Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

COVID-19 infection may trigger poor asthma control in children

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Clinical Implications

This is the first large-scale nationwide study demonstrating a worsening of asthma outcomes in children during the 6 months after a PCR-confirmed COVID-19 infection.

Respiratory viral infections are major triggers of asthma exacerbations, including coronaviruses.[1] It was therefore unexpected that asthmatic children have not experienced increased exacerbations during the COVID-19 pandemic caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-COV-2) virus.[2] In fact, we previously found a dramatic reduction in asthma morbidity after mid-March 2020 compared with previous years, which was plausibly associated with fewer respiratory viral illnesses during stay-at-home measures.[3] Another hypothesis is that SARS-CoV-2 itself is not a major asthma trigger, as suggested by two recent studies. Ruano et al[4] compared 29 asthmatic children with probable COVID-19 with 183 non-COVID-19 cases and found no significant differences in oral corticosteroid (OCS) use or asthma-related emergency department (ED) visits or hospitalizations but significantly increased use of short-acting β-agonists (SABA) and asthma controllers. More recently, Amat et al[5] found no change in asthma control or FEV_1 in 51 asthmatic children who developed PCR-positive COVID-19. These studies suggest that COVID-19 in asthmatic children does not worsen asthma outcomes, but the studies were limited by small sample sizes and/or the lack of a comparison group. Our study objective was to establish whether the SARS CoV-2 virus is an asthma trigger resulting in poor asthma control.

We identified 61,916 asthmatic children aged 2 to 17.9 years in the Cerner Real-World Data,[6] encompassing 108 health systems across the United States, as having received a SARS-CoV-2 PCR test from March 2020 through February 2021. This encapsulates the original strains of SARS-COV-2 and possibly variants α, β, and γ, which were designated as variants of concern in December 2020, but not variants being monitored until September 2021 according to the Centers for Disease Control and Prevention.[7] Asthma control was measured by OCS fills, ED, hospitalization, and SABA fill (greater than 3 cannisters/6 mo) rates/1,000 patients per 6 months. Incidence rates were compared using Poisson regression via generalized estimating equations analyses. We performed comparisons within and between groups that tested positive for SARS-CoV-2 PCR. The study was approved by the Children's Hospital of Orange County's Institutional Review Board (No. 210445).

Characterization of asthmatic children shows that PCR-positive SARS-CoV-2 ($COVID^+$) was associated with older average age, Hispanic ethnicity, and non−high-risk asthma compared with those who were PCR-negative ($COVID^-$) ($P < .05$) (Table I). As expected from our previous study,[3] $COVID^-$ children showed significant reductions in asthma-related hospitalizations, ED visits, OCS fill rates, and SABA use in the 6 months after PCR compared with 6 months before PCR testing ($P < .001$) (Figure 1). However, $COVID^+$ asthmatic patients showed significant increases in ED visits (incidence rate ratio [IRR] = 1.17; $P = .018$) and OCS fills (IRR = 1.23; $P < .001$) in the post-PCR period, and only slight increases in hospitalizations (IRR = 1.13; $P = .336$) or SABA use (IRR = 1.02; $P = .861$) (Figure 1) after infection. However,

TABLE I. Characteristics of patient population at baseline* described by COVID status (N = 61,916)

Characteristic	Overall (n= 61,916)	$COVID^-$ (n = 54,170)	$COVID^+$ (n = 7,746)	*P*†
Age at baseline,* y (means [SD])	10.3 (4.5)	10.2 (4.6)	11.2 (4.4)	<.001§
2-4	13.5%	14.2%	9.2%	<.001§
5-11	42.3%	42.8%	39.1%	
12-17	44.1%	43.0%	51.7%	
Sex, male	43.2%	43.1%	43.5%	.495
Race or ethnicity				<.001§
American Indian or Alaskan Native	1.1%	1.0%	1.3%	
Asian	1.3%	1.3%	1.3%	
Black or African American	20.9%	20.9%	21.2%	
Hispanic	2.8%	2.5%	4.9%	
Native Hawaiian or other Pacific Islander	0.2%	0.2%	0.3%	
White	58.0%	58.7%	53.7%	
Other or unknown	12.5%	12.3%	13.9%	
Asthma, high-risk‡	7.2%	7.3%	6.6%	.029§
Asthma pharmacotherapy (before 3 mo)				.186
No reliever or controller medications	84.8%	84.8%	84.7%	
Reliever(s) only	7.2%	7.1%	7.7%	
Controller, monotherapy	6.6%	6.7%	6.2%	
Controllers, combination therapy	1.4%	1.4%	1.4%	

Other includes Middle Eastern or North African, Abenaki, Afghanistani, Bahamian, Bangladeshi, European, mixed racial group, Pakistani, data refused, not asked, not stated.

*Baseline defined as date of COVID test.

†*P* indicates significance of distributional difference between $COVID^+/^-$ groups based on χ^2 test for categorical and ANOVA for age on a continuous scale ($P < .05$).

‡High risk is defined by any of the following morbidity events in past year: two or more emergency department visits, two or more oral corticosteroid fills, or one or more hospitalization.

