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ORIGINAL RESEARCH ARTICLE

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 ≤ 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.

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1 Introduction

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 β_2-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., β_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. (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 χ^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.

$$\text{Incidence porportion} = \frac{\text{Frequecy of ADEs per year}}{\text{Total persons at risk}} \times 1000.$$

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% [SE 0.13%] vs 55.1% [SE 0.54%], $p < 0.001$). Non-Hispanic black individuals were the most prevalent (39.2% [SE 1.42%]) ethnic group who experienced an ADE from anti-asthmatic medications followed by non-Hispanic white individuals (34.8% [SE 1.06%]), Hispanic individuals (18.0% [SE 1.03%]), and other race/ethnicities (8.0% [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% [SE 0.94%] vs 53.7% [SE 0.46%], $p < 0.001$) and quartile 1 (lowest) median household income (36.7% [SE 1.34%] vs 34.8% [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% [SE 0.93%] vs 14.6% [SE 0.29%]), infectious and parasitic disease (18.2% [SE 0.68%] vs 11.2% [SE 0.26%]), and diseases of blood and blood-forming organs (15.9% [SE 0.59%] vs 5.8% [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% [SE 1.25%] vs 66.5% [SE 0.91%], $p < 0.001$) or in the Southern region (38.7% [SE 2.56%] vs 37.8% [SE 1.29%], $p < 0.001$).

Table 1 also shows 48.4% (SE 0.89%) of visits involving an ADE from corticosteroids were for adolescents aged 12–20 years while the majority of visits involved bronchodilator ADEs for children aged 5–11 years (41.9% [SE 0.71%]). Slightly more boys were discharged with ADEs from bronchodilators than from corticosteroids (58.5% [SE 0.64%] vs 51.1% [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% CI 0.4–0.8] per 1000 discharges in 2000 to 14.3 [95% 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[b]
	Corticosteroids	Bronchodilators	Any[a]		
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[d]	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)	
12–20,% (SE)	48.4 (0.89)	20.8 (0.68)	33.4 (0.88)	25.1 (0.34)	
Sex,% (SE)[e]					< 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)[f]					< 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)[g]					< 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)[c,h]					
Quartile 1 (lowest)	32.8 (0.89)	36.8 (2.34)	36.7 (1.34)	34.8 (0.67)	0.064
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)					
Infectious and parasitic disease	14.9 (0.56)	21.3 (0.99)	18.2 (0.68)	11.2 (0.26)	< 0.001
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)[i]					
Small	12.6 (0.90)	12.3 (2.60)	12.6 (1.69)	13.5 (0.90)	0.744
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)[i]					
Rural	8.3 (0.32)	1.8 (0.21)	4.9 (0.37)	10.2 (0.35)	< 0.001
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)					

Table 1 (continued)

	Discharges with ADE by medication type			Discharges without ADE	*p*-value[b]
	Corticosteroids	Bronchodilators	Any[a]		
Northeast	17.3 (1.10)	19.3 (2.63)	18.4 (1.83)	23.8 (1.26)	< 0.001
Midwest	22.0 (1.15)	26.8 (3.58)	24.8 (2.35)	19.2 (0.96)	
South	42.2 (1.52)	35.6 (3.75)	38.7 (2.56)	37.8 (1.29)	
West	18.4 (1.09)	18.2 (2.46)	18.1 (1.74)	19.1 (1.03)	

ADE adverse drug events, *SE* standard error

[a]There were 405 discharges with ADEs from both corticosteroids and bronchodilators, thus the total number of 12,640 is less than the sum of the events of individual medications

[b]Two-sample *t*-test or Rao–Scott Chi-square test to compare patients with and without ADEs

[c]Quartile classification of the estimated median household income of residents in the patient's ZIP code. The quartiles are identified by values of 1–4, indicating the poorest to wealthiest populations

[d]$N_{missing} = 19$

[e]$N_{missing} = 27$

[f]$N_{missing} = 1349$

[g]$N_{missing} = 7$

[h]$N_{missing} = 160$

[i]$N_{missing} = 333$

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, musculoskeletal 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

