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Association of corticosteroid use and attention deficit/hyperactivity disorder in asthmatic children varies by age

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ABSTRACT

Objective: We aim to examine the impact of corticosteroids use on ADHD among children with asthma by administration routes.

Methods: A population-based, cross-sectional analysis included pediatric patients ages 5–20 years old from the 2016 and 2019 Kids Inpatient Database (unweighted $N=111,702$). ICD-10-CM codes were used to identify corticosteroids use, asthma, and ADHD cases. Survey logistic regression models with purposeful variable selection algorithms were built to examine the association between corticosteroids use, and ADHD by asthma severity and age. An inverse probability weighting (IPW) approach was used to help further control residual confounding.

Results: Among children aged 5–11 years old, the odds of ADHD were significantly higher in children with moderate to severe asthma who used inhaled corticosteroids than nonusers (moderate asthma: adjusted odds ratios [aOR] 1.46, 95% confidence interval [CI] 1.14–2.44; severe asthma: aOR 1.61, 95% CI 1.18–2.21). Although oral corticosteroid use was not independently associated with ADHD in young children, combined use of inhaled and oral corticosteroid had almost 5 times higher odds of use among ADHD in children with severe asthma vs. nonusers (aOR 4.85, 95% CI 2.07–11.35). No associations were found between any corticosteroid use and ADHD among asthmatic children aged 12–20 years.

Conclusions: In this retrospective analysis, we found inhaled corticosteroids were positively associated with ADHD in younger children with moderate to severe asthma, but not in older children.

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Asthma; ADHD; corticosteroids; Kids Inpatient Database

Introduction

Asthma is a common childhood disease and associated with airway hyperresponsiveness that is caused by immunological responses¹. Attention-deficit/hyperactivity disorder (ADHD) is another common childhood disease that may be highly immune-relevant.² Various studies have reported children with asthma are more likely to have concomitant behavioral disorders, including ADHD, compared to those who do not have asthma.^{3–8} In the United States, the estimated prevalence of asthma in children with ADHD is 17.2% vs. 8.1% in children without ADHD.³ Additionally, one previous study suggested patients

with severe asthma were more likely to have ADHD than those with mild asthma.⁴

Despite the repeated reported association between asthma and ADHD^{3–8} that has been confirmed by a large-scale meta-analysis⁶, the underlying mechanisms remain unclear. Limited studies have investigated the role of asthma medications, including corticosteroids, in this relationship. Biologically, corticosteroids are known to decrease cytokine and serotonin levels, which may contribute to an increased risk of behavioral and neurodevelopmental disorders including ADHD.^{8,9} A retrospective cohort study from Denmark ($n=875,996$) found children who were prenatally exposed to oral or inhaled corticosteroids had 1.4

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(95% confidence interval [CI] 1.24–1.65) and 1.2 (95% CI 1.15–1.31) times higher risk, respectively, of developing ADHD in later life compared to non-exposure after adjusting for confounding variables.¹⁰ However, this transgenerational study did not examine asthma severity as a potential confounder or moderator.¹⁰

Conversely, some studies suggest asthma medications do not contribute to the association between asthma and ADHD.^{4,5} A Swedish study with 20,072 twins aged 9 or 12 years reported childhood asthma and ADHD were associated, but asthma medications including inhaled corticosteroids did not increase ADHD risk (OR 0.69, 95% CI 0.15–1.87).⁴ Another prospective study also did not find any significant difference in ADHD symptoms between middle-school children with asthma who received inhaled corticosteroids and those who did not.⁵ However, neither study included children with younger or older age, or assessed the use of oral corticosteroids in any models.^{4,5}

Given the inconsistent results and lack of literature on children of different ages and oral corticosteroids use, there is a need to further examine the intersection of childhood asthma, ADHD, and the use of corticosteroids by administration routes using nationally representative data. It was hypothesized the use of corticosteroids would increase the odds of ADHD in children with mild to severe asthma.

Methods

Study design, setting, and participants

This population-based, cross-sectional analysis was conducted in children aged 5–20 years who were diagnosed with mild to severe asthma from the 2016 and 2019 Kids' Inpatient Database (KID) (unweighted total $n = 111,702$) (Supplemental Figure 1). We excluded children younger than 4 years because ADHD is rarely diagnosed in children this young.¹¹ KID was developed for the Healthcare Cost and Utilization Project (HCUP) and sponsored by the Agency for Healthcare Research and Quality (AHRQ). It is the largest publicly available all-payer (Medicaid, Medicare, private insurance, or uninsured) pediatric inpatient care database in the US representing approximately 7 million pediatric patients annually, which allows national studies of common and rare pediatric conditions. The sampling frame of 2016 KID includes pediatric discharges data from 4200 US community (i.e. nonfederal, short-term, general, and specialty hospitals) and non-rehabilitation hospitals. Additional details of the KID can be found elsewhere.¹²

Measurements

A Directed Acyclic Graph (DAG) was created to demonstrate the associations among the following variables of interest (Figure 1).