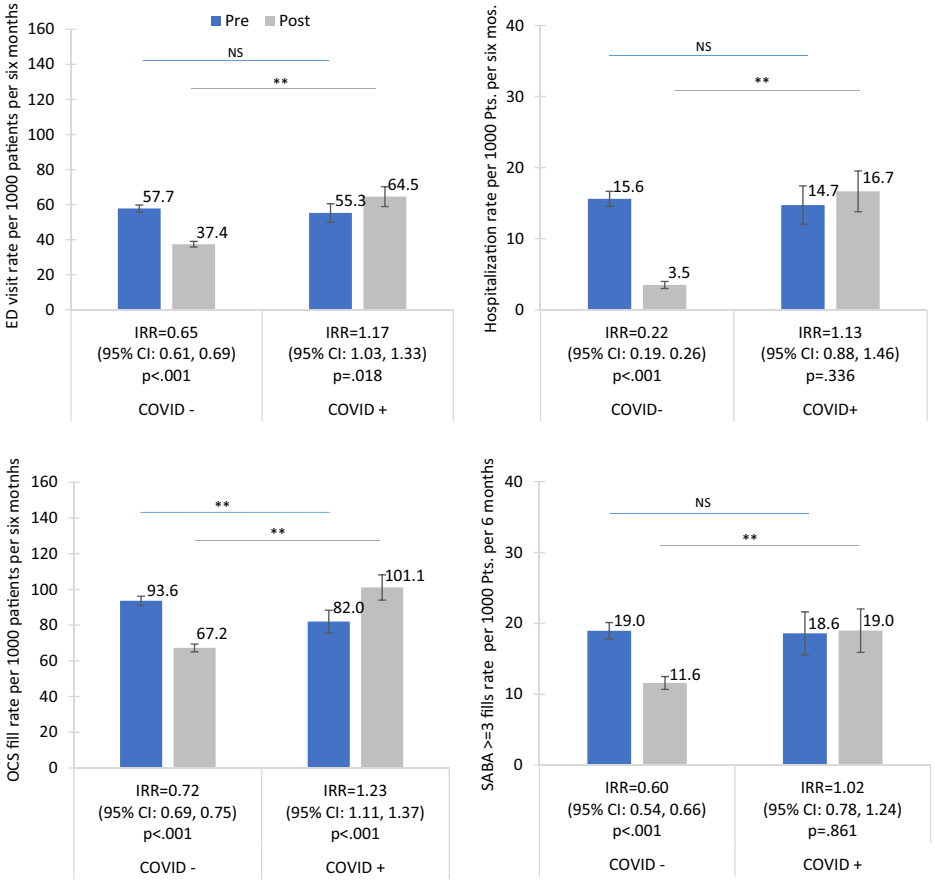

FIGURE 1. Morbidity rates per 1,000 patients per 6 months. Poisson regression using generalized estimating equations analyses with the specification of repeat measures. Comparison of COVID$^+$ versus COVID$^-$ in the pre-PCR (blue line) and post-PCR (gray line) periods: *$P <$ .05, **$P <$ .01. *ED*, emergency department; *IRR*, incidence rate ratios; *NS*, nonsignificant ($P > .05$); *OCS*, oral corticosteroids.

these slight increases in hospitalization and SABA fill rates in the COVID$^+$ group after infection contrast starkly with the significant decrease in the COVID$^-$ group after PCR testing. In the 6 months before SARS-CoV-2 PCR testing, no significant differences were seen in either the COVID$^+$ or COVID$^-$ cohorts for the ED rate, hospitalization rate, and SABA fill rates. The OCS fill rate was slightly lower in the COVID$^+$ group compared with the COVID$^-$ group (IRR = 0.88; $P = .002$). Conversely, during the 6 months after SARS-COV-2 testing, COVID$^+$ patients had significantly higher morbidities in all measures compared with those who were COVID$^-$ (ED rate [IRR = 1.73; $P < .001$], hospitalization rate [IRR = 4.81; $P < .001$], OCS fill rate [IRR = 1.50; $P < .001$], and SABA fill rate [IRR = 1.66; $P < .001$]) (Figure 1).

Our data demonstrate that although asthma outcomes were again improved for those who tested negative for SARS-COV-2 PCR, asthmatic children who were given a definitive diagnosis of COVID-19 have worse asthma control in the first 6 months after infection. The overall improvement in asthma control during the pandemic[3-5] is hypothesized to result from hygiene and public health measures, and/or decreased exposures to particulate matter and viral triggers. In our study, the effect of COVID-19 on asthma became discernable when we compared children who were PCR-positive with those who were PCR-negative in the post-6 month period, because all metrics showed highly significant differences with this comparison. Thus, the asthma-triggering effect of SARS-CoV-2 was likely masked by the overall decrease in asthma exacerbations during the stay-at-home measures when other asthma triggers were less present in the community.

The apparent protective effect against SARS-CoV-2 infection in high-risk asthma patients could be attributed to several factors. Increased inhaled corticosteroid use[8] and/or atopic status with reduced expression of angiotensin-converting enzyme-2,[9] an entry receptor for SARS-COV-2, may be possible explanations. The effects of medication and atopy are out of the scope of this brief communication and will be further explored in full-length articles along with analyses of other select variables such as age, race, and regional or temporal factors. A potential limitation of our study is that the retrospective design limits the proof of causation between SARS-CoV-2 and poor asthma control. However, the strengths of our study are the large sample representing diverse ethnic populations across the United States in multiple health care systems and the inclusion of a comparison group.

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