.08 ± 0.63	0.03 ± 0.53	<.001	0.07 ± 0.73	.15
≥1 all-cause ED visit, n (%)	5481 (22.9)	5264 (12.2)	<.001	5602 (23.4)	.12
≥1 asthma-related ED visit, n (%)	3085 (12.9)	1532 (3.5)	<.001	3362 (14.1)	<.001
≥1 non–asthma-related ED visit, n (%)	3071 (12.9)	4054 (9.4)	<.001	3018 (12.6)	.39
All-cause ED visits, mean ± SD	0.30 ± 0.67	0.15 ± 0.52	<.001	0.32 ± 0.71	.02
Asthma-related ED visits, mean ± SD	0.15 ± 0.41	0.04 ± 0.22	<.001	0.16 ± 0.42	<.001
Non–asthma-related ED visits, mean ± SD	0.16 ± 0.49	0.11 ± 0.46	<.001	0.16 ± 0.51	.92
≥1 all-cause OP office visit, n (%)	22,499 (94.1)	40,704 (94.3)	.58	22,668 (94.9)	<.001

J Allergy Clin Immunol Pract. Author manuscript; available in PMC 2022 April 01.

	Pre-weighted			Weighted	
Health care resource	**All SCS users N = 23,898**	**All controls N = 43,183**	***P* value**	**All controls N = 23,898**	***P* value**
≥1 asthma-related OP office visit, n (%)	12,139 (50.8)	19,327 (44.8)	<.001	11,237 (47.0)	<.001
≥1 non–asthma-related OP office visit, n (%)	21,403 (89.6)	38,606 (89.4)	.52	21,678 (90.7)	<.001
All-cause OP office visits, mean ± SD	6.7 ± 8.6	6.0 ± 8.1	<.001	6.8 ± 8.9	.01
Asthma-related OP office visits, mean ± SD	1.2 ± 2.3	0.93 ± 2.2	<.001	1.04 ± 2.3	<.001
Non–asthma-related OP office visits, mean ± SD	5.5 ± 8.2	5.1 ± 7.6	<.001	5.8 ± 8.5	<.001
≥7 SABA prescriptions, n (%)	1351 (5.7)	986 (2.3)	<.001	1247 (5.2)	.01
All-cause prescriptions, mean ± SD	11.8 ± 8.3	10.3 ± 7.1	<.001	10.9 ± 7.9	<.001
Asthma-related prescriptions, mean ± SD	6.8 ± 4.7	5.8 ± 3.8	<.001	6.1 ± 4.6	<.001
Non–asthma-related prescriptions, mean ± SD	5.1 ± 5.9	4.5 ± 5.4	<.001	4.8 ± 5.7	<.001

ED, Emergency department; *IP*, inpatient; *OP*, outpatient; *SABA*, short-acting β-agonist; *SCS*, systemic corticosteroids; *SD*, standard deviation.

J Allergy Clin Immunol Pract. Author manuscript; available in PMC 2022 April 01.

TABLE IV.

Health care resource utilization during the first year of follow-up

Health care resource	SCS use ≥4 N = 986	SCS use 1-3 N = 22,912	All controls Weighted N = 23,898	*P* value ≥4 SCS vs controls	*P* value 1-3 SCS vs controls
≥1 asthma-related IP or ED visit, n (%)	314 (31.8)	3233 (14.1)	1803 (7.5)	<.001	<.001
≥1 non–asthma-related IP or ED visit, n (%)	218 (22.1)	3290 (14.4)	2676 (11.2)	<.001	<.001
≥1 all-cause IP admission, n (%)	125 (12.7)	762 (3.3)	583 (2.4)	<.001	<.001
≥1 asthma-related IP admission, n (%)	97 (9.8)	561 (2.4)	369 (1.5)	<.001	<.001
≥1 non–asthma-related IP admission, n (%)	33 (3.3)	237 (1.0)	231 (1.0)	<.001	.37
All-cause IP admissions, mean ± SD	0.17 ± 0.52	0.04 ± 0.25	0.04 ± 0.38	<.001	.79
Asthma-related IP admissions, mean ± SD	0.13 ± 0.45	0.03 ±0.19	0.03 ± 0.33	<.001	.60
Non–asthma-related IP admissions, mean ± SD	0.04 ± 0.25	0.01 ± 0.14	0.01 ± 0.17	<.001	.72
Length of stay per all-cause admission (d), mean ± SD	0.32 ± 1.22	0.07 ± 0.53	0.06 ± 0.87	<.001	.09
Length of stay per asthma-related admission (d), mean ± SD	0.10 ± 0.30	0.02 ± 0.15	0.02 ± 0.12	<.001	<.001
Length of stay per non–asthma-related admission (d), mean ± SD	0.22 ± 1.07	0.04 ± 0.45	0.04 ± 0.84	<.001	.90
≥1 all-cause ED visit, n (%)	380 (38.5)	5348 (23.3)	3642 (15.2)	<.001	<.001
≥1 asthma-related ED visit, n (%)	257 (26.1)	2787 (12.2)	1485 (6.2)	<.001	<.001
≥1 non–asthma-related ED visit, n (%)	192 (19.5)	3125 (13.6)	2511 (10.5)	<.001	<.001
All-cause ED visits, mean ± SD	0.68 ± 0.13	0.32 ± 0.68	0.21 ± 0.63	<.001	<.001
Asthma-related ED visits, mean ± SD	0.42 ± 0.86	0.15 ± 0.43	0.08 ± 0.34	<.001	<.001
Non–asthma-related ED visits, mean ± SD	0.26 ± 0.62	0.17 ± 0.49	0.13 ± 0.48	<.001	<.001
≥1 all-cause OP office visit, n (%)	974 (98.8)	22,338 (97.5)	22,790 (95.4)	<.001	<.001

J Allergy Clin Immunol Pract. Author manuscript; available in PMC 2022 April 01.

Health care resource	SCS use ≥4 N = 986	SCS use 1-3 N = 22,912	All controls Weighted N = 23,898	*P* value ≥4 SCS vs controls	*P* value 1-3 SCS vs controls
≥1 asthma-related OP office visit, n (%)	844 (85.6)	16,319 (71.2)	12,227 (51.2)	<.001	<.001
≥1 non–asthma-related OP office visit, n (%)	932 (94.5)	20,919 (91.3)	21,430 (89.7)	<.001	<.001
All-cause OP office visits, mean ± SD	12.7 ± 11.3	8.1 ± 9.4	6.8 ± 9.5	<.001	<.001
Asthma-related OP office visits, mean ± SD	4.1 ± 4.2	1.9 ± 2.7	1.2 ± 2.6	<.001	<.001
Non–asthma-related OP office visits, mean ± SD	8.5 ± 10.7	6.2 ± 8.9	5.6 ± 8.9	<.001	<.001
≥7 SABA prescriptions, n (%)	173 (17.5)	1622 (7.1)	1260 (5.3)	<.001	<.001
All-cause prescriptions, mean ± SD	24.3 ± 12.3	14.8 ± 8.6	12.2 ± 8.3	<.001	<.001
Asthma-related prescriptions, mean ± SD	15.1 ± 7.0	9.0 ± 5.2	7.4 ± 4.7	<.001	<.001
Non–asthma-related prescriptions, mean ± SD	9.2 ± 8.6	5.8 ± 6.0	4.8 ± 6.0	<.001	<.001

ED, Emergency department; *IP*, inpatient; *OP*, outpatient; *SABA*, short-acting β-agonist; *SCS*, systemic corticosteroids; *SD*, standard deviation.