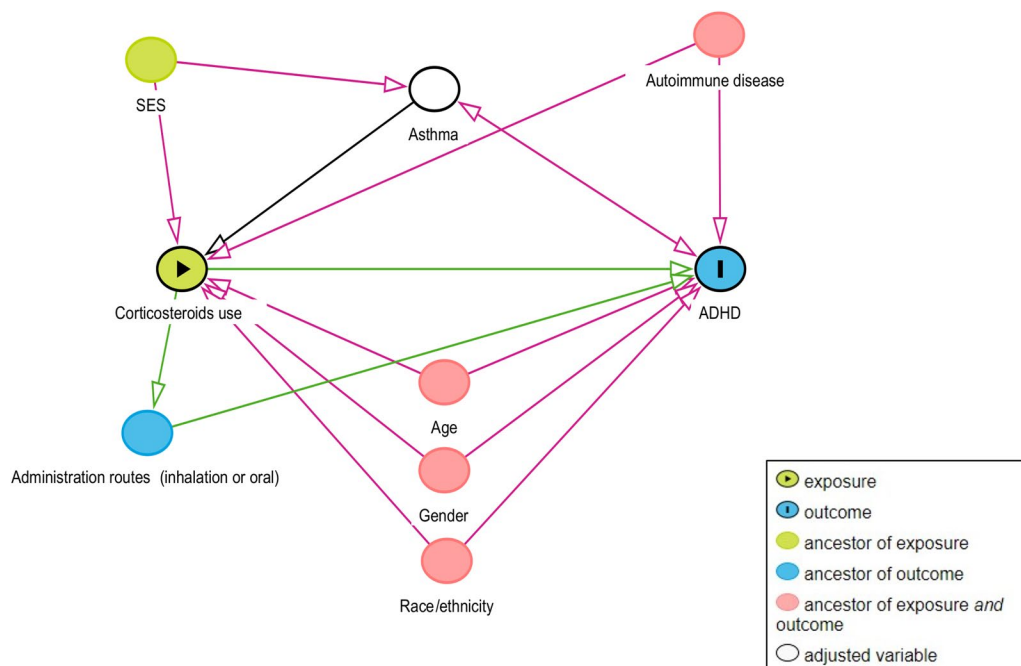


Figure 1. Directed acyclic graph (DAG) to visualize potential associations among variables of interest. Exposure variable: corticosteroids use by administration method; outcome variable: ADHD; covariate and effect modifier: asthma severity; other covariates: age, gender, race/ethnicity, socioeconomic status (SES), and autoimmune disease.

Exposure variables

The use of corticosteroids was measured by administration routes (inhalation only, oral use only, both inhalation and oral use, and nonuse) and determined by International Classification of Disease, Tenth Revision, Clinical Modification (ICD-10-CM) codes. If patients received any of the following ICD codes during the study period, they were considered corticosteroids users. Specifically, the sample size by categories are as follows; (a) *Inhalation only*. A total of 11,189 (9.9%, 95% CI 8.7–11.2%) children only used inhaled corticosteroids according to the ICD-10-CM codes Z79.; (b) *Oral use*. A total of 1170 (1.0%, 95% CI 0.9–1.2%) only used oral corticosteroids according to ICD-10-CM codes Z79.52. (c) *Both inhalation and oral use*. 686 (0.6%, 95% CI 0.5–0.8%) children used both inhaled and oral corticosteroids (ICD-10-CM codes: Z79.51 and Z79.52). (d) *Nonuse*. The majority (88.4%) of the study population did not use any types of corticosteroids and was the comparison group.

Outcome variable

ADHD is the outcome of interest. ICD-10-CM codes F90.x were used to identify children with ADHD ($n=8607$ [7.7%, 95% CI 7.2–8.3%]).

Covariates

We used ICD-10-CM codes J45.2 and J45.3 to capture patients with mild asthma ($n=67,130$ [60.0%, 95% CI 59.0–61.1%]), J45.4 for patients with moderate asthma ($n=32,779$ [29.4%, 95% CI 28.7–30.1%]) and J45.5 for patients with severe asthma ($n=11,793$ [10.6%, 95% CI 10.1–11.1%]).

Other covariates of interest include patient age, sex (male and female), race/ethnicity (non-Hispanic White [NHW], non-Hispanic Black [NHB], Hispanic, and other), insurance information (Medicare, Medicaid, private, and other/self-pay), and comorbidities. Age was categorized into two groups (5–11 years and 12–20 years) based upon the current asthma treatment guideline.¹³ Additionally, because some diseases are commonly prescribed with corticosteroids and associated with an increased risk of behavioral disorders^{14,15}, patients with nephrotic syndrome, cystic fibrosis, Crohn's disease, and common pediatric autoimmune diseases, such as juvenile arthritis and lupus, were included as covariates and adjusted for in the models.

Statistical analysis

Categorical variables were presented as weighted percentages with 95% CI, and continuous variables were

summarized as weighted means with 95% CI. The normality of continuous variables was assumed based on the Central Limit Theorem¹⁶, therefore, analysis of variance (ANOVA) and Rao-Scott χ^2 analysis was used to compare continuous and categorical variables, respectively, among patients with different corticosteroid use status, i.e. inhalation only, oral only, both inhalation and oral use, and nonuse.

Two sets of logistic regression models incorporating a purposeful selection of covariates built algorithms to examine the association between the use of corticosteroids and ADHD based upon asthma severity and by age group. The first set of models included asthmatic patients aged 5–11 years, and the second set included those aged 12–20 years. For each age group, crude and adjusted multivariate models were used to assess the odds of having ADHD among patients with mild, moderate, and severe asthma, respectively. To further assess the multiplicative joint effect of age and corticosteroids use on ADHD risks, interaction term age groups*corticosteroids were added to the models.

Data were analyzed from August 31, 2021, to February 16, 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). Two-sided p values < 0.05 was considered significant.

Sensitivity analysis

An inverse probability weighting (IPW) approach was used to help further control residual confounding of age, sex, and race/ethnicity between patients with and without ADHD. This is an effective statistical method that can be used to address residual confounding, and selection bias in particular, due to a lack of randomization.^{17,18} First, we generated predictive probability using logistic regression models, then computed the inverse of predictive weighting (i.e. IPW). For patients with ADHD, $IPW = 1/\text{predictive probability}$, and for patients without ADHD, $IPW = 1/(1 - \text{predictive probability})$. The final weights used in prediction models were generated by using sampling weight multiply by IPW.¹⁹

Results

Table 1 shows the demographics and comorbidities of corticosteroids users and nonusers. The average age of patients who only used inhaled, oral, or both corticosteroids was 10.26 (standard error [SE] 0.08)

Table 1. Characteristics of children with asthma by corticosteroids administration method and nonuse, HCUP KID 2016–2019 ($N = 111,702$).

	Inhalation only ($n = 11,189$)	Oral use only ($n = 1170$)	Both inhalation and oral use ($n = 686$)	Nonuse ($n = 98,657$)	p Value ^a
Age, mean (SE), years	10.26 (0.08)	11.81 (0.17)	11.03 (0.29)	10.94 (0.06)	<0.001
5–11 years, weighted% (95% CI)	60.0 (58.5–61.5)	43.8 (40.5–47.1)	52.8 (46.2–59.4)	53.6 (52.4–54.8)	<0.001
12–20 years, weighted% (95% CI)	40.0 (38.5–41.5)	56.2 (52.9–59.5)	47.2 (40.6–53.8)	46.4 (45.2–47.5)	–
Sex, weighted % (95% CI)					<0.001
Male	54.7 (53.7–55.8)	49.0 (45.5–52.6)	53.7 (48.6–58.8)	52.1 (51.6–52.7)	–
Female	45.3 (44.2–46.3)	51.0 (47.4–54.5)	46.3 (41.2–51.4)	47.9 (47.3–48.4)	–
Race/ethnicity, weighted% (95% CI)					0.093
Non-Hispanic White	30.9 (28.4–33.3)	34.3 (30.9–37.7)	32.0 (27.5–36.6)	31.4 (29.5–33.3)	–
Non-Hispanic Black	39.6 (35.6–43.6)	36.6 (32.8–40.5)	42.5 (37.8–47.3)	36.7 (34.5–38.9)	–
Hispanic	21.1 (18.3–23.9)	21.2 (17.9–24.5)	19.1 (14.9–23.4)	22.9 (20.9–24.9)	–
Other	8.4 (7.0–9.8)	7.8 (5.8–9.8)	6.3 (4.3–8.3)	9.0 (7.9–10.0)	–
Insurance, weighted% (95% CI)					0.030
Medicare	0.3 (0.1–0.4)	0.3 (0.0–0.7)	0.6 (0.01–1.1)	0.3 (0.2–0.4)	–
Medicaid	64.1 (62.5–65.8)	58.4 (55.1–61.7)	61.6 (57.8–65.3)	62.3 (60.9–63.6)	–
Private	30.0 (28.4–31.7)	34.8 (31.6–38.0)	33.4 (29.7–37.2)	31.8 (30.6–33.0)	–
Other/self-pay	5.6 (4.9–6.2)	6.5 (4.9–8.0)	4.4 (2.8–6.0)	5.6 (5.0–6.2)	–
Median household income, weighted% (95% CI)					0.474
Quartile 1 (lowest)	39.7 (36.3–43.0)	39.1 (35.5–42.8)	37.4 (32.9–41.8)	38.9 (36.4–41.3)	–
Quartile 2	22.3 (20.9–23.7)	24.8 (22.0–27.6)	23.7 (18.4–29.1)	22.6 (21.5–23.7)	–
Quartile 3	22.7 (20.9–24.4)	19.9 (17.0–22.9)	21.4 (17.2–25.7)	21.6 (20.6–22.7)	–
Quartile 4 (highest)	15.4 (13.4–17.4)	16.2 (13.4–18.9)	17.5 (12.8–22.2)	17.0 (15.6–18.3)	–
Asthma severity, weighted% (95% CI)					<0.001
Mild asthma	38.6 (36.8–40.4)	40.3 (36.9–43.9)	24.3 (20.9–27.7)	62.9 (61.9–63.9)	–
Moderate asthma	43.6 (42.2–44.9)	32.6 (29.6–35.7)	42.1 (37.8–46.5)	27.7 (26.9–28.4)	–
Severe asthma	17.8 (16.4–19.1)	27.0 (23.6–30.4)	33.5 (28.9–38.2)	9.4 (8.9–9.9)	–
ADHD, weighted% (95% CI)	7.5 (6.8–8.2)	7.4 (5.8–8.9)	7.6 (4.9–10.4)	7.8 (7.2–8.4)	0.847
Comorbidities ^b					
Nephrotic syndrome	0.1 (0.05–0.2)	5.2 (3.6–6.8)	0.4 (0–0.9)	0.2 (0.1–0.3)	<0.001
Cystic fibrosis	2.3 (1.6–3.0)	1.5 (0.7–2.2)	1.5 (0.6–2.3)	1.4 (1.1–1.6)	<0.001
Crohn's disease	0.3 (0.2–0.4)	2.3 (1.4–3.2)	0.3 (0–0.7)	0.4 (0.3–0.4)	<0.001
Juvenile arthritis	0.2 (0.1–0.3)	0.9 (0.2–1.5)	0.3 (0–0.7)	0.2 (0.1–0.2)	<0.001
Systemic lupus erythematosus	0.1 (0.05–0.2)	2.1 (1.1–3.1)	0.6 (0–1.1)	0.1 (0.1–0.2)	<0.001

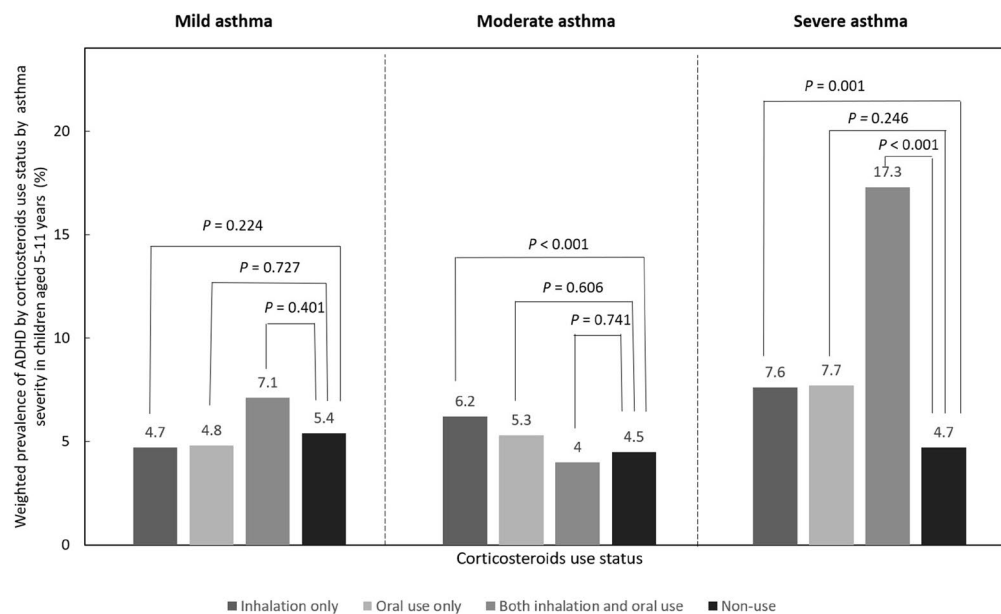
^aANOVA or chi-square analysis.^bMedical conditions that are commonly prescribed with chronic corticosteroids.

years, 11.81 (SE 0.17), or 11.03 (SE 0.29) years, respectively, and they were significantly older than nonusers (10.94 [SE 0.06] years, $p < 0.001$) except for the inhalation only group. Boys were most likely to use inhaled corticosteroids (54.7% [95% CI 53.7–55.8%]) than girls (45.3% [95% CI 44.2–46.3%]), but girls were more likely to use oral corticosteroids (51.0%; 95% CI 47.4–54.5%) than boys (49.0%; 95% CI 45.5–52.6). No ethnic differences were found for corticosteroids use. The majority of children had Medicaid insurance and low median household income in all four comparison groups.

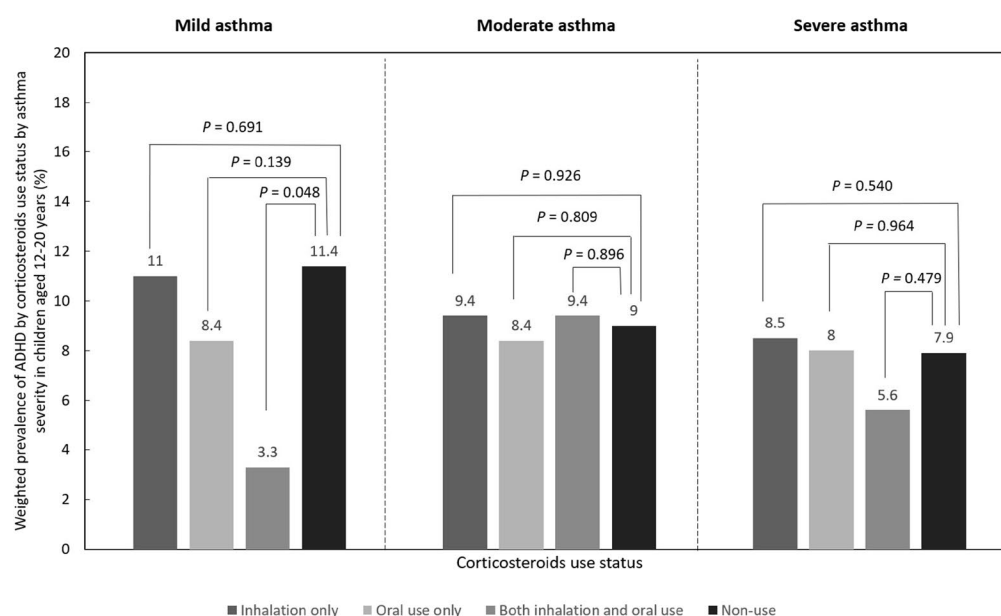
One out of every three who were both inhalation and oral corticosteroid users (33.5% [95% CI 28.9–38.2%]) had severe asthma, while about every 1 in 5 children (17.8% [95% CI 16.4–19.1%]) who only used inhaled corticosteroids had severe asthma. Likewise, the majority (42.1% [95% CI 37.8–46.5%]) of both inhalation and oral users were children with moderate asthma. The most prevalent asthma group in nonusers was those with mild asthma (62.9%, 61.9–63.9%). The prevalence estimates of ADHD were very similar across all four groups (7.5% [95% CI 6.8–8.2%]) in the inhalation only group, 7.4% [95% CI 5.8–8.9%]

in the oral only group, 7.6% [4.9–10.4%] in both inhalation and oral group, and 7.8% [95% CI 7.2–8.4%] in the nonuser group, $p = 0.847$). Table 1 also summarized the proportion of children who had comorbidities that are commonly prescribed with corticosteroids including nephrotic syndrome, cystic fibrosis, Crohn's disease, juvenile arthritis, and systemic lupus erythematosus.

In 5–11-year-old children who had moderate to severe asthma, the estimated prevalence of ADHD was significantly higher among the inhalation only use group vs. the nonuse group (moderate asthma: 6.2% [95% CI 5.3–7.1%] vs. 4.5% [95% CI 4.2–4.9%], $p < 0.001$; severe asthma: 7.6% [95% CI 5.9–9.3%] vs. 4.7% [95% CI 3.9–5.5%], $p = 0.001$). The prevalence of ADHD increased to 17.3% (95% CI 6.2–28.4%) in patients with severe asthma who used both inhaled and oral corticosteroids. However, the prevalence of ADHD did not significantly differ between oral users and nonusers in any asthma severity group (Figure 2, Panel A). In children aged 12–20 years old, no differences were found in inhalation or the oral only group compared to the nonuse group among those with mild to severe asthma (all $p > 0.05$) (Figure 2, Panel B).



(a)

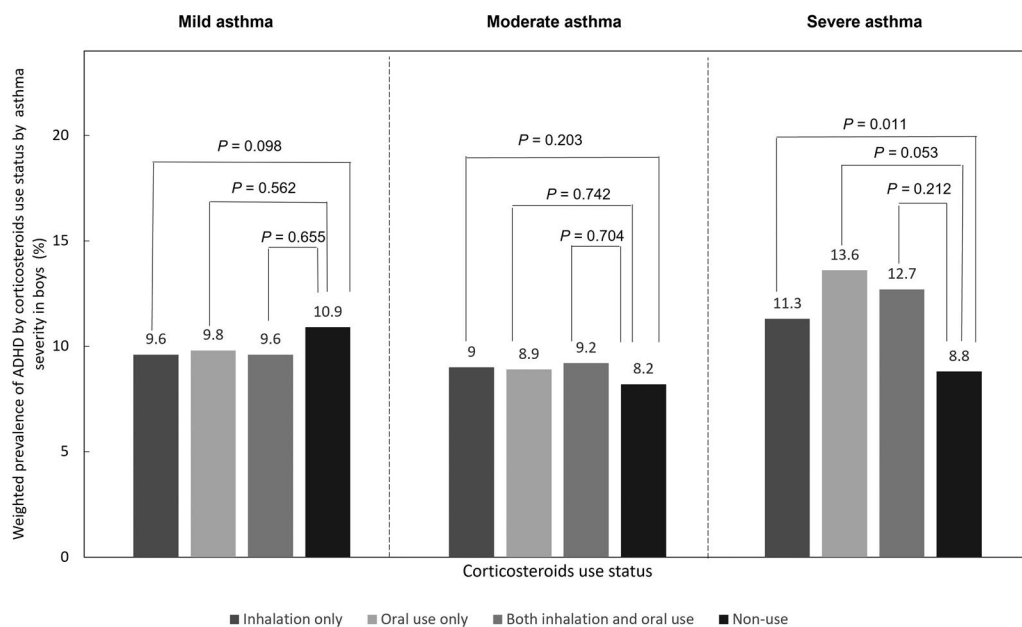


(b)

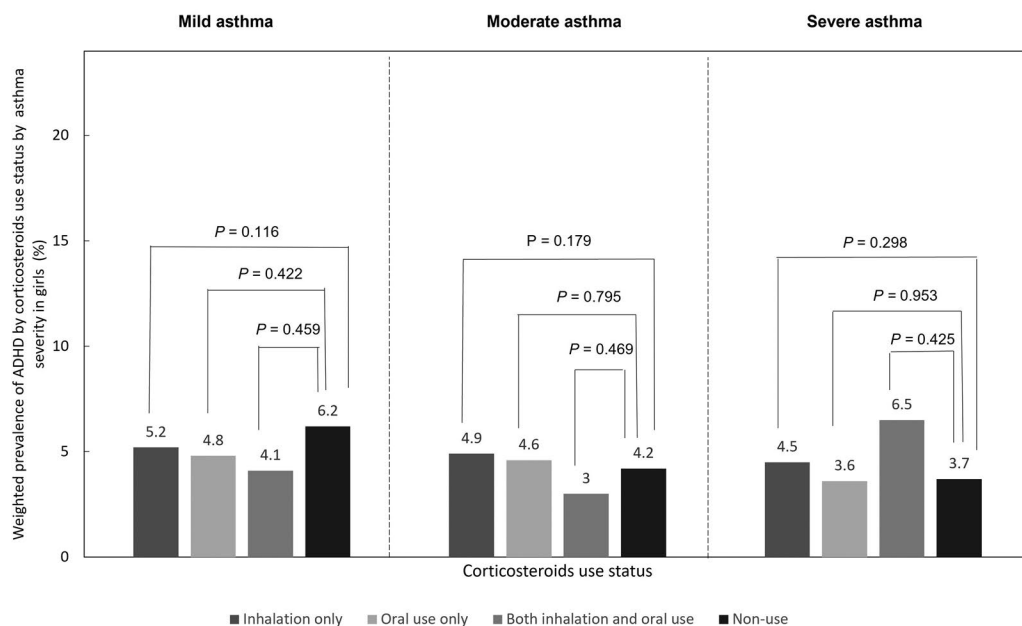
Figure 2. Panel A. Estimated prevalence of ADHD by corticosteroid administration method and use status in asthma patients aged 5–11 years old. Panel B. Estimated prevalence of ADHD by corticosteroid administration method and use status in asthma patients aged 12–20 years old.

In addition, the weighted prevalence of ADHD by asthma severity and corticosteroids use is demonstrated in Figure 3, Panels A and B. Among boys with severe asthma, 11.3% inhaled corticosteroids users had ADHD compared to 8.8% in nonusers ($p = 0.011$). However, there were no statistical differences for boys with mild to moderate asthma or girls with mild to severe asthma (all $p > 0.05$).

Table 2 shows the moderating effect of asthma severity on the association of corticosteroids use and ADHD in different age groups. Among 5–11-year-old children who had moderate asthma, after adjusting for age, sex, race/ethnicity, insurance, family income, and comorbidities, the use of inhaled corticosteroids resulted in 1.46 times higher odds of ADHD (adjusted odds ratio [aOR] = 1.46, 95% CI 1.14–2.44) compared to nonusers.



(a)



(b)

Figure 3. Panel A. Estimated prevalence of ADHD by corticosteroid administration method and use status in boys with asthma. Panel B. Estimated prevalence of ADHD by corticosteroid administration method and use status in girls with asthma.

Additionally, among young children with severe asthma, the odds of ADHD increased significantly in those who used only inhaled (aOR = 1.61, 95% CI 1.18–2.21), or both inhaled and oral corticosteroids (aOR = 4.85, 95% CI 2.07–11.35) compared to nonusers. The use of corticosteroids was not significantly associated with ADHD in children aged 12 years and above. After applying the IPW approach as described in the sensitivity analysis, all observed associations remained significant (Supplemental Table 1).

To further test the multiplicative joint effect of age and corticosteroids use on the odds of ADHD, we included an interaction term in the logistic regression models (Table 3). In the fully adjusted models, younger children were less likely to have ADHD than older children (aOR = 0.39, 95% CI 0.36–0.42 for mild asthma, aOR = 0.43, 95% CI 0.38–0.48 for moderate asthma, and aOR = 0.49, 95% CI 0.39–0.61 for severe asthma). Compared to older children who did not use any corticosteroids, the joint effect of younger

Table 2. Association between ADHD and corticosteroid use and administration routes among children with mild to moderate asthma by age groups.

5–11 years old					
Asthma severity	Corticosteroids use and administration routes	ADHD			
		OR ^a (95% CI)	p Value	aOR ^b (95% CI)	P Value
Mild asthma	Inhalation only	0.89 (0.73–1.08)	0.691	0.88 (0.72–1.08)	0.213
	Oral use only	0.89 (0.47–1.68)	0.143	0.92 (0.49–1.75)	0.807
	Both inhalation and oral use	1.36 (0.67–2.76)	0.067	0.72 (0.24–2.14)	0.553
	Nonuse	1 (ref)	–	1 (ref)	–
Moderate asthma	Inhalation only	1.39 (1.17–1.65)	<0.001	1.46 (1.14–2.44)	<0.001
	Oral use only	1.19 (0.62–2.28)	0.606	1.25 (0.63–2.48)	0.519
	Both inhalation and oral use	0.88 (0.41–1.89)	0.741	0.86 (0.35–2.13)	0.747
	Nonuse	1 (ref)	–	1 (ref)	–
Severe asthma	Inhalation only	1.64 (1.22–2.22)	0.001	1.61 (1.18–2.21)	0.003
	Oral use only	1.68 (0.69–4.10)	0.252	1.39 (0.62–3.70)	0.506
	Both inhalation and oral use	4.20 (1.91–9.25)	<0.001	4.85 (2.07–11.35)	<0.001
	Nonuse	1 (ref)	–	1 (ref)	–
12–20 years old					
Mild asthma	Inhalation only	0.96 (0.78–1.18)	0.691	0.91 (0.73–1.12)	0.363
	Oral use only	0.71 (0.46–1.12)	0.143	0.67 (0.40–1.12)	0.123
	Both inhalation and oral use	0.27 (0.06–1.10)	0.067	0.30 (0.07–1.31)	0.109
	Nonuse	1 (ref)	–	1 (ref)	–
Moderate asthma	Inhalation only	0.99 (0.81–1.21)	0.896	0.96 (0.78–1.18)	0.675
	Oral use only	0.93 (0.50–1.71)	0.809	0.97 (0.52–1.82)	0.927
	Both inhalation and oral use	1.04 (0.56–1.94)	0.926	1.15 (0.62–2.15)	0.658
	Nonuse	1 (ref)	–	1 (ref)	–
Severe asthma	Inhalation only	1.09 (0.82–1.45)	0.541	1.08 (0.80–1.44)	0.619
	Oral use only	1.01 (0.58–1.79)	0.964	0.89 (0.48–1.66)	0.722
	Both inhalation and oral use	1.09 (0.82–1.45)	0.482	0.73 (0.27–1.96)	0.528
	Nonuse	1 (ref)	–	1 (ref)	–

^aCrude logistic regression.^bMultivariable logistic regression adjusting for age, sex, race/ethnicity, insurance, family income, and comorbidities.**Table 3.** Interaction between age and corticosteroid use and administration routes on ADHD risks by asthma severity.

Asthma severity	Interactions	Model 1 ^a		Model 2 ^b	
		aOR (95% CI)	p Value	aOR (95% CI)	p Value
Mild asthma	Inhalation only	0.96 (0.78–1.18)	0.691	0.92 (0.74–1.14)	0.444
	Oral use only	0.71 (0.46–1.12)	0.143	0.67 (0.40–1.11)	0.123
	Both inhalation and oral use	0.27 (0.06–1.10)	0.067	0.31 (0.07–1.31)	0.111
	Nonuse	1 (ref)	–	1 (ref)	–
	Age group (5–11 vs. 12–20 years)	0.44 (0.41–0.47)	<0.001	0.39 (0.36–0.42)	<0.001
	Inhalation only*5–11 years	0.92 (0.71–1.20)	0.551	0.92 (0.74–1.14)	0.675
	Oral use only*5–11 years	1.25 (0.59–2.63)	0.553	1.44 (0.65–3.18)	0.365
	Both inhalation and oral use*5–11 years	5.10 (1.04–35.08)	0.045	2.94 (0.49–17.54)	0.236
	Nonuse*12–20 years	1 (ref)	–	1 (ref)	–
	Nonuse*5–11 years	1 (ref)	–	1 (ref)	–
Moderate asthma	Inhalation only	0.99 (0.81–1.21)	0.926	0.96 (0.78–1.19)	0.727
	Oral use only	0.93 (0.50–1.71)	0.809	1.00 (0.53–1.89)	0.992
	Both inhalation and oral use	1.04 (0.56–1.94)	0.896	1.18 (0.63–2.21)	0.600
	Nonuse	1 (ref)	–	1 (ref)	–
	Age group (5–11 vs. 12–20 years)	0.48 (0.43–0.54)	<0.001	0.43 (0.38–0.48)	<0.001
	Inhalation only*5–11 years	1.40 (1.08–1.81)	0.010	1.41 (1.07–1.85)	0.014
	Oral use only*5–11 years	1.29 (0.50–3.25)	0.602	1.20 (0.45–3.21)	0.710
	Both inhalation and oral use*5–11 years	0.84 (0.37–1.94)	0.689	0.79 (0.30–2.08)	0.631
	Nonuse*12–20 years	1 (ref)	–	1 (ref)	–
	Nonuse*5–11 years	1 (ref)	–	1 (ref)	–
Severe asthma	Inhalation only	1.09 (0.83–1.45)	0.541	1.09 (0.80–1.45)	0.605
	Oral use only	1.01 (0.57–1.79)	0.964	0.90 (0.49–1.68)	0.750
	Both inhalation and oral use	0.69 (0.25–1.92)	0.481	0.73 (0.27–1.98)	0.540
	Nonuse	1 (ref)	–	1 (ref)	–
	Age group (5–11 vs. 12–20 years)	0.58 (0.47–0.72)	<0.001	0.49 (0.39–0.61)	<0.001
	Inhalation only*5–11 years	1.50 (1.01–2.27)	0.052	1.53 (1.01–2.35)	0.050
	Oral use only*5–11 years	1.66 (0.55–4.98)	0.365	1.77 (0.51–6.12)	0.369
	Both inhalation and oral use*5–11 years	6.05 (1.95–18.77)	0.001	6.53 (2.12–20.18)	0.001
	Nonuse*12–20 years	1 (ref)	–	1 (ref)	–
	Nonuse*5–11 years	1 (ref)	–	1 (ref)	–

^aModel 1: logistic regression model controlling for corticosteroids use, age, and interaction terms.^bModel 2: logistic regression model controlling for covariates in model 1 and age, sex, race/ethnicity, insurance, family income, and comorbidities.

children who used inhaled medications only was significant for those with moderate (aOR = 1.41, 95% 1.07–1.85) and severe asthma (aOR = 1.53, 95% 1.01–2.35), suggesting a possible age-varying effect of corticosteroids on ADHD among asthma patients.

Discussion

Using a nationally representative dataset, we comprehensively examined the cross-sectional associations among ADHD and corticosteroids use among asthmatic children while taking administration routes, child age, and asthma severity into consideration. Our results agree with previous studies^{4,5} showing that inhaled corticosteroids did not increase the likelihood of ADHD in adolescents with asthma. However, the use of inhaled corticosteroids was significantly associated with ADHD in young asthmatic children with moderate to severe asthma. Although no association were found between oral corticosteroids and ADHD in asthmatic children, the concomitant use of inhaled and oral corticosteroids showed the highest odds of ADHD in children with severe asthma. Collectively, our study showed a moderating effect of age and asthma severity on the association between corticosteroids use and ADHD. These findings suggest more studies are needed to understand the complex intersection between corticosteroids use and ADHD in relation to asthma severity and age, and individualized therapeutic regimen should be recommended to provide a comprehensive care for asthmatic children with comorbidities.

The association between asthma and ADHD has received been previously reported in the literature. A large-scale meta-analysis included more than 200,000 participants with ADHD from 49 datasets reported the pooled adjusted OR was 1.53 (95% CI 1.41–1.65; $I^2 = 50.76$) indicating a significant association between ADHD and asthma.⁶ Similarly, a recent population-based cross-sectional study also found children with asthma are about 2 times (aOR 2.01, 95% 1.68–2.42) more likely to have concomitant ADHD after adjusting for potential confounders.³ Several other studies also suggested a strong and significant association between asthma and ADHD^{4,5,7,8}, and the degree of the association amplified with asthma severity.⁴

The onset of ADHD is multifactorial and determined by both genetic and environmental factors.²⁰ Shared risk factors between ADHD and asthma, such as genetic variants, could be one possible explanation for the increased susceptibility of concurrent

conditions.²¹ On the other hand, inflammation may be the link for these two disorders.^{22,23} Serotonin levels are usually elevated in patients with asthma, but asthma medications, such as corticosteroids, have been shown to decrease serotonin levels.²⁴ Decreased serotonin levels have been associated with ADHD.²⁴ Therefore, asthma medications might have some impact on behavioral disturbances through the changes of serotonin levels.

Results here suggest the odds of having ADHD are not impacted by corticosteroids use in older asthmatic children. However, for children under age 12, the use of corticosteroids may be associated with ADHD health risks. Notably, children may be even more susceptible to adverse drug events from corticosteroids than adults even after controlling for weight-based dosing.²⁵ Significantly higher incidences of growth retardation, osteoporosis, glaucoma, and cataracts were noted in pediatric patients treated with glucocorticoids than in adult patients.²⁵ Although such a comparison for psychiatric behaviors is not available, studies suggested the change of behaviors and psychosis in young children using inhaled corticosteroids⁵, but larger studies did not find any major adverse neuropsychiatric effects associated with inhaled corticosteroids in older children.⁴

Interestingly, our results showed that oral corticosteroids use did not increase the odds of ADHD while rigorously controlling for potential confounders including autoimmune disease and other comorbidities requiring systemic steroids treatment. Although oral use of corticosteroids has been found to increase risks of behavioral disturbances^{26–28}, no previous studies have examined the association between oral corticosteroids and ADHD in asthmatic children, in particular. Prospective studies are needed to further examine this finding because we also found the concurrent use of oral and inhaled corticosteroids was associated the highest odds of ADHD in children with severe asthma.

To avoid treatment-related adverse drug events, the most recent guidelines recommend biologicals (i.e. omalizumab) as a preferred therapy over chronic oral corticosteroids for severe asthma.^{13,29} To date, inhaled corticosteroids combine with short-acting β_2 agonist are usually considered as treatment of choices for patients with asthma. For example, as suggested by the most recent GINA guideline, children with mild asthma could use long-acting bronchodilators with inhaled corticosteroids only at times of exacerbation in lieu of chronic daily inhaled corticosteroids. However, due to the limitation of the KID data, we are unable to assess the adherence of inhaled/oral corticosteroids or examine the appropriateness of inhaler techniques (with

spacers) among our study population. While better alternatives (e.g. biologicals) may be needed for patients with co-morbid ADHD risks, medication adherence, and inhaler techniques should be examined before switching to more costly biologicals.³⁰

Limitations

Our study also has some limitations that should be noted. First, the use of ICD-10-CM diagnostic codes to identify medication use, asthma, and ADHD cases might result in misclassification bias, although ICD codes were considered relatively accurate for inpatient data.³¹ Second, despite having controlled for multiple covariates including autoimmune diseases that often requires oral steroids therapy, there is the possibility of some residual confounding we could not control for. However, the results did not change after our application of inverse of propensity weights to specifically address this potential limitation, indicating the influence of selection bias may be minimal in this study. Third, due to the cross-sectional design, we can only generate associations between selected variables at one point in time, rather than establishing any temporal relationships that would infer causality. Fourth, in addition to the unknown duration and dose of corticosteroids use of each patient, the appropriateness of inhaler techniques is also unknown. Incorrect inhaler techniques may lead to mental distress, such as anxiety, due to poorly controlled asthma, which may be co-diagnosed with ADHD.³² In the future, a prospective cohort study or randomized controlled trial could be conducted to further affirm the effect of corticosteroids on ADHD in relation to asthma status.

Conclusion

The co-occurrence of asthma and ADHD increases healthcare cost and utilization, and also decrease quality of life in both children and caregivers. Collectively, this population-based, retrospective analysis suggests inhaled corticosteroids were significantly associated with ADHD in younger children with moderate to severe asthma.

Ethical approval

The UTHealth Committee for the Protection of Human Subjects ruled this study to be exempt from review and informed consent because of the use of publicly available, deidentified data for analysis.

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Declaration of interest

The authors declare that there is no conflict of interest.

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