Adverse Drug Events Related to Common Asthma Medications in US Hospitalized Children, 2000–2016

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Abstract

Background The reduction in adverse drug events is a priority in healthcare. Medications are frequently prescribed for asthmatic children, but epidemiological trends of adverse drug events related to anti-asthmatic medications have not been described in hospitalized children.

Objective The objective of this study was to report incidence trends, risk factors, and healthcare utilization of adverse drug events related to anti-asthmatic medications by major drug classes in hospitalized children in the USA from 2000 to 2016.

Methods A population-based temporal analysis included those aged 0–20 years who were hospitalized with asthma from the 2000 to 2016 Kids Inpatient Database. Age-stratified weighted temporal trends of the inpatient incidence of adverse drug events related to anti-asthmatic medications (i.e., corticosteroids and bronchodilators) were estimated. Stepwise multivariate logistic regression models generated risk factors for adverse drug events.

Results From 2000 to 2016, 12,640 out of 698,501 pediatric asthma discharges (1.7%) were associated with adverse drug events from anti-asthmatic medications. 0.83% were adverse drug events from corticosteroids, resulting in a 1.14-fold increase in the length of stay (days) and a 1.42-fold increase in hospitalization charges (dollars). The overall incidence (per 1000 discharges) of anti-asthmatic medication adverse drug events increased from 5.3 (95% confidence interval [CI] 4.6–6.1) in 2000 to 21.6 (95% CI 18.7–24.6) in 2016 (\(p\)-trend = 0.024). Children aged 0–4 years had the most dramatic increase in the incidence of bronchodilator adverse drug events from 0.2 (95% CI 0.1–0.4) to 19.3 (95% CI 15.2–23.4) [\(p\)-trend \(\leq\) 0.001]. In general, discharges among asthmatic children with some comorbidities were associated with an approximately two to five times higher odds of adverse drug events.

Conclusions The incidence of adverse drug events from common anti-asthmatic medications quadrupled over the past decade, particularly among preschool-age children who used bronchodilators, resulting in substantial increased healthcare costs. Those asthmatic children with complex medical conditions may benefit the most from adverse drug event monitoring.

Key Points

- National (US) pediatric inpatient data show the incidence of adverse drug events related to anti-asthmatic medications has increased nearly five times from 2000 to 2016, particularly among preschool-age children who used bronchodilators.
- Adverse drug events related to anti-asthmatic medications is associated with prolonged hospital stay and excess healthcare charges.
- Very young asthmatic children with complex medical conditions may benefit the most from adverse drug event monitoring.
One in five children in the USA uses at least one prescription drug to prevent or treat various health conditions [1]. The extensive advances in pharmacotherapy have improved quality of life and cured millions of people of illness. However, medications can cause unintended harm through adverse drug events (ADEs) [2]. Adverse drug events are defined as “an injury resulting from medical intervention related to a drug” [2]. An estimated one out of every three hospital adverse events are attributing to ADEs, which cause ~2 million hospital stays annually and extend the hospital length of stay by ~3 days [3].

Preventing ADEs is one of the top priorities in US healthcare [2]. In 2014, the US Department of Health and Human Services published the National Action Plan for Adverse Drug Event Prevention (ADE Action Plan) to inform the public and key stakeholders that preventing ADEs and achieving high-quality healthcare are top priorities for the US government [2]. The report highlights that identifying ADEs, a key aspect of patient safety, can result in harm prevention, lower healthcare costs, and improved healthcare quality.

Asthma is one of the most common chronic diseases in childhood affecting 7% of US children [4]. Recent data show that asthma accounted for about 178,530 hospitalizations and $81.9 billion in direct and indirect costs annually [5]. Medications are frequently prescribed to treat this condition and manage symptoms. The two most commonly prescribed drug classes for asthma treatment are anti-inflammatory corticosteroids and bronchodilators, both of which have been shown to be associated with various ADEs [6]. Specifically, corticosteroids are known to cause decreased bone mineral density, skin thinning and bruising, cataracts, and impaired growth [7]. Notably, more recent studies suggested growth velocity of pre-pubertal children may only be affected by a short-term (1–2 years) use of corticosteroids, but in the long term, the difference in adult height was less than 1% [8, 9]. Furthermore, poorly controlled asthma itself has a negative impact on adult height. [10] Some bronchodilators, such as β2-agonists, are associated with tachycardia, hypokalemia, hypoglycemia, and even mortality when used as a long-term monotherapy [11, 12].

Most prior ADE research focused on a specific asthma medication and was funded by industry [6]. To date, there have been no efforts to assess temporal trends in inpatient ADEs related to asthma medications by major drug classes. By using nationally representative 2000–2016 Healthcare Cost and Utilization Project (HCUP) Kids’ Inpatient Database (KID) data, we identified relevant asthma ADEs based on International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) and Tenth Revision (ICD-10-CM) codes. We aimed to (1) describe the decade incidence trends of ADEs related to anti-asthmatic medications by major drug class among asthmatic children in the USA; (2) estimate healthcare outcomes, including the length and charges of stay and mortality associated with anti-asthmatic medication-related ADEs; and (3) identify risk factors for asthmatic children who have experienced ADEs from common asthma medications. Given the historic increase in asthma medication prescriptions, it was hypothesized that there would be an increasing incidence trend of ADEs related to asthma treatment.

2 Methods

Our report follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

2.1 Data Source and Sample Design

A population-based temporal analysis of inpatient children who experienced ADEs as a result of anti-asthmatic medication use in 2000, 2003, 2006, 2009, 2012, and 2016 using the KID was conducted. The KID was developed for the HCUP and sponsored by the Agency for Healthcare Research and Quality. Researchers are encouraged to use these data for generating national estimates and conducting temporal analyses for US pediatric population estimates across various health conditions [13]. The KID is the largest, publicly available, all-payer, pediatric inpatient care database in the USA and includes approximately 3 million (i.e., unweighted) hospitalizations from selected hospitals. After applying appropriate sampling weights assigned by the KID, samples are weighted to represent the population of all pediatric discharges in the USA, representing approximately 7 million pediatric discharges per year. The KID has been conducted every 3 years since 1997. However, because there was a significant change in sampling between 1997 data and the following years, the present analysis included KID data beginning from 2000. Additionally, hospital discharge data for 2015 contain a mixture of ICD-9 and ICD-10 data; therefore, the KID was released for 2016 instead of 2015 to avoid the complexities of analyzing mixed ICD codes. The 2016 KID contains ICD-10-CM data only. The sampling frame for KID data includes pediatric discharge data from community (i.e., non-federal, short-term, general, and specialty hospitals) and non-rehabilitation hospitals provided by HCUP partner states. Pediatric discharges are defined as all discharges that had an age at admission of 20 years or less. The number of states and hospitals represented over 2000–16 in the KID are as follows: 27 states and 4839 hospitals in 2000, 36 states and 4836 hospitals in 2003, 38 states
and 5124 hospitals in 2006, 44 states and 5128 hospitals in 2009, and 47 states and 5001 hospitals in 2016. Additional details of the KID can be found elsewhere [13].

Our analysis included an unweighted total of 698,501 pediatric discharges, which represented slightly over one million pediatric discharges aged 0–20 years during the past 16 years after applying the sampling weights (unweighted \( n = 84,479, 102,101, 86,968, 97,117, 90,642, \) and 237,194 for 2000, 2003, 2006, 2009, 2012, and 2016, respectively), who had asthma as the primary diagnosis (ICD-9-CM code starts with 493 from 2000 to 2012, or ICD-10-CM code starts with J45 in 2016).