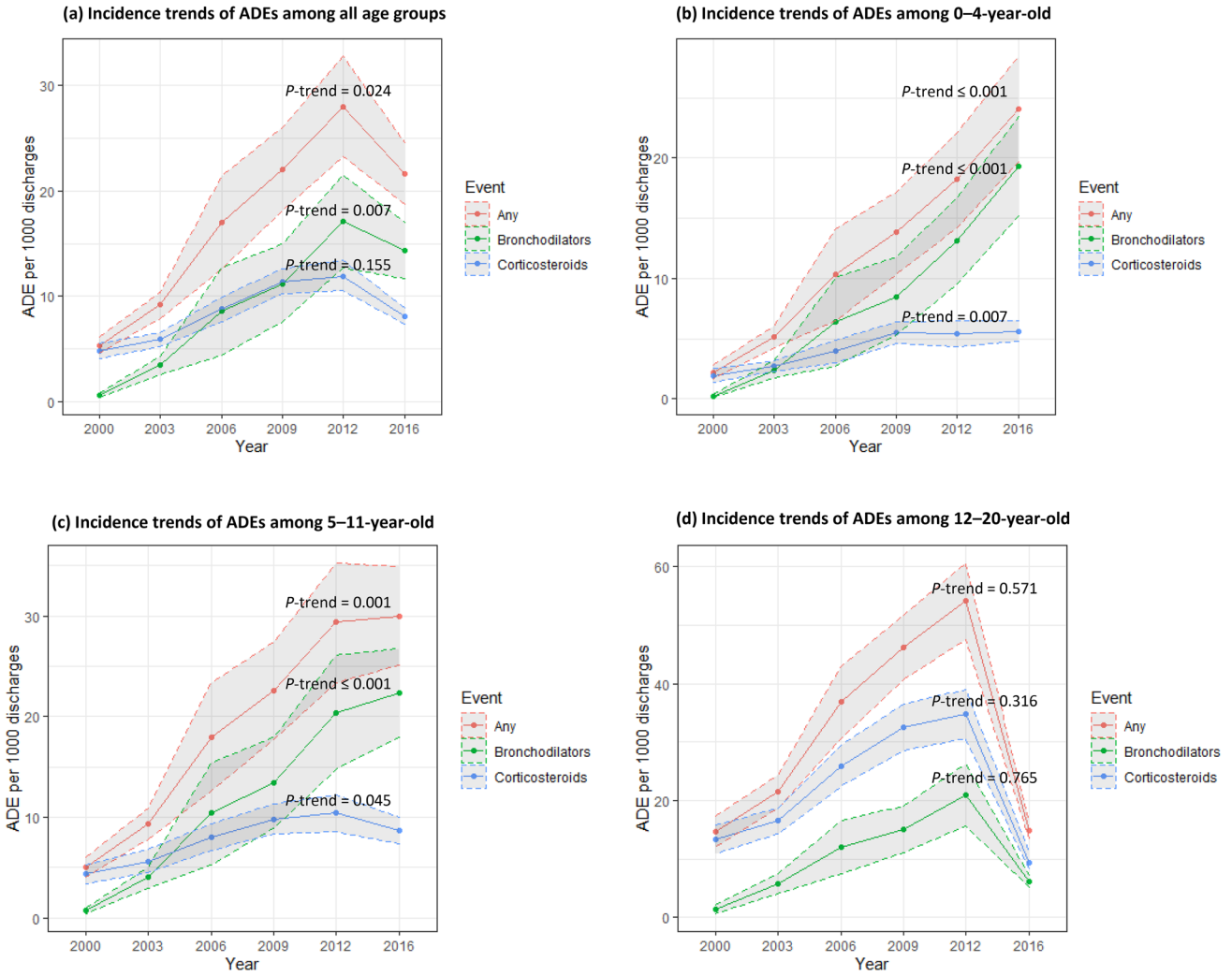

Fig. 1 **A–D** Incidence trends of inpatient adverse drug events (ADEs) related to anti-asthmatic medications by age groups, 2000–16

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 β_2 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

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[a] (95% CI)	1 (ref)	**1.39 (1.36–1.41)**	1 (ref)	0.99 (0.97–1.01)
p-value[a]	–	**< 0.001**	–	0.325
Adjusted IRR[b] (95% CI)	1 (ref)	**1.14 (1.12–1.17)**	1 (ref)	**0.91 (0.89–0.93)**
p-value[b]	–	**< 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[c] (95% CI)	1 (ref)	**1.79 (1.75–1.84)**	1 (ref)	**1.32 (1.29–1.36)**
p-value[c]	–	**< 0.001**	–	**< 0.001**
Adjusted ratio ADE vs no ADE[d] (95% CI)	1 (ref)	**1.42 (1.39–1.46)**	1 (ref)	**1.07 (1.05–1.09)**
p-value[d]	–	**< 0.001**	–	**< 0.001**
Mortality				
N (%)	437 (0.06)	10 (0.18)	446 (0.06)	1 (0.01)
Crude OR[e] (95% CI)	1 (ref)	**2.9 (1.4–6.1)**	1 (ref)	0.2 (0–1.4)
p-value[e]	–	**0.005**	–	0.102
Adjusted OR[f] (95% CI)	1 (ref)	1.5 (0.7–3.3)	1 (ref)	0.2 (0–1.0)
p-value[f]	–	0.338	–	0.052

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

[a]Univariate negative binomial regression

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

[c]Univariate generalized linear model with a gamma distribution and log link

[d]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

[e]Univariate logistic regression

[f]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 ($p < 0.05$)

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 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[a], 95% CI	Adjusted OR[b], 95% CI	Crude OR[a], 95% CI	Adjusted OR[d], 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[c]	1.0 (0.95–1.05)	N/A[c]
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[c]	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 (2.8–3.24)**
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

*$p < 0.05$; *$p < 0.001$

[a]Univariate logistic regression

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

[c]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, suggesting the incidence estimates of our study may be conservative. The KID contains discharge-level records, not patient-level records, which may lead to a medical surveillance 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) dosing and duration of treatment because of KID data limitations, our study provided the first national trend estimates of ADEs from asthma medications in the US pediatric population.

6 Conclusions

Nationally representative, pediatric inpatient data incidence estimates of ADEs related to anti-asthmatic medications 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 conditions may benefit the most from ADE monitoring. Further research is needed to explore the specific ADEs from individual asthma medications and the impact of variations in dose and duration.

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Consent to participate Not applicable.

Consent to publication Not applicable.

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

Code availability The codes generated during and/or analyzed during 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 and GD provided clinical guidance, critically reviewed the manuscript for important intellectual content, and revised the manuscript. MM coordinated, supervised data acquisition, reviewed and revised the manuscript. FA supervised data analyses, provided interpretation of the results, reviewed and revised the manuscript. NS helped with data cleaning, reviewed and revised the manuscript. SEM helped with data acquisition, analysis, interpretation, reviewed and revised the manuscript. All authors read and approved the final version.

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