

ORIGINAL ARTICLE

Asthma and Lower Airway Disease

Childhood asthma outcomes during the COVID-19 pandemic: Findings from the PeARL multinational cohort

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Abstract

Background: The interplay between COVID-19 pandemic and asthma in children is still unclear. We evaluated the impact of COVID-19 pandemic on childhood asthma outcomes.

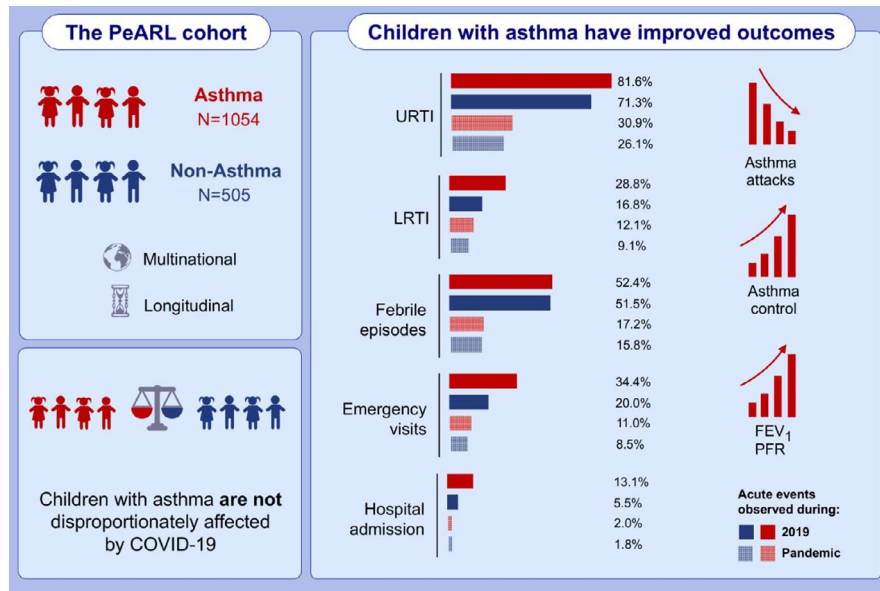
Methods: The PeARL multinational cohort included 1,054 children with asthma and 505 non-asthmatic children aged between 4 and 18 years from 25 pediatric departments, from 15 countries globally. We compared the frequency of acute respiratory and febrile presentations during the first wave of the COVID-19 pandemic between groups and with data available from the previous year. In children with asthma, we also compared current and historical disease control.

Results: During the pandemic, children with asthma experienced fewer upper respiratory tract infections, episodes of pyrexia, emergency visits, hospital admissions, asthma attacks, and hospitalizations due to asthma, in comparison with the preceding year. Sixty-six percent of asthmatic children had improved asthma control while in 33% the improvement exceeded the minimal clinically important difference. Pre-bronchodilatation FEV₁ and peak expiratory flow rate were improved during the pandemic. When compared to non-asthmatic controls, children with asthma were not at increased risk of LRTIs, episodes of pyrexia, emergency visits, or hospitalizations during the pandemic. However, an increased risk of URTIs emerged.

Conclusion: Childhood asthma outcomes, including control, were improved during the first wave of the COVID-19 pandemic, probably because of reduced exposure to asthma triggers and increased treatment adherence. The decreased frequency of acute episodes does not support the notion that childhood asthma may be a risk factor for COVID-19. Furthermore, the potential for improving childhood asthma outcomes through environmental control becomes apparent.

KEