


ORIGINAL ARTICLE

Asthma as a risk factor for hospitalization in children with COVID-19: A nested case-control study

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Abstract

Background: Most pediatric studies of asthma and COVID-19 to date have been ecological, which offer limited insight. We evaluated the association between asthma and COVID-19 at an individual level.

Methods: Using data from prospective clinical registries, we conducted a nested case-control study comparing three groups: children with COVID-19 and underlying asthma ("A+C" cases); children with COVID-19 without underlying disease ("C+" controls); and children with asthma without COVID-19 ("A+" controls).

Results: The cohort included 142 A+C cases, 1110 C+ controls, and 140 A+ controls. A+C cases were more likely than C+ controls to present with dyspnea and wheezing, to receive pharmacologic treatment including systemic steroids (all $p < .01$), and to be hospitalized (4.9% vs. 1.7%, $p = .01$). In the adjusted analysis, A+C cases were nearly 4 times more likely to be hospitalized than C+ controls (adjusted OR = 3.95 [95%CI = 1.4–10.9]); however, length of stay and respiratory support level did not differ between groups. Among A+C cases, 8.5% presented with an asthma exacerbation and another 6.3% developed acute exacerbation symptoms shortly after testing positive for SARS-CoV-2. Compared to historic A+ controls, A+C cases had less severe asthma, were less likely to be on controller medications, and had better asthma symptom control (all $p < .01$).

Conclusions: In our cohort, asthma was a risk factor for hospitalization in children with COVID-19, but not for worse COVID-19 outcomes. SARS-CoV-2 does not seem to be a strong trigger for pediatric asthma exacerbations. Asthma severity was not associated with higher risk of COVID-19.

KEYWORDS

asthma, COVID-19, SARS-CoV-2

Traci M. Kazmerski and Erick Forno are shared senior authors.

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1 | INTRODUCTION

There have been conflicting reports on whether asthma increases COVID-19 risk or severity,¹⁻⁶ with scarce data in children.⁷ While the majority of COVID-19 cases have occurred in adults,⁸ pediatric COVID-19 cases in the United States have been steadily increasing since July 2021.⁹ The rise of the highly infectious Delta variant coincides with the return of millions of unimmunized students to in-person classrooms this fall with highly variable mitigation strategies, making it critically important that we better elucidate the impact of COVID-19 on children, particularly those with common chronic diseases such as asthma.

Most pediatric studies on COVID-19 and asthma to date have been epidemiological or ecological, which examine associations at a large scale but provide limited inferences into the individual characteristics driving the findings. For instance, there have been ecological reports describing reduced pediatric asthma exacerbations and morbidity during the pandemic,¹⁰⁻¹³ likely as a result of physical distancing, masks, and perhaps other factors such as decreases in air pollution. Yet, those have focused on the concurrent effects of the pandemic on population-level asthma morbidity and healthcare utilization, rather than the direct potential associations between asthma and incident COVID-19 characteristics in children.

In this study, we examined the association between asthma and COVID-19 in children using nested case-control analyses. We hypothesized that (1) there is an association between asthma and COVID-19 presentation and outcomes and (2) that asthma severity is correlated with COVID-19 risk.

2 | METHODS

2.1 | Study population and data collection

The Western Pennsylvania COVID-19 Registry (WPACR) is a secure database established in March 2020 to record baseline characteristics, acute presentation, and initial outcomes of pediatric patients (ages 0–21 years) presenting with a SARS-CoV-2 infection to UPMC Children's Hospital of Pittsburgh (CHP, the largest pediatric referral center in the region) and Children's Community Pediatrics (CCP, the associated primary care network)¹⁴ For this analysis, we extracted data from children with pre-existing asthma who presented with COVID-19 between March and December 2020 ("A+C" cases). As disease controls, we selected from the WPACR children without pre-existing conditions who presented with COVID-19 ("C+" controls) during the same period, as well as non-overlapping children with asthma ("A+" controls) recruited to the CHP Asthma Registry during the same period the year prior to the pandemic (March to December 2019). The Asthma Registry includes children seen for asthma in the CHP Pulmonary or Allergy clinics, the Emergency Department, who are hospitalized for asthma, or who participate in asthma research studies at our center.

Key Message

Asthma severity was not associated with higher risk of COVID-19 in children, and SARS-CoV-2 was not a strong trigger for asthma exacerbations. Asthma was a risk factor for hospitalization in children with COVID-19, but not for worse COVID-19 outcomes.

We have previously described details of the WPACR¹⁴ in brief, we included subjects if they had a positive SARS-CoV-2 RT-PCR or if they met criteria for the multisystem inflammatory syndrome in children (MIS-C), and a multidisciplinary team representing the different pediatric specialties involved in the care of patients with COVID-19 at our institution (including primary care, pulmonology, hospital medicine, adolescent medicine, infectious disease, and critical care medicine) extracted relevant clinical data from the EHR. Data abstracted included patient demographics, symptoms and initial presentation, healthcare utilization data, laboratory results, and acute disease outcomes.

For all patients with asthma (A+C cases and A+ controls), we also directly abstracted EHR data on baseline asthma severity, asthma controller medications, symptom control (Asthma Control Test [ACT]¹⁵ scores for adolescents ≥ 12 years old or Childhood Asthma Control Test [C-ACT]¹⁶ scores for children 4–11 years old), lung function (FEV1 and FVC as percent of predicted [%pred], as well as FEV1/FVC ratio), and atopy biomarkers (total and specific IgE, allergy skin testing, and peripheral blood eosinophil counts). We defined asthma severity based on National Asthma Education and Prevention Program (NAEPP) guidelines¹⁷ and poor control as an ACT or C-ACT ≤ 19 . We evaluated asthma exacerbations in both the A+C and A+ groups from January 1, 2018, to December 31, 2019, to avoid any potential impact of the pandemic on asthma control, management, or healthcare utilization.

The WPACR and the CHP Asthma Registry are both approved by the Institutional Review Board at the University of Pittsburgh (protocols STUDY20110072 and STUDY19020359, respectively).

2.2 | Statistical analysis

For the analysis of A+C cases vs C+ controls (i.e., the differences in COVID-19 between children with and without asthma), we compared initial symptoms at presentation, history of recent travel, and known exposures. Our primary outcomes of interest were hospitalization, hospital length of stay (LOS), PICU admission, and the maximal respiratory support required during hospitalization. For the analysis between A+C cases and A+ controls (i.e., to assess whether patients presenting with COVID-19 had more severe pre-existing asthma than expected from our usual hospital population), our primary variables were asthma severity and symptom control, and secondary characteristics were asthma exacerbations, lung function, and

atopy biomarkers. We conducted bivariate analyses using 2-tailed *t* tests or Wilcoxon rank-sum (Mann-Whitney *U*) tests for continuous variables, and chi-squared or Fisher's exact tests for categorical variables. We conducted adjusted analyses using logistic regression for categorical variables (e.g., hospitalization), Poisson regression for count data (e.g., number of severe asthma exacerbations), or linear regression for continuous variables. We adjusted models for hospitalization for age, sex, and covariates that were significant in the bivariate analyses of asthma and hospitalization: race, zip code median household income, BMI, days from symptom onset to presentation, and non-asthma symptoms (fever, fatigue, and vomiting). In addition, we performed a sensitivity analysis using propensity score matching (PSM) to account for differences in relevant potential confounders such as age and race (see Online Supplement). We performed all analyses using STATA v16.1 (StataCorp, College Station, TX) or SAS v9.4 (SAS Institute, Cary, NC).

3 | RESULTS

From March 11, 2020, to December 21, 2020, there were 1,802 cases with SARS-CoV-2 RT-PCR+ in the WPACR (Figure 1). Of those, 142 had asthma and were extracted as A+C cases; and 1,110 had no reported pre-existing conditions and were selected as C+ controls. Distribution of COVID-19 cases over time showed a significant peak in the summer and a larger peak in the late fall/early winter (Figure 2). We also extracted 140 non-overlapping asthma controls (A+ controls) recruited to the CHP Asthma Registry during the same period in 2019.

Baseline cohort characteristics are shown in Table 1. A+C cases (COVID-19 with pre-existing asthma) were approximately 4 years older than both C+ and A+ controls (median ages 14.6, 12.0, and 10.2 years, respectively), but there were no differences in sex

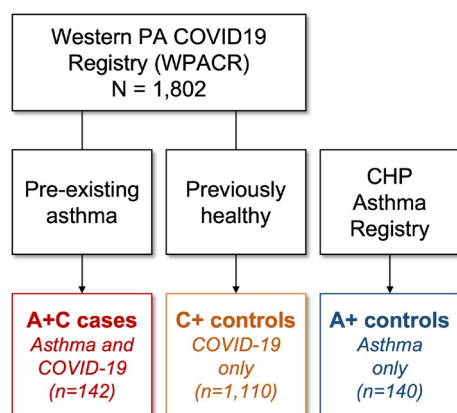


FIGURE 1 Diagram of study cohort selection. A+C cases and C+ controls were recruited from March to December 2020. A+ controls were selected from patients recruited from March to December 2019. Data on asthma characteristics (for both A+C cases and A+ controls) were collected for 2018–2019 to avoid any potential impact of the pandemic on asthma control, management, or healthcare utilization

distributions between the three groups. Compared to children without asthma, those with asthma (with or without COVID-19) were more likely to be Black (A+C cases 25.4% and A+ controls 23.6%, vs. C+ controls 10.2%), had a higher BMI (median BMI percentiles 79.0 and 78.6, respectively, vs. 63.0), and were more likely to live in zip codes with lower household income (Table 1).

3.1 | COVID-19 hospitalizations

Altogether, 26 children (2.1%) in the WPACR were hospitalized during the study period (Table S1), including 9 PICU admissions and no deaths. Compared to children with COVID-19 who were not hospitalized, hospitalized patients were more likely to have asthma (26.9% vs. 11.0%). They were also younger (median ages 7.4 vs. 12.6 years) and more likely to be Black (38.5% vs. 12.3%); to live in zip codes with lower median household income; to present with fever, fatigue, wheezing, dyspnea, chest pain, and/or vomiting; and to receive pharmacologic treatment (38.5% vs. 1.2%) (Table S1). There were no clear discernible hospitalization patterns over time (Figure S1). PICU admissions were few but included 1/7 (14.3%) A+C cases and 8/19 (42.1%) C+ controls.

3.2 | COVID-19 in children with asthma vs. no underlying disease

A+C cases were more likely than C+ controls to endorse recent travel; to present with wheezing, dyspnea, chest pain, and loss of taste; and to be hospitalized (4.9% vs. 1.7%) (Table 2). They were also more likely to receive pharmacologic treatment including albuterol (17.6% vs. 0.7%) and systemic steroids (8.5% vs. 0.8%). Among the 142 A+C cases, 12 (8.5%) had an asthma exacerbation upon initial presentation leading to SARS-CoV-2 testing, and 9 (6.3%) developed an asthma exacerbation shortly after they tested positive for COVID-19. In the remaining 118 cases, asthma was either solely a pre-existing condition with no active symptoms upon COVID-19 presentation (80.1%) or there was insufficient data to determine asthma symptoms (4.2%). A+C cases presenting with acute asthma symptoms were more likely to be hospitalized than those with no acute asthma symptoms (3/21 [14.3%] vs. 3/118 [2.5%], $p = .04$).

In the multivariable analysis (Table 3), asthma was a risk factor for hospitalization with COVID-19: After adjustment for age, sex, race, recent travel, and known exposure, A+C cases were nearly 4 times more likely to be hospitalized than C+ controls (aOR = 3.95 [95%CI = 1.4–10.9]; Table 3 Model 1). Results were similar after additionally adjusting for zip code household income, BMI percentile, and the number of days between symptom onset and presentation (Table 3 Model 2), or after adjusting for non-asthma symptoms that were associated with hospitalization (fever, fatigue, and vomiting; Table 3 Model 3). In our sensitivity analysis, PSM adequately balanced for relevant covariates (Figure S2, Table S2) and results were similar to those from the adjusted regression models, with odds ratios ranging from 3.38 to 4.08 (Table S3). Among hospitalized

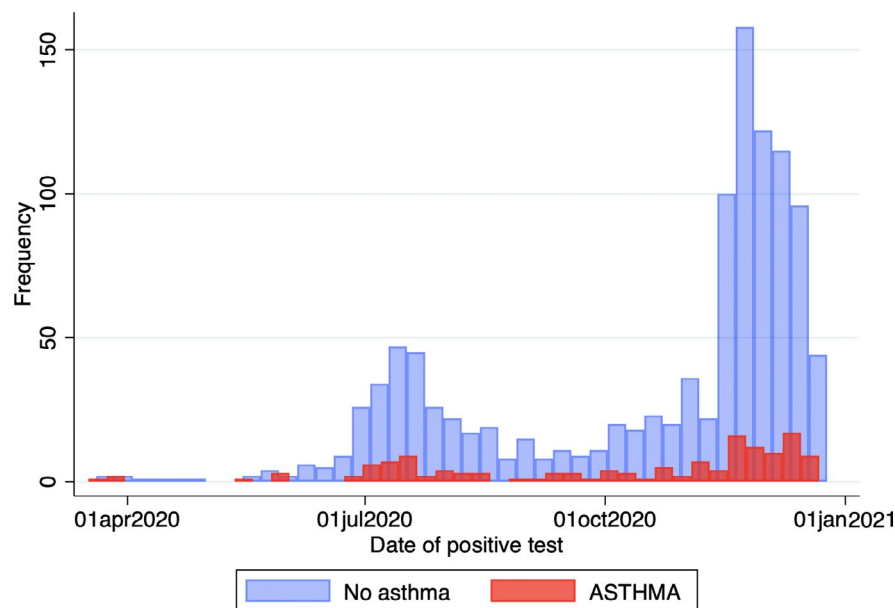


FIGURE 2 Distribution of cases over time during the study period. Distribution of COVID-19 (A+C cases and C+ controls) over time

TABLE 1 Sociodemographic characteristics of the participants in the study

	A+C Cases (Asthma and COVID-19)	C+ Controls (COVID-19 only)	<i>p</i> -value	A+ Controls (Asthma only)	<i>p</i> -value
N	142	1,110		140	
Age, years	14.6 [10.7–17.9]	12.0 [4.8–16.9]	<.001	10.2 [7.8–13.9]	<.001
Male sex	79 (55.6%)	560 (50.5%)	.24	87 (62.1%)	.27
Race:			<.001		.88
White	103 (72.5%)	905 (81.5%)		103 (73.6%)	
Black	36 (25.4%)	113 (10.2%)		33 (23.6%)	
Other/unknown	3 (2.1%)	92 (8.3%)		4 (2.9%)	
Hispanic	1 (0.7%)	8 (0.7%)	.96	7 (5%)	.03
BMI, percentile	79.0 [50.0–95.2]	63.0 [30.6–87.6]	<.001	78.6 [48.1–95.3]	.93
Household income					
Zip code median ^a	\$66.9 (\$24.9)	\$68.7 (\$22.7)	.38	\$61.7 (\$19.0)	.048
Below median ^b	80 (57.6%)	514 (47.6%)	.028	81 (58.3%)	.90

Note: Numbers represent mean (SD) or median [interquartile range] for continuous variables and *n* (%) for categorical variables. *p*-values for the comparison of each control group vs A+C cases.

Bold indicates statistically significant *p*-value (*p*<.05).

Abbreviations: BMI, Body mass index; LOS, Length of stay (days).

^aAverage of the median household incomes (in thousands of USD) for all participants' zip codes, based on US Census American Community Survey (ACS) 5-year data (2015–2019).

^bNumber of participants who live in zip codes with median household income below the median for all zip codes in the study.

patients, however, LOS and respiratory support level did not significantly differ by asthma status, although sample sizes were very small (Table 2).

3.3 | Comparison between cases and asthma controls

In our evaluation of whether children with asthma presenting with COVID-19 differ from children with asthma usually seen at our center

(Table 4), A+C cases had less severe asthma (58% vs. 23% had intermittent asthma) and lower eosinophil counts (median 110 vs. 300 cells/ μ l), and they were less likely to be on controller medications, and less likely to have poor symptom control (13.6% vs. 30.7%). This was driven by adolescent A+C cases who had better ACT scores compared to A+ controls (mean 22.1 vs. 20.3), with no differences in C-ACT scores among the younger children. There were no differences in lung function (FEV1, FVC, or FEV1/FVC), but A+C cases were less likely to have atopic comorbidities, and they had lower rates of severe exacerbations compared to A+ controls (median 1.0 vs. 1.5 events per year,

TABLE 2 COVID-19 characteristics in COVID-19 cases (A+C) and (C+) controls

	A+C Cases	C+ Controls	p-value
Initial presentation:			.58
ED or urgent care	19 (13.4%)	113 (10.2%)	
Primary care or telemedicine	122 (85.9%)	974 (87.8%)	
Other/unknown	1 (0.7%)	23 (2.1%)	
Recent travel	10 (7.0%)	34 (3.1%)	.009
Known exposure	86 (62.3%)	746 (68.3%)	.16
Interval, days:			
Symptoms to presentation	2 [1–3]	2 [1–3]	.37
Symptoms to test	2.5 [1–4]	2 [1–4]	.47
Initial symptoms:			
Asymptomatic	16 (11.3%)	124 (11.2%)	.97
Fever	53 (37.3%)	443 (39.9%)	.55
Fatigue	24 (16.9%)	162 (14.6%)	.47
Cough	62 (43.7%)	477 (43.0%)	.88
Wheezing	7 (4.9%)	5 (0.5%)	<.001
Dyspnea	13 (9.2%)	25 (2.3%)	<.001
Chest pain	7 (4.9%)	16 (1.4%)	.004
Loss of smell	23 (16.2%)	125 (11.3%)	.09
Loss of taste	26 (18.3%)	129 (11.6%)	.02
Abdominal pain	8 (5.6%)	52 (4.7%)	.62
Vomiting	6 (4.2%)	36 (3.2%)	.54
Initial treatment:			
Any pharmacologic treatment	10 (7%)	15 (1.3%)	<.001
Albuterol	25 (17.6%)	8 (0.7%)	<.001
Systemic steroids	12 (8.5%)	9 (0.8%)	<.001
Main outcomes			
Hospitalized	7 (4.9%)	19 (1.7%)	.01
Hospital LOS (days)	1 [1–4]	2 [1–4]	.51
Respiratory support ^a :			.72
None (room air)	6	14	
Nasal cannula (NC)	0	2	
High-flow NC or NPAP	1	2	
Invasive ventilation	0	1	

Note: Numbers represent mean (SD) or median [interquartile range] for continuous variables and n (%) for categorical variables.

Bold indicates statistically significant p -value ($p < .05$). Abbreviation: LOS, Length of stay (days); NPAP, Non-invasive positive airway pressure (includes CPAP and BiPAP).

^aAmong hospitalized patients.

Mann-Whitney $p = .042$); this difference persisted after adjustment for age, sex, and race (difference -0.43 events per year [95%CI -0.77 to -0.10], Poisson $p = .01$).

We then evaluated the subgroup of cases and controls who had been previously seen at one of the asthma subspecialty clinics (17 A+C cases and 86 A+ controls seen in either Pulmonology or Allergy clinics; Table S4). In the analysis restricted to this subgroup, A+C cases and A+ controls were similar in most asthma characteristics, except for persistent differences in eosinophil counts and the proportion of patients with no atopic comorbidities.

4 | DISCUSSION

Our study is one of the first individual-level, case-control studies on pediatric COVID-19 and asthma. To our knowledge, it is also one of the first studies to report the incidence of asthma exacerbations among children with asthma and acute SARS-CoV-2 infection.

Of the 1,802 patients in our pediatric COVID-19 registry during the study period, 142 (7.9%) had asthma. In our initial report over the first five months of the pandemic, asthma cases

	Model 1 (N = 1,252)	Model 2 (N = 857)	Model 3 (N = 1,252)
Asthma	3.95 (1.43–10.9)**	4.87 (1.44–16.43)**	3.33 (1.19–9.33)*
Age, years	0.88 (0.82–0.95)**	0.91 (0.83–1.01)	0.91 (0.85–0.98)*
Male sex	0.55 (0.24–1.26)	0.42 (0.14–1.27)	0.49 (0.21–1.15)
Race:			
White	Ref.	Ref.	Ref.
Black	3.00 (1.28–7.07)*	1.41 (0.35–5.71)	4.55 (1.87–11.1)*
Other/unknown	0.54 (0.07–4.23)	2.69 (0.30–24.3)	0.51 (0.06–4.18)
Recent travel	1.39 (0.52–3.68)	2.79 (0.29–26.5)	1.34 (0.40–4.52)
Known exposure	0.27 (0.52–0.62)**		
Low zip code income		2.54 (0.75–8.58)	
BMI, percentile		1.01 (0.99–1.03)	
Days from symptom onset to presentation		1.002 (0.99–1.01)	
Initial symptoms:			
Fever			1.90 (0.40–4.52)
Fatigue			3.15 (1.23–8.09)*
Vomiting			8.62 (3.15–23.6)**

TABLE 3 Association between asthma and hospitalization for COVID-19

Note: Numbers shown are odds ratios (95% confidence intervals) for hospitalization. All models adjusted for age, sex, race, recent travel, and known exposure. Model 2 additionally adjusted for zip code's median household income, BMI percentile, and the time interval (days) between symptom onset and presentation; these were not included in Model 1 because of greater missingness (~30% were missing BMI or time interval data, thus $N = 873$). Model 3 additionally adjusted for non-asthma related symptoms that were significant in the unadjusted analysis (fever, fatigue, and vomiting; see Table S1).

* $p < .05$.

** $p < .01$.

comprised 10.6% of the registry¹⁴ Thus, asthma does not appear to be over-represented among pediatric cases of COVID-19 compared to local (8%) or national (7%) asthma prevalence^{18,19} consistent with previous retrospective studies²⁰ Other studies have reported asthma prevalence rates among pediatric COVID-19 cases to vary from 0.5% (Wuhan, China)²¹ to 20% (Washington, DC)²² and from 2% (Lombardy and Liguria, Italy)²³ to 24% (New York City)²⁴ among hospitalized pediatric COVID-19 patients. This may be partly explained by variability in local asthma prevalence, though at least one study reported lower asthma prevalence rate among children with COVID-19 compared to the local pediatric asthma prevalence (13% vs. 20%–25%), suggesting that there may be other contributing factors.²⁵

In our cohort, children with asthma were nearly 4 times more likely to be hospitalized for COVID-19 compared to children without asthma, even after adjusting for potential confounders like age, sex, race/ethnicity, zip code household income, BMI, recent travel, known exposures, and the number of days between symptom development and the patient's initial presentation to care. Results remained essentially unchanged after further adjusting for non-asthma-related symptoms that could have independently increased likelihood of hospitalization, such as fever, vomiting, and fatigue. Consistent with our results, some studies have reported asthma as a risk factor for hospitalization in children with COVID-19,^{26,27} while others have

reported conflicting results.^{20,22} Although our sample size was small and thus results need to be interpreted with caution, hospital LOS and the need for respiratory support or PICU admission did not seem to differ by asthma status. Taken together, these results suggest that the increased hospitalization rate may have been due to a different threshold to admit children with asthma, rather than truly because of a more severe presentation. Given the paucity of data on pediatric asthma and COVID-19, providers may have been subjectively more concerned about potential severe course or outcomes in a child with asthma compared to one without pre-existing conditions. A survey of 174 centers in Europe similarly reported that 33/49 (67%) children with asthma and COVID-19 were hospitalized, but only 19 (39% of the total) required any respiratory support and concluded that this “may suggest the children were admitted for safety reasons and uncertainty about the course of COVID-19”.²⁸ While some studies in adults have reported associations between non-atopic asthma and severe COVID-19,³ our results are consistent with a recent meta-analysis (also in adults) showing no association between asthma and hospital LOS or ICU admission for COVID-19.²⁹ More detailed, prospective, multi-center pediatric studies will be necessary to further examine this issue.

We found that SARS-CoV-2 does not seem to be a particularly strong trigger of asthma exacerbations, with only ~15% of children with asthma presenting with significant asthma symptoms during

TABLE 4 Asthma characteristics in COVID-19 cases (A+C) and asthma (A+) controls

	A+C cases	A+ controls	p-value
Asthma severity			
Intermittent	81 (57.9%)	32 (22.9%)	<.001
Mild persistent	40 (28.6%)	53 (37.9%)	.08
Moderate persistent	16 (11.4%)	42 (30.0%)	<.001
Severe persistent	3 (2.1%)	13 (9.3%)	.009
Controller medication:			
ICS	40 (28.2%)	75 (53.6%)	<.001
ICS/LABA	10 (7.0%)	22 (15.7%)	.02
Symptom control:			
C-ACT score	23.2 (4.03)	21.6 (4.01)	.13
ACT score	22.1 (3.97)	20.3 (4.62)	.03
Poorly controlled ^a	12 (13.6%)	27 (30.7%)	.007
Lung function^b:			
FEV1, %pred	95.2 (13.3)	94.3 (17.9)	.85
FVC, %pred	98.7 (10.7)	90.9 (37.8)	.28
FEV1/FVC	84.3 (8.6)	71.4 (29.4)	.19
History of atopy:			
Eczema	27 (19.0%)	64 (45.7%)	<.001
Allergic rhinitis	72 (50.7%)	105 (75.0%)	<.001
Food allergies	11 (7.8%)	40 (28.6%)	<.001
Any specific IgE+	3 (2.1%)	7 (5.0%)	.19
Any skin test+	1 (0.7%)	6 (4.3%)	.05
None	53 (37.3%)	21 (15.0%)	<.001
Atopy biomarkers:			
Eosinophils, percent	2 [1–4]	4 [2–11]	<.001
Eosinophils, cells/ μ L	110 [50–270]	300 [200–580]	<.001
Total IgE, UI/mL	380 [182–1036]	195 [80–704]	.30
Subspecialist care:			
Pediatric Pulmonology	20 (14.1%)	84 (60.0%)	<.001
Allergy / Immunology	11 (7.8%)	72 (51.4%)	<.001
Severe exacerbations:			
Any events ^c	30 (22.5%)^d	73 (54.5%)^e	<.001
Events in the past year ^f	1 [0.5–1.5]	1.5 [1.0–2.0]	.04

Note: Numbers represent mean (SD) or median [interquartile range] for continuous variables and n (%) for categorical variables.

Bold indicates statistically significant p-value ($p < .05$).

Abbreviations: ACT, Asthma control test (ages ≥ 12 years, range 5–25); C-ACT, Childhood asthma control test (ages 4–11 years, range 0–27).

^aDefined as C-ACT or ACT ≤ 19 .

^bFor A+C cases, N=17 with spirometry data.

^cNumber of patients with ≥ 1 asthma-related ED visit, hospitalization, or systemic steroid course from January 2018 to December 2019.

^dN = 133 with asthma event data.

^eN = 134 with asthma event data.

^fRate among those who had at least one event.

acute COVID-19. While we cannot rule out that some patients with asthma may have had exacerbations triggered by mild COVID-19 that were managed at home and who never sought medical attention, our estimates are consistent with a recent study of adolescents

and adults with COVID-19 that similarly reported that only 13% of patients with asthma had acute wheezing.³⁰ As expected, children with asthma were more likely to receive systemic steroids as part of their management, and those presenting with acute asthma

symptoms were more likely to be hospitalized—again suggesting that at least some of those admissions may have been due to asthma rather than COVID-19 severity.

In our analysis of cases vs historic asthma controls, we found that asthma severity was not associated with higher risk of SARS-CoV-2 infection. Due to the nature of our registries, we were unable to compare these patients to children with asthma managed by community providers (i.e., without subspecialty referral or recent admissions to our hospital). However, our findings suggest that children with asthma and COVID-19 were at least not as severe as those who would have been usually referred to subspecialty asthma care at our center. When we restricted our analyses to children with asthma who had been followed by a specialty clinic in the years prior to the pandemic, there was no significant difference in severity or symptoms compared to controls. While the sample size for this subgroup analysis was small, it again suggests that asthma severity was no different in children with COVID-19 than what we would have expected from the population our center usually serves.

Several factors contribute to a complex relationship between asthma and COVID-19. Obesity is a risk factor for asthma³¹ and has been identified as a risk factor for COVID-19 infection and worse outcomes.³² In our analysis, children with asthma had higher BMI, but this did not alter the association between asthma and hospitalization. Likewise, African American children in our cohort were more likely to have asthma and to be hospitalized for COVID-19, consistent with prior studies identifying racial disparities in asthma and severe COVID-19.^{33–35} We also found that children with asthma presenting with COVID-19 had lower eosinophil counts and fewer atopic comorbidities than asthma controls. Eosinopenia has been associated with worse outcomes and mortality in adult COVID-19.^{36,37} Eosinophils play an important role in the immune response to respiratory viruses; atopic patients with higher eosinophil counts may be somewhat “protected” from SARS-CoV-2 infection,³⁸ and A+C cases with relatively lower counts may have thus been more susceptible. Gene expression of *ACE2*, which plays a crucial role in SARS-CoV-2 cell entry, is lower in asthma and in younger ages,^{39,40} and ICS can downregulate *ACE2* expression⁴¹; however, large epidemiological studies have linked high-dose ICS to worse risk of death from COVID-19 in both asthma and COPD.⁴² These and other factors may partly explain the conflicting findings on asthma and COVID-19, which may vary by age, asthma severity and treatment, degree of atopy, and other determinants.

There are several key strengths to this study. It is one of the first studies to compare COVID-19 presentation and outcomes between children with and without asthma using individual-level characteristics rather than ecological data and is likely the first such study in a cohort from the United States. There has been a significant knowledge gap regarding COVID-19 outcomes of children with underlying pulmonary diseases; this study starts to fill some of these gaps, which is of utmost importance for counseling families of children with asthma. Data for this study are based on registries in which information is manually abstracted from the EHR by a multidisciplinary

team who is involved in the care of patients with COVID-19, providing more detailed, complete, and accurate information than reports based on diagnostic or billing codes. Furthermore, all asthma information for both cases and historic controls was abstracted by a single asthma provider, eliminating concerns for inter-rater bias. Finally, given our sample size, we were able to evaluate subgroup characteristics, such as those patients with asthma referred to subspecialty care at our center.

Our study also has several limitations. Given the nature of the pandemic, follow-up duration has been short, precluding the ability to track long-term outcomes. However, it seems unlikely that asthma would have a lasting impact on COVID-19 outcomes, given the generally mild courses of the children in this study. Yet, future studies should also focus on long-term consequences such as changes in lung function or asthma severity and control in children who recovered from acute COVID-19. Another limitation is the small number of hospitalized patients in this study; it is unclear whether this is secondary to regional variation in severity or management, possibly due to local variants, or whether the low proportion of hospitalized children is secondary to our ability to include even mild and asymptomatic cases in the registry. It will be crucial to analyze multi-center data to evaluate whether findings vary across different settings. In addition, our analysis was limited to data from the EHR, and thus, other relevant covariates were not included. Moreover, the current study period preceded the emergence of the Delta variant of the virus; our registry is ongoing, and we plan to analyze potential differences as we see the already surging wave of pediatric cases across the country.

In summary, we found that asthma severity does not seem to be associated with increased risk of SARS-CoV-2 infection in children. Pre-existing asthma did increase the risk of hospitalization for COVID-19 in our population, but hospital LOS, need for respiratory support, and disposition did not differ from children without asthma. Furthermore, SARS-CoV-2 infection was not commonly a trigger for asthma exacerbations, but children presenting with symptoms of an asthma exacerbation were more likely to be admitted. With the advent of the Delta variant and current rise in COVID-19 cases, it will be important to conduct multi-center, individual-level, case-control, or cohort studies of COVID-19 and asthma to better understand this evolving disease and its impact on children with asthma.

CONFLICT OF INTERESTS

The authors declare no conflicts of interest related to the current work.

AUTHOR CONTRIBUTIONS

Kristina Gaietto: Conceptualization (equal); Data curation (lead); Formal analysis (lead); Investigation (equal); Writing-original draft (lead); Writing-review & editing (lead). **Megan Culler Freeman:** Conceptualization (equal); Data curation (lead); Validation (equal); Writing-review & editing (equal). **Leigh Anne DiCicco:** Conceptualization (equal); Data curation (equal); Validation (lead); Writing-review & editing (equal). **Sherry Rauenswinter:** Data curation

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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