### 2.2 Measurements

#### 2.2.1 Exposure Variables: ADEs from Anti-Asthmatic Medications

**ADEs from Corticosteroids** ICD-9-CM codes E932.0, 365.31, 365.32, and 962.0 and ICD-10-CM codes T38.0X1 to T38.0X5, H40.6 in all diagnosis fields were used to determine ADEs related to corticosteroids. Corticosteroids can be further categorized into mineralocorticoids and glucocorticoids and the ICD-10-CM had different codes for ADEs of these two subclasses. However, because mineralocorticoids were not intended to treat asthma and rarely used in children, only four (out of 237,194) discharges reported ADEs from mineralocorticoids in KID 2016 data. Thus, the primary analysis here did not include relevant ICD-10 codes for mineralocorticoids.

**ADEs from Bronchodilators** ICD-9-CM codes E945.7 and 975.7 and ICD-10-CM codes T48.6X1 to T48.6X5 in all diagnosis fields were used to classify ADEs related to bronchodilators. Although the ICD codes label those codes as “anti-asthmatics,” the relevant drugs only included bronchodilators (i.e., \( \beta_2 \)-agonists, xanthine derivatives, and anticholinergics). The detailed description of each ICD code, including a comprehensive drug list, can be found at [https://www.cdc.gov/nchs/icd/index.htm](https://www.cdc.gov/nchs/icd/index.htm). (The description and frequency for each ICD code mentioned above is summarized in Table 1 of the Electronic Supplementary Material.)

#### 2.2.2 Outcome Variables: Healthcare Utilization

**Length of Stay** Hospital length of stay is a continuous variable that ranged from 0 to 365 days. It was calculated by the HCUP data team by subtracting the admission date from the discharge date. Same-day stays are therefore coded as 0. Leave days were not included.

**Hospitalization Charges** The total charges for hospitalization are also a continuous variable provided by the KID dataset. The total charges were rounded to the nearest dollar.

**Inpatient Mortality** Inpatient mortality is a dichotomous variable (yes/no). It was coded from the discharge disposition of the patient by the HCUP team.

### 2.2.3 Covariates

Covariates of interest include patient characteristics, such as age, sex, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other), insurance type (Medicare, Medicaid, private, and other/self-pay), median household income, and health conditions. Age was categorized into three groups (0–4 years, 5–11 years, and 12–20 years) based upon the current asthma treatment guideline [14]. Median household income was estimated by a quartile classification system according to a patient’s ZIP code. The quartiles are identified by values of 1–4, indicating the poorest to wealthiest populations. Health conditions were categorized based upon 11 major diagnostic categories using ICD-9-CM in 2000–2012 [15] and ICD-10-CM in 2016 [16]. Hospital characteristics, such as children’s hospital (yes/no), bed size (small, medium, and large), location and teaching status (rural, urban non-teaching, and urban teaching), and region (Northeast, Midwest, South, and West) were also examined in this analysis.

### 2.3 Statistical Analysis

Categorical variables were presented as weighted percentages (standard error [SE]), and continuous variables were summarized as weighted means (SE). Because of the large sample size of our analysis, the normality of continuous variables was assumed based on the central limit theorem. Two-sample t-tests with equal or unequal variance and the Rao–Scott \( \chi^2 \) analysis was used to compare continuous and categorical variables between pediatric discharges with and without anti-asthmatic medication ADEs.

Weighted ADE incidence proportion estimates and 95% confidence intervals (CIs) were generated by two major drug classes of anti-asthmatic medications, i.e., corticosteroids and bronchodilators, for 2000, 2003, 2009, 2012, and 2016, respectively. Incidence proportion (thereafter refers to incidence) was expressed as the number of estimated hospitalizations per 1000 discharges.

\[
\text{Incidence proportion} = \frac{\text{Frequency of ADEs per year}}{\text{Total persons at risk}} \times 1000.
\]

A crude generalized linear model by age groups was created to examine temporal trends of anti-asthmatic medication ADEs.
that only included the survey year as the independent variable. Four logistic regression models were built to identify potential predictors for ADEs of corticosteroids and bronchodilators (one unadjusted and one adjusted for each outcome). Specifically, a stepwise logistic regression \((p < 0.1\) for entering and \(p < 0.05\) for retaining) model adjusting for both patient-level variables (i.e., age, sex, race/ethnicity, insurance, and health conditions) and hospital-level characteristics (hospital location teaching status and hospital region) was created.

In addition, we also examined the overall burden of healthcare utilization among pediatric patients who experienced ADEs from anti-asthmatic medications over the past 16 years. Univariate and multivariate negative binomial regression adjusting for age, sex, race/ethnicity, insurance, other health conditions, hospital location teaching status, hospital region, and survey year were used to compute incidence rate ratios for hospital length of stay. A generalized linear model with a gamma distribution and log link was created to calculate ratios for hospitalization charges in relation to ADE status (yes/no). Univariate and multivariate logistic regression adjusting for the same covariates as above were used for inpatient mortality (yes/no). Goodness-of-fit tests were performed to assess model fitting.

A complete case analysis was performed. Data were analyzed from 20 March, 2021 to 2 April, 2022. All statistical analyses included the complex sampling plan (strata, cluster, and weight) provided by HCUP to produce national estimates and were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 4.0.5 (R core team, 2021). A two-sided \(p\)-value < 0.05 was considered significant.

### 2.4 Sensitivity Analysis

A priori sensitivity analyses were conducted to provide more insightful results for anti-asthmatic medication ADEs in the US pediatric population because ADEs can be further categorized into preventable accidental poisoning and adverse effects at the therapeutic dose. After excluding a very small proportion of accidental poisoning from anti-asthmatic medications \((n = 97, 0.01\%\)), we also reported the incidence trends of adverse effects related to anti-asthmatic medications.

### 3 Results

From 2000 to 2016, 12,640 out of 698,501 pediatric asthma discharges (weighted percentage 1.7%) were associated with ADEs from anti-asthmatic medications in this nationally representative sample. Specifically, 0.83\% \((n = 5898)\) and 0.97\% \((n = 7147)\) had ADEs from corticosteroids and bronchodilators (total \(n = 12640\)), respectively, indicating there were 405 discharges as a result of ADEs from both classes. The mean age for visits involving anti-asthmatic medication-related ADEs was 8.7 (SE 0.17) years, while the mean age for discharges without ADEs was 7.2 (SE 0.05) years \((p < 0.001)\). Significantly more boys were discharged with asthma ADEs than those without ADEs \((58.3\% \text{ [SE 0.13\%]} vs 55.1\% \text{ [SE 0.54\%]}, p < 0.001)\). Non-Hispanic black individuals were the most prevalent \((39.2\% \text{ [SE 1.42\%]}\) ethnic group who experienced an ADE from anti-asthmatic medications followed by non-Hispanic white individuals \((34.8\% \text{ [SE 1.06\%]}\), Hispanic individuals \((18.0\% \text{ [SE 1.03\%]}\), and other race/ethnicities \((8.0\% \text{ [SE 0.54\%]}\). Children who were discharged with anti-asthmatic medication ADEs had a lower socioeconomic status compared with non-ADEs, including a higher proportion with Medicaid insurance \((55.0\% \text{ [SE 0.94\%]} vs 53.7\% \text{ [SE 0.46\%]}, p < 0.001)\) and quartile 1 (lowest) median household income \((36.7\% \text{ [SE 1.34\%]} vs 34.8\% \text{ [SE 0.67]}, p = 0.064)\) (Table 1).

Compared with the non-ADE group, discharges involving an anti-asthmatic medication ADE were more frequently associated with other comorbidities, such as endocrine, nutritional, and metabolic diseases \((40.4\% \text{ [SE 0.93\%]} vs 14.6\% \text{ [SE 0.29\%]}), infectious and parasitic disease \((18.2\% \text{ [SE 0.68\%]} vs 11.2\% \text{ [SE 0.26\%]}), and diseases of blood and blood-forming organs \((15.9\% \text{ [SE 0.59\%]} vs 5.8\% \text{ [SE 0.19\%]}). All \(p\)-values were < 0.001. In addition, ADEs from anti-asthmatic medications predominantly occurred at an urban teaching hospital \((79.1\% \text{ [SE 1.25\%]} vs 66.5\% \text{ [SE 0.91\%]}, p < 0.001)\) or in the Southern region \((38.7\% \text{ [SE 2.56\%]} vs 37.8\% \text{ [SE 1.29\%]}, p < 0.001)\).

Table 1 also shows 48.4\% \text{ [SE 0.89\%]} of visits involving an ADE from corticosteroids were for adolescents aged 12–20 years while the majority of visits involving bronchodilator ADEs for children aged 5–11 years \((41.9\% \text{ [SE 0.71\%]}). Slightly more boys were discharged with ADEs from bronchodilators than from corticosteroids \((58.5\% \text{ [SE 0.68\%]} vs 51.1\% \text{ [SE 0.74\%]}), Other patient and hospital characteristics by drug classes are also included in Table 1.

Figure 1 shows the incidence trends of anti-asthmatic medication-related ADEs by two major drug classes (i.e., bronchodilators and corticosteroids) during the past 16 years. Overall, the incidence (per 1000 discharges) of anti-asthmatic medication-related ADEs increased almost five times from 5.3 (95\% CI 4.6–6.1) in 2000 to 28.0 (95\% CI 23.2–32.8) in 2012, but slightly decreased to 21.6 (95\% CI 18.7–24.6) in 2016 (\(p\)-trend = 0.024). Adverse drug events from bronchodilators demonstrated a significant increasing trend \((0.6 [95\% \text{ CI 0.4–0.8}]\ per 1000 discharges in 2000 to 14.3 [95\% \text{ CI 11.7–17}] per 1000 discharges in 2016, \(p\)-trend = 0.007), while the overall trend was insignificant for corticosteroids \((p\)-trend = 0.155). Notably, younger children
### Table 1
Patient discharge and hospital characteristics by ADE discharge status and medication type, Healthcare Cost and Utilization Project Kids’ Inpatient Database 2000–16 (n = 698,501)

|                        | Discharges with ADE by medication type | Discharges without ADE | p-value<sup>b</sup> |
|------------------------|----------------------------------------|------------------------|---------------------|
|                        | Corticosteroids | Bronchodilators | Any<sup>a</sup> |                        |                        |
| Total number (weighted%) | 5898 (0.83) | 7147 (0.97) | 12,640 (1.7) | 685,861 (98.3) | < 0.001            |
| Patient characteristics |                        |                        |                    |                        |                      |
| Age, mean (SE), year<sup>d</sup> | 10.9 (0.12) | 7.12 (0.10) | 8.7 (0.17) | 7.2 (0.05) | < 0.001            |
| 0–4, % (SE) | 22.0 (0.64) | 37.3 (0.81) | 30.5 (0.69) | 44.1 (0.33) | < 0.001            |
| 5–11, % (SE) | 29.6 (0.71) | 41.9 (0.71) | 36.1 (0.61) | 30.9 (0.16) | < 0.001            |
| 12–20, % (SE) | 48.4 (0.89) | 20.8 (0.68) | 33.4 (0.88) | 25.1 (0.34) | < 0.001            |
| Sex, % (SE)<sup>f</sup> |                        |                        |                    |                        | < 0.001            |
| Male | 51.1 (0.74) | 58.5 (0.64) | 58.3 (0.13) | 55.1 (0.54) |                        |
| Female | 48.9 (0.74) | 41.5 (0.64) | 41.7 (0.13) | 44.9 (0.54) |                        |
| Race/ethnicity, % (SE)<sup>f</sup> |                        |                        |                    |                        | < 0.001            |
| Non-Hispanic white | 40.4 (0.99) | 29.8 (1.36) | 34.8 (1.06) | 38.4 (0.68) |                        |
| Non-Hispanic black | 34.8 (1.11) | 42.7 (1.98) | 39.2 (1.42) | 32.1 (0.73) |                        |
| Hispanic | 18.0 (0.88) | 18.4 (1.46) | 18.0 (1.03) | 21.2 (0.64) |                        |
| Other | 6.8 (0.42) | 9.1 (0.83) | 8.0 (0.54) | 8.3 (0.35) |                        |
| Insurance, % (SE)<sup>g</sup> |                        |                        |                    |                        | < 0.001            |
| Medicare | 0.5 (0.12) | 0.1 (0.04) | 0.3 (0.06) | 0.3 (0.03) |                        |
| Medicaid | 50.3 (0.88) | 59.0 (1.26) | 55.0 (0.94) | 53.7 (0.46) |                        |
| Private | 38.4 (0.85) | 33.2 (1.43) | 35.6 (0.99) | 38.5 (0.47) |                        |
| Other/self-pay | 10.7 (0.53) | 7.6 (0.89) | 9.1 (0.58) | 7.5 (0.25) |                        |
| Median household income, % (SE)<sup>c,h</sup> |                        |                        |                    |                        | 0.064              |
| Quartile 1 (lowest) | 32.8 (0.89) | 36.8 (2.34) | 36.7 (1.34) | 34.8 (0.67) |                        |
| Quartile 2 | 25.7 (0.68) | 24.8 (1.37) | 24.1 (0.56) | 25.4 (0.30) |                        |
| Quartile 3 | 23.1 (0.68) | 22.9 (1.38) | 22.0 (0.64) | 21.6 (0.31) |                        |
| Quartile 4 (highest) | 18.4 (0.76) | 15.4 (1.44) | 17.2 (0.88) | 18.1 (0.47) |                        |
| Health conditions, % (SE) |                        |                        |                    |                        | < 0.001            |
| Infectious and parasitic disease | 14.9 (0.56) | 21.3 (0.99) | 18.2 (0.68) | 11.2 (0.26) |                        |
| Neoplasms | 3.3 (0.42) | 0.29 (0.06) | 1.7 (0.21) | 1.0 (0.06) | < 0.001            |
| Endocrine, nutritional, and metabolic diseases | 53.8 (0.78) | 30.3 (1.08) | 40.4 (0.93) | 14.6 (0.29) | < 0.001            |
| Diseases of blood and blood-forming organs | 28.1 (0.7) | 5.8 (0.37) | 15.9 (0.59) | 5.8 (0.19) | < 0.001            |
| Mental disorders | 20.4 (0.62) | 10.1 (0.40) | 14.8 (0.44) | 11.8 (0.32) | < 0.001            |
| Nervous system diseases | 11.5 (0.48) | 6.8 (0.40) | 9.0 (0.34) | 12.2 (0.19) | < 0.001            |
| Circulatory system diseases | 13.8 (0.62) | 10.7 (1.04) | 12.0 (0.73) | 3.4 (0.12) | < 0.001            |
| Digestive system diseases | 16.5 (0.66) | 7.0 (0.37) | 11.4 (0.44) | 9.5 (0.29) | < 0.001            |
| Genitourinary system diseases | 4.9 (0.33) | 1.0 (0.12) | 2.8 (0.19) | 2.6 (0.09) | 0.173              |
| Skin and subcutaneous tissue diseases | 11.2 (0.51) | 16.7 (0.68) | 14.1 (0.50) | 8.1 (0.18) | < 0.001            |
| Musculoskeletal system diseases | 6.0 (0.37) | 1.5 (0.17) | 3.6 (0.23) | 2.8 (0.13) | < 0.001            |
| Hospital characteristics |                        |                        |                    |                        |                      |
| Children’s hospital, % (SE) | 17.4 (1.85) | 33.1 (4.37) | 23.7 (6.39) | 18.1 (2.75) | 0.105              |
| Bed size, % (SE)<sup>j</sup> |                        |                        |                    |                        | 0.744              |
| Small | 12.6 (0.90) | 12.3 (2.60) | 12.6 (1.69) | 13.5 (0.90) |                        |
| Medium | 25.7 (1.20) | 25.5 (3.24) | 25.7 (2.18) | 26.1 (1.02) |                        |
| Large | 61.7 (1.34) | 62.2 (3.46) | 61.7 (2.37) | 60.3 (1.18) |                        |
| Location teaching status, % (SE)<sup>j</sup> |                        |                        |                    |                        | < 0.001            |
| Rural | 8.3 (0.32) | 1.8 (0.21) | 4.9 (0.37) | 10.2 (0.35) |                        |
| Urban non-teaching | 25.6 (0.95) | 7.6 (1.14) | 16.0 (1.09) | 23.3 (0.77) |                        |
| Urban teaching | 66.1 (1.08) | 90.6 (1.20) | 79.1 (1.25) | 66.5 (0.91) |                        |
| Region, % (SE) |                        |                        |                    |                        |                      |

<sup>a</sup>Any includes corticosteroids and bronchodilators.

<sup>b</sup>p-values are based on chi-square test.

<sup>c</sup>Quartiles are defined by distribution of household income.

<sup>d</sup>Age is defined as the mean age (standard error) at discharge.

<sup>e</sup>Sex is defined as male or female.

<sup>f</sup>Race/ethnicity is defined as non-Hispanic white, non-Hispanic black, Hispanic, or Other.

<sup>g</sup>Insurance is defined as Medicare, Medicaid, Private, Other/self-pay.

<sup>h</sup>Median household income is defined as the 10th, 25th, 50th, 75th, or 90th percentile.

<sup>i</sup>Bed size is defined as small, medium, or large.

<sup>j</sup>Location teaching status is defined as rural, urban non-teaching, or urban teaching.
aged 0–4 years had the most dramatic increase in terms of the incidence for ADEs. Specifically, for bronchodilators, the incidence of ADEs increased almost ten times from 0.2 (95% CI 0.1–0.4) to 19.3 (95% CI 15.2–23.4) per 1000 discharges between 2000 and 2016 ($p$-trend ≤ 0.001). For corticosteroids, it tripled from 1.9 (95% CI 1.4–2.5) to 5.6 (95% CI 4.8–6.5) per 1000 discharges ($p$-trend = 0.007).

The incidence trends showed significant increases in those aged 5–11 years ($p$-trend < 0.05 for all categories); however, not in those aged older than 12 years ($p$-trend > 0.05 for all categories). After excluding accidental poisoning, the results of the sensitivity analyses did not differ from the primary results (data not shown).

Table 2 illustrates a comparison of healthcare utilization between patients who experienced an ADE from common asthma medications and patients without ADEs. After adjusting for demographic factors, insurance, other health conditions, hospital location teaching status, hospital region, and survey year, ADEs caused by corticosteroids were associated with a 1.14-fold (95% CI 1.12–1.17) increase in the length of stay and a 1.42-fold (95% CI 1.39–1.46) increase in hospitalization charges. However, ADEs from bronchodilators were associated with a shorter length of hospital stay compared with those without ADEs (incidence rate ratio = 0.91, 95% CI 0.89–0.93, $p < 0.001$) but a modest increase of hospitalization charges (charge ratio = 1.07, 95% CI 1.05–1.09, $p < 0.001$). Adverse drug events from both classes were not associated with inpatient mortality.

Stepwise logistic regression models generated potential predictors for anti-asthmatic medication ADEs (Table 3). In the fully adjusted model, the results elucidate potential risk factors for corticosteroid ADEs including increasing age, other/self-pay insurance, comorbidities (from the highest to the lowest odds) including endocrine, nutritional, and metabolic diseases, diseases of blood and blood-forming organs, circulatory system diseases, skin and subcutaneous tissue diseases, neoplasms, and an urban non-teaching hospital. However, potential protective factors were Hispanic and other race/ethnicity, having mental disorders, nervous system diseases, digestive system diseases, circulatory system diseases, skeletal system diseases, and Northeast, Midwest, and West hospital regions.

In addition, potential risk factors for bronchodilator ADEs were age between 5 and 11 years, Non-Hispanic black and other race/ethnicity, comorbidities (from the highest to the lowest odds) including circulatory system diseases, endocrine, nutritional, and metabolic diseases, skin and subcutaneous tissue diseases, and infectious disease, and the Midwest hospital region. On the contrary, potential protective factors seem to be age between 12 and 20 years, private insurance, neoplasms, diseases of blood and blood-forming organs, mental disorders, nervous system diseases, digestive system diseases, musculoskeletal system diseases, rural and urban nonteaching hospital, and the Northeast hospital region.

4 Discussion

4.1 Increasing Trends of ADEs from Anti-Asthmatic Medications

Currently, the reported asthma medication adherence rate is less than 50% [17]. Fear of ADEs is one of the main reasons
for nonadherence in asthmatic children [18]. Therefore, it is crucial to understand incidence trends and risk factors of ADEs related to anti-asthmatic medications in order to help improve medication adherence and pulmonary health risks. This analysis underscored the incidence of ADEs from anti-asthmatic medications has alarmingly increased nearly five times in US inpatient children from 2000 to 2016. Among preschoolers who used bronchodilators, the incidence rose ten times during the past 16 years, which is a particular healthcare concern. Although no similar trend analysis is available to compare these results, one population-based study using the 2006 KID suggested corticosteroids and anti-asthmatic medications (bronchodilators) [ranked the second and eighth most common drug classes associated with ADEs] accounted for 12.5% and 3.2% of all pediatric inpatient ADEs, respectively [19].

The incidence rates of ADEs continuing to rise in children with asthma is a major public health concern. Although this could be because of a better reporting system and an increased awareness of documentation, real-world evidence suggests a possible rising trend of over-use short-acting β2 agonists compared with previous years [20, 21], which may partially explain the upward trending of ADEs from bronchodilators.

4.2 Deleterious Health Effects of ADEs from Anti-Asthmatic Medications

In the short term, ADEs from anti-asthmatic medications will cause direct harm, prolong hospital stay, and increase healthcare utilization as demonstrated in the present study. Despite the ADEs from either anti-asthmatic drug class not being associated with inpatient mortality, corticosteroid-related ADEs were attributed to excess days and excess healthcare costs during a hospital stay. However, ADEs from bronchodilators were associated with excess charges but a
shorter length of stay compared with those without ADEs. Although there is no clear explanation for this negative association, the findings indeed align with the same study by Tundia et al. [19]. In 2006, ADEs from corticosteroids were associated with a 2.34 (0.47) excess length of stay and a $5620 (891) excess cost, but ADEs from bronchodilators were associated with 0.09 (0.42) fewer days of hospital stay [19]. One possible explanation is the trend of higher dose bronchodilator use, thus patients with asthma were more efficiently treated leading to a reduced length of stay but increased costs.

In the long term, ADEs from anti-asthmatic medications can decrease medication adherence leading to poorly controlled asthma [17, 18], which in turn decreases the quality of life of children with asthma [22, 23]. In addition to the direct impacts, poorly controlled asthma may lead to missed school days [23], poor academic performance [23], and mental health problems such as depression and anxiety for patients [24] and their caregivers [25].

### 4.3 Differences in Risk Profiles for Various Bronchodilators and Corticosteroids

We present here the overall burden of ADEs from two major anti-asthmatic drug classes from ICD codes. Remarkably, the risk profiles for various bronchodilators and corticosteroids are indeed different. For instance, two types of corticosteroids: long-acting dexamethasone versus short-acting prednisone/prednisolone are commonly used to treat acute asthma. Clinical trials [26, 27] and a meta-analysis [28] suggested dexamethasone had fewer ADEs than prednisone/prednisolone. Hence, more research is needed to assess such differences at the population level.

### Table 2 Comparison of healthcare utilization between patients who experienced an ADE from common asthma medications and patients without ADEs, Healthcare Cost and Utilization Project Kids’ Inpatient Database 2000–2016

|                     | Corticosteroids | Bronchodilator |
|---------------------|-----------------|----------------|
|                     | No ADE          | ADE            | No ADE          | ADE            |
| **Length of stay**  |                 |                |                 |                |
| Mean (SE), days     | 2.65 (0.03)     | 3.70 (0.28)    | 2.66 (0.03)     | 2.66 (0.06)    |
| Unadjusted IRR* (95% CI) | 1 (ref)        | **1.39 (1.36–1.41)** | 1 (ref)        | 0.99 (0.97–1.01) |
| p-value             | –               | < 0.001        | –               | 0.325          |
| Adjusted IRR* (95% CI) | 1 (ref)        | **1.14 (1.12–1.17)** | 1 (ref)        | **0.91 (0.89–0.93)** |
| p-value             | –               | < 0.001        | –               | < 0.001        |
| **Charges**         |                 |                |                 |                |
| Mean (SE), dollars  | 16 769 (497.6)  | 30 099 (1344.1) | 16 827 (500.4)  | 22 252 (1281.9) |
| Unadjusted ratio ADE vs no ADE* (95% CI) | 1 (ref) | **1.79 (1.75–1.84)** | 1 (ref)        | **1.32 (1.29–1.36)** |
| p-value             | –               | < 0.001        | –               | < 0.001        |
| Adjusted ratio ADE vs no ADE* (95% CI) | 1 (ref) | **1.42 (1.39–1.46)** | 1 (ref)        | **1.07 (1.05–1.09)** |
| p-value             | –               | < 0.001        | –               | < 0.001        |
| **Mortality**       |                 |                |                 |                |
| N (%)               | 437 (0.06)      | 10 (0.18)      | 446 (0.06)      | 1 (0.01)       |
| Crude OR* (95% CI)  | 1 (ref)         | **2.9 (1.4–6.1)** | 1 (ref)         | 0.2 (0–1.4)    |
| p-value             | –               | **0.005**      | –               | 0.102          |
| Adjusted OR* (95% CI) | 1 (ref)        | 1.5 (0.7–3.3)  | 1 (ref)         | 0.2 (0–1.0)    |
| p-value             | –               | 0.338          | –               | 0.052          |

ADE adverse drug events, CI confidence interval, IRR incidence rate ratio, OR odds ratio, ref reference, SE standard error

*Univariate negative binomial regression

*Multivariate negative binomial adjusting for age, sex, race/ethnicity, insurance, other health conditions, hospital location teaching status, hospital region, and survey year

*Univariate generalized linear model with a gamma distribution and log link

*Multivariate gamma distribution and log link adjusting for age, sex, race/ethnicity, insurance, other health conditions, hospital location teaching status, hospital region, and survey year

*Univariate logistic regression

*Multivariate logistic regression adjusting for age, sex, race/ethnicity, insurance, other health conditions, hospital location teaching status, hospital region, and survey year

Significant results are bolded ($p < 0.05$)
Table 3 ORs and 95% CIs of patient and hospital predictors for ADEs related to common asthma medications in hospitalized US children, 2000–2016

| Variables                              | Corticosteroid ADEs | Bronchodilator ADEs |
|----------------------------------------|---------------------|---------------------|
|                                        | Crude OR<sub>a</sub>, 95% CI | Adjusted OR<sub>b</sub>, 95% CI | Crude OR<sub>a</sub>, 95% CI | Adjusted OR<sub>d</sub>, 95% CI |
| Age, years                             |                     |                     |                     |                     |
| 0–4 (ref)                              | 1.0                 | 1.0                 | 1.0                 | 1.0                 |
| 5–11                                   | 1.93 (1.78–2.09)**  | 1.74 (1.63–1.85)**  | 1.59 (1.49–1.71)**  | 1.45 (1.38–1.52)**  |
| 12–20                                  | 3.89 (3.56–4.25)**  | 2.17 (2.03–2.31)**  | 0.97 (0.87–1.07)    | 0.83 (0.78–0.89)**  |
| Sex                                    |                     |                     |                     |                     |
| Male (ref)                             | 1.0                 | 1.0                 | 1.0                 | 1.0                 |
| Female                                 | 1.35 (1.27–1.43)**  | N/A<sup>c</sup>     | 1.0 (0.95–1.05)     | N/A<sup>c</sup>     |
| Race/ethnicity                         |                     |                     |                     |                     |
| Non-Hispanic white (ref)               | 1.0                 | 1.0                 | 1.0                 | 1.0                 |
| Non-Hispanic black                     | 1.03 (0.93–1.13)    | 0.96 (0.91–1.02)    | 1.71 (1.47–1.99)**  | 1.29 (1.22–1.36)**  |
| Hispanic                               | 0.81 (0.73–0.89)**  | 0.88 (0.82–0.95)**  | 1.12 (0.93–1.35)    | 0.94 (0.88–1.00)    |
| Other                                  | 0.78 (0.68–0.89)**  | 0.88 (0.80–0.97)*   | 1.41 (1.17–1.69)**  | 1.23 (1.13–1.33)**  |
| Insurance                              |                     |                     |                     |                     |
| Government (ref)                       | 1.0                 | 1.0                 | 1.0                 | 1.0                 |
| Private                                | 1.06 (0.99–1.13)    | 1.15 (1.09–1.21)**  | 0.79 (0.70–0.88)    | 0.91 (0.87–0.95)    |
| Other/self-pay                         | 1.52 (1.35–1.71)**  | 1.46 (1.35–1.58)**  | 0.92 (0.74–1.16)    | 0.96 (0.88–1.04)    |
| Comorbidities (yes/no)                 |                     |                     |                     |                     |
| Infectious and parasitic disease       | 1.38 (1.27–1.50)**  | N/A<sup>c</sup>     | 2.14 (1.92–2.39)**  | 1.65 (1.57–1.74)**  |
| Neoplasms                              | 3.37 (2.65–4.30)**  | 1.22 (1.07–1.39)*   | 0.28 (0.18–0.44)**  | 0.19 (0.13–0.28)**  |
| Endocrine, nutritional, and metabolic diseases | 6.74 (6.29–7.23)**  | 4.83 (4.60–5.07)**  | 2.48 (2.24–2.74)**  | 2.31 (2.20–2.42)**  |
| Diseases of blood and blood-forming organs | 6.39 (5.84–6.99)**  | 4.01 (3.79–4.24)**  | 0.98 (0.85–1.12)    | 0.76 (0.69–0.83)**  |
| Mental disorders                       | 1.92 (1.76–2.10)**  | 0.92 (0.86–0.98)*   | 0.84 (0.76–0.92)    | 0.76 (0.70–0.82)    |
| Nervous system diseases                | 0.93 (0.85–1.02)    | 0.67 (0.62–0.72)**  | 0.52 (0.46–0.59)**  | 0.49 (0.45–0.54)**  |
| Circulatory system diseases            | 4.49 (4.04–4.99)**  | 1.75 (1.63–1.88)**  | 3.36 (2.70–4.19)**  | 3.01 (2.83–3.24)**  |
| Digestive system diseases              | 1.88 (1.71–2.07)**  | 0.81 (0.76–0.87)**  | 0.71 (0.63–0.80)**  | 0.52 (0.48–0.57)**  |
| Skin and subcutaneous tissue diseases  | 1.42 (1.28–1.57)**  | 1.26 (1.17–1.35)**  | 2.28 (2.07–2.50)**  | 1.69 (1.59–1.79)**  |
| Musculoskeletal system diseases        | 2.19 (1.89–2.54)**  | 0.87 (0.79–0.96)*   | 0.53 (0.42–0.68)    | 0.41 (0.34–0.48)**  |
| Hospital location, teaching status     |                     |                     |                     |                     |
| Rural                                  | 0.83 (0.72–0.95)**  | 1.08 (0.99–1.19)    | 0.13 (0.09–0.18)    | 0.15 (0.13–0.18)**  |
| Urban non-teaching                     | 1.12 (1.01–1.24)*   | 1.40 (1.32–1.48)**  | 0.24 (0.18–0.33)**  | 0.27 (0.25–0.29)**  |
| Urban teaching (ref)                   | 1.0                 | 1.0                 | 1.0                 | 1.0                 |
| Hospital region                        |                     |                     |                     |                     |
| Northeast                              | 0.65 (0.56–0.76)**  | 0.75 (0.70–0.80)**  | 0.86 (0.59–1.26)    | 0.69 (0.65–0.73)**  |
| Midwest                                | 1.03 (0.90–1.17)    | 0.92 (0.86–0.98)*   | 1.48 (1.02–2.17)*   | 1.36 (1.29–1.44)**  |
| South (ref)                            | 1.0                 | 1.0                 | 1.0                 | 1.0                 |
| West                                   | 0.86 (0.75–0.99)*   | 0.86 (0.81–0.92)**  | 1.01 (0.71–1.43)    | 1.04 (0.98–1.11)    |

ADE adverse drug events, CI confidence interval, N/A not available, OR odds ratio, ref reference

<sup>a</sup>p < 0.05; <sup>b</sup>p < 0.001

<sup>a</sup>Univariate logistic regression

<sup>b</sup>Stepwise multivariate logistic regression adjusting for age, sex, race/ethnicity, insurance, other health conditions, hospital location teaching status, and hospital region

<sup>c</sup>Dropped by the stepwise model
4.4 Potential Risk Factors for ADEs from Anti-Asthmatic Medications

4.4.1 Age

Older age was associated with a higher odds of corticosteroid ADEs, which aligns with the previous literature in adults [29]. However, children aged older than 12 years were associated with a lower odds of bronchodilator ADEs compared with preschoolers. This difference may be explained by the increased tolerability of long-term exposure to bronchodilators as an individual ages [30].

4.4.2 Race/Ethnicity

Additionally, our study revealed non-Hispanic black individuals were more likely to experience bronchodilator-related ADEs. This is interesting because it is well known that non-Hispanic black children usually have a poorer response to inhalers versus non-Hispanic white children [31]. A recent large-scale genome-wide association study identified new genetic variants associated with a reduced albuterol (a bronchodilator) response in non-Hispanic black individuals, which can explain the individualized response [31]. In the future, another genome-wide association study can be conducted to examine the pharmacogenetics of bronchodilator-related ADEs.

Hispanic and other race/ethnicity also had a lower odds of experiencing corticosteroids ADEs in the present study. In addition to the possible genetic variations [32], more efforts are needed to explore the reasons behind this because currently only a very few studies have investigated disparities in ADEs in Hispanic individuals [33]. Previous pediatric studies [34, 35] found that inhaled corticosteroid use was significantly associated with an enhanced bronchodilator response only among Mexican Americans, not but not African Americans or Puerto Ricans, nevertheless whether the risk of ADEs alters with race needs to be further explored.

4.4.3 Insurance and Hospital Characteristics

We also observed private insurance is a risk factor for corticosteroid ADEs, but a protective factor for bronchodilator ADEs. So far, few studies explored the impact of insurance on ADEs; therefore, more healthcare services research is needed to disentangle this finding. Significant variations of hospital location, teaching status, and region were also found. Urban non-teaching was associated with a higher odds of ADEs from corticosteroids but a lower odds from bronchodilators. Hospitals from the Northeast region were less likely to have ADEs from anti-asthmatic medications than the Southern region hospitals. Those findings may be prone to a reporting bias, i.e., the differences in the likelihood of reporting an ADE.

4.4.4 Comorbidities

Our results suggested complex health conditions in addition to asthma are significant predictors for anti-asthmatic medication-related ADEs. For example, we found patients diagnosed with endocrine/metabolic or circulatory system diseases had approximately a two to five times higher odds of experiencing ADEs from corticosteroids or bronchodilators. These findings are similar to an adult study that included 10-year ADE data from a US tertiary teaching hospital [36]. One possible explanation is patients with chronic endocrinal diseases or severe pediatric heart diseases are more likely to be hospitalized leading to an increased chance of a co-diagnosis with ADEs from anti-asthmatic medications. Furthermore, given the cross-sectional nature of this study (no temporal relationship can be established), we cannot rule out the possible reverse association, that is, ADEs of anti-asthmatic medications may increase the odds of endocrine/metabolic or circulatory system diseases when corticosteroids are well known to cause endocrinal disturbances such as weight gain, which may increase the likelihood of cardiometabolic diseases [7, 37].

However, some comorbidities, such as mental disorders, nervous system diseases, digestive system diseases, and musculoskeletal system diseases seem to have protective effects. We also found some comorbidities had an opposite effect in terms of the odds of ADEs from corticosteroids and bronchodilators, respectively. For instance, neoplasms and diseases of blood and blood-forming organs were associated with a higher odds of experiencing corticosteroid ADEs, but a decreased odds of having bronchodilator ADEs. Most previous studies only reported the risks of ADEs increased with the number of comorbidities, few have examined the effect of specific diseases [36, 38]. Hence, future studies are needed to determine the mechanisms of these phenomena.

5 Limitations

This study has several limitations. In the present study, we used the number of asthmatic patients as the denominator to calculate the incidence rates for anti-asthmatic medication-related ADEs; however, a recent study found only 60–70% of pediatric patients receive corticosteroids [39]. This implies the actual incidence rate of ADEs may be even higher than the observed results if we had known the number of patients exposed to corticosteroids. It should also be noted that the pattern of asthma medication use may change over time following the change in treatment guidelines [40]. Additionally,
under-reporting of ADEs is common [41]; therefore, our
estimates are conservative.

The use of ICD-9-CM and ICD-10-CM diagnostic codes
to identify ADEs or medical conditions might result in a
misclassification bias, although ICD codes were considered
relatively accurate for inpatient data [42–45]. The change
of ICD codes from the ninth to the tenth version may also
cause a misclassification bias; however, the change should
have a minimal impact on the study results because only
a few patients had ADEs related to mineralocorticoids as
previously mentioned. Moreover, our study only applies to
inpatient ADEs, no estimates were available for ADEs that
occurred during outpatient or emergency room visits, sug-
 ranging the incidence estimates of our study may be con-
servative. The KID contains discharge-level records, not
patient-level records, which may lead to a medical surveil-
lance bias from repetitive measures of a single patient. Race
is missing on ~ 9% of discharges in the 2016 KID (~ 10% for
all years’ data) because some hospitals and HCUP state
partners do not supply it, as a result, race-specific estimates may
be biased because of missing not at random data. Finally,
although we cannot identify (1) if ADEs were preventable;
(2) specific symptoms related to ADEs; (3) ADEs from each
individual medication; or (4) dosage and duration of treat-
ment because of KID data limitations, our study provided
the first national trend estimates of ADEs from asthma medi-
cations in the US pediatric population.

6 Conclusions

Nationally representative, pediatric inpatient data inci-
dence estimates of ADEs related to anti-asthmatic medi-
cations have been substantially increasing among younger
children in the USA over the past two decades, resulting in
substantially increased healthcare costs. Collectively, these
findings can inform healthcare systems that more efforts are
needed to prevent ADEs from anti-asthmatic medications.
Very young asthmatic children with complex medical condi-
tions may benefit the most from ADE monitoring. Further
research is needed to explore the specific ADEs from indi-
 vidual asthma medications and the impact of variations in
dose and duration.

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Declarations

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Subjects ruled this study to be exempt from review and informed con-
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sis.

Consent to participate Not applicable.

Consent to publication Not applicable.

Availability of data and material The datasets analyzed during the cur-
rent study are available in the Kids’ Inpatient Database repository, available at https://www.hcup-us.ahrq.gov/db/nation/kid/kiddbdou-
entation.jsp.

Code availability The codes generated during and/or analyzed dur-
ing the current study are available from the first author on reasonable
request.

Authors’ contributions LX conceptualized and designed the study,
drafted the initial manuscript, and carried out the initial analyses. AG
coordinated, supervised data acquisition, reviewed and revised the
manuscript. FA supervised data analyses, provided interpretation of
the results, reviewed and revised the manuscript. MM helped with data
cleaning, reviewed and revised the manuscript. SEM helped with data
acquisition, analysis, interpretation, reviewed and revised the manu-
script. All authors read and approved the final version.

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References

1. National Center for Health Statistics. Health, United States, 2019:
Table 039. Hyattsville, MD. 2021. https://www.cdc.gov/nchs/hus/
contents2019.htm. Accessed 22 Jun 2021.

2. U.S. Department of Health and Human Services. National Action
Plan for Adverse Drug Event Prevention. U.S. Department of
Health and Human Services. 2014. https://health.gov/hcq/pdfs/
ade-action-plan-508c.pdf. Accessed 22 Jun 2021.

3. U.S. Department of Health and Human Services. Adverse Drug
Events. 2021. https://health.gov/our-work/health-care-quality/
adverse-drug-events. Accessed 22 Jun 2021.

4. CDC. Most recent national asthma data. https://www.cdc.gov/
asthma/most_recent_national_asthma_data.htm. Accessed 30 Aug
2021.

5. Agency for Healthcare Research and Quality. Healthcare Cost
and Utilization Project (2018). U.S. Department of Health and
Human Services, Centers for Disease Control and Prevention.
2019. https://www.cdc.gov/asthma/national-surveillance-data/healthcare-use.htm. Accessed 17 Jun 2021.
6. Leung JS, Johnson DW, Sperou AJ, et al. A systematic review of adverse drug events associated with administration of common asthma medications in children. PLoS ONE. 2017;12(8):e0182738.
7. Dahl R. Systemic side effects of inhaled corticosteroids in patients with asthma. Respir Med. 2006;100(8):1307–17. https://doi.org/10.1016/j.rmed.2005.11.020.
8. Loke YK, Blanco P, Thavarajah M, Wilson AM. Impact of inhaled corticosteroids on growth in children with asthma: systematic review and meta-analysis. PLoS ONE. 2015;10(7):e0133428. https://doi.org/10.1371/journal.pone.0133428.
9. Kelly HW, Sternberg AL, Lescher R, et al. Effect of inhaled glucocorticoids in childhood on adult height. N Engl J Med. 2012;367(10):904–12. https://doi.org/10.1056/NEJMoa1203229.
10. Pedersen S. Do inhaled corticosteroids inhibit growth in children? Am J Respir Crit Care Med. 2001;164(4):521–35. https://doi.org/10.1164/ajrccm.164.4.2101050.
11. Sears MR. Adverse effects of beta-agonists. J Allergy Clin Immunol. 2002;110(6 Suppl.):S322–8. https://doi.org/10.1016/S1091-2508(02)82849-6.
12. Hasford J, Virchow JC. Excess mortality in patients with asthma on long-acting beta-2-agonists [published correction appears in Eur Respir J 2007 Apr;29(4):823]. Eur Respir J. 2006;28(5):900–2. https://doi.org/10.1183/09031936.00085606.
13. Kid Related Reports. Healthcare cost and utilization project. Agency for Healthcare Research and Quality; Rockville, MD. http://www.hcupus.ahrq.gov/kidoverview.jsp. Accessed 22 June 2021.
14. Cloutier MM, Baptist AP, Expert Panel Working Group of the National Heart, Lung, and Blood Institute (NHLBI) administered and coordinated National Asthma Education and Prevention Program Coordinating Committee (NAEPPCC), et al. 2020. Accessed 11 May 2022.
15. Medicode. ICD-9-CM: international classification of diseases, 9th revision, clinical modification. Salt Lake City: Medicode; 1996.
16. World Health Organization. ICD-10: international statistical classification of diseases and related health problems: tenth revision, 2nd ed. 2004. https://apps.who.intiris/handle/10665/42980. Accessed 11 May 2022.
17. Gillisena A. Patient’s adherence in asthma. J Physiol Pharmacol. 2007;58 Suppl. 5(Pt 1):205–22.
18. Desager K, Vermeulen F, Bodart E. Adherence to asthma treatment in childhood and adolescence: a narrative literature review. Acta Clin Belg. 2018;73(5):348–55. https://doi.org/10.1016/j.actacli.2018.01.024.
19. Tundia NL, Heaton PC, Kelton CM. The national burden of E-code-identified adverse drug events among hospitalized children using a national discharge database. Pharmacoepidemiol Drug Saf. 2011;20(8):866–78. https://doi.org/10.1002/pds.2150.
20. Lugogo N, Gilbert I, Tkacz J, Gandhi H, Goshi N, Lanz MJ. Real-world patterns and implications of short-acting beta-2-agonist use in patients with asthma in the United States. Ann Allergy Asthma Immunol. 2021;126(6):681–9.e1. https://doi.org/10.1016/j.anai.2021.01.024.
21. Nwaru BI, Ekström HS, Hasvold P, Wiklund F, Telg G, Janson C. Overuse of short-acting beta-2-agonists in asthma is associated with increased risk of exacerbation and mortality: a nationwide cohort study of the global SABINA programme. Eur Respir J. 2020;55(4):1901872. https://doi.org/10.1183/13993003.01872-2019.
22. Banjari M, Kano Y, Almadani S, Basakran A, Al-Hindi M, Alahmadi T. The relation between asthma control and quality of life in children. Int J Pediatr. 2018;2018:6517329. https://doi.org/10.1155/2018/6517329.
23. Hsu J, Qin X, Beavers SF, Mirabelli MC. Asthma-related school absenteeism, morbidity, and modifiable factors. Am J Prev Med. 2016;51(1):23–32. https://doi.org/10.1016/j.amepre.2015.12.012.
24. Goodwin RD, Robinson M, Sly PD, et al. Severity and persistence of asthma and mental health: a birth cohort study. Psychol Med. 2013;43(6):1313–22. https://doi.org/10.1017/S0033291713001754.
25. Easter G, Sharpe L, Hunt CJ. Systematic review and meta-analysis of anxious and depressive symptoms in caregivers of children with asthma. J Pediatr Psychol. 2015;40(7):623–32. https://doi.org/10.1093/jpepsy/jsv012.
26. Kravitz J, Dominici P, Ulberg J, et al. Two days of dexamethasone versus 5 days of prednisone in the treatment of acute asthma: a randomized controlled trial. Ann Emerg Med. 2011;58:200–4.
27. Rehre MJ, Liu B, Rodriguez M, et al. A randomized controlled noninferiority trial of single dose of oral dexamethasone versus 5 days of oral prednisone in acute adult asthma. Ann Emerg Med. 2016;68:608–13.
28. Cai KJ, Su SQ, Wang YG, Zeng YM. Dexamethasone versus prednisone or prednisolone for acute pediatric asthma exacerbations in the emergency department: a meta-analysis. Pediatr Emer Care. 2021;37(12):e1139–44.
29. Sikdar KC, Alaghebehbandan R, MacDonald D, et al. Adverse drug events in adult patients leading to emergency department visits. Ann Pharmacother. 2010;44(4):614–9. https://doi.org/10.1345/aph.1M146.
30. Wraight JM, Hancox RJ, Herbison GP, Cowan JO, Flannery EM, Taylor DR. Bronchodilator tolerance: the impact of increasing bronchodilator constrictor. Eur Respir J. 2003;21(5):810–5. https://doi.org/10.1183/09031936.00067503.
31. Mak ACY, White MJ, Eckalbar WL, Szpiech ZA, Oh SS, Pinoyanes N, NHLBI Trans-Omics for Precision Medicine (TOPMed) Consortium, et al. Whole-genome sequencing of pharmacogenetic drug response in racially diverse children with asthma. Am J Respir Crit Care Med. 2018;197(12):1552–64.
32. Choudhry S, Ung N, Avila PC, et al. Pharmacogenetic differences in response to albuterol between Puerto Ricans and Mexicans with asthma. Am J Respir Crit Care Med. 2005;171(6):563–70. https://doi.org/10.1164/rccm.200409-1286OC.
33. Baehr A, Peña JC, Hu DJ. Racial and ethnic disparities in adverse drug events: a systematic review of the literature. J Racial Ethn Health Disparities. 2015;2(4):527–36.
34. Samedy-Bates LA, Oh SS, Nuckton TJ, et al. Racial/ethnic-specific differences in the effects of inhaled corticosteroid use on bronchodilator response in patients with asthma. Clin Pharmacol Ther. 2019;106(5):1133–40. https://doi.org/10.1002/cpt.1555.
35. Naqvi M, Tcheurekdjian H, DeBoard JA, et al. Inhaled corticosteroids and augmented bronchodilator responsiveness in Latino and African American asthmatic patients. Ann Allergy Asthma Immunol. 2008;100(6):551–7. https://doi.org/10.1016/j.anai.2006.04.005.
36. Evans RS, Lloyd JF, Stoddard GJ, Nebecker JR, Samore MH. Risk factors for adverse drug events: a 10-year analysis. Ann Pharmacother. 2005;39(7–8):1161–8. https://doi.org/10.1345/aph.1J642.
37. Allen DB. Inhaled corticosteroids and endocrine effects in childhood. Endocrinol Metab Clin North Am. 2020;49(4):651–65. https://doi.org/10.1016/j.ecl.2020.07.003.
38. Sikdar KC, Alaghebehbandan R, Macdonald D, Barrett B, Collins KD, Gadag V. Adverse drug events among children presenting to a hospital emergency department in Newfoundland and Labrador.
Canada Pharmacoepidemiol Drug Saf. 2010;19(2):132–40. https://doi.org/10.1002/pds.1900.

39. Peterson R, Young KD. Dexamethasone versus prednisone for pediatric acute asthma exacerbations: specialists’ practice patterns. Pediatr Emerg Care. 2021;37(7):343–7. https://doi.org/10.1097/PEC.0000000000002036.

40. Reddel HK, FitzGerald JM, Bateman ED, et al. GINA 2019: a fundamental change in asthma management: treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents. Eur Respir J. 2019;53(6):1901046. https://doi.org/10.1183/13993003.01046-2019.

41. Hazell L, Shakir SA. Under-reporting of adverse drug reactions: a systematic review. Drug Saf. 2006;29(5):385–96. https://doi.org/10.2165/00002018-200629050-00003.

42. Saff RR, Camargo CA Jr, Clark S, Rudders SA, Long AA, Banerji A. Utility of ICD-9-CM codes for identification of allergic drug reactions. J Allergy Clin Immunol Pract. 2016;4(1):114-9.e1.

43. Saff RR, Li Y, Santhanakrishnan N, et al. Identification of inpatient allergic drug reactions using ICD-9-CM codes. J Allergy Clin Immunol Pract. 2019;7(1):259-64.e1. https://doi.org/10.1016/j.jaip.2018.07.022.

44. O’Malley KJ, Cook KF, Price MD, Wildes KR, Hurdle JF, Ashton CM. Measuring diagnoses: ICD code accuracy. Health Serv Res. 2005;40(5 Pt 2):1620–39. https://doi.org/10.1111/j.1475-6773.2005.00444.x.

45. Joos C, Lawrence K, Jones AE, Johnson SA, Witt DM. Accuracy of ICD-10 codes for identifying hospitalizations for acute anticoagulation therapy-related bleeding events. Thromb Res. 2019;181:71–6. https://doi.org/10.1016/j.thromres.2019.07.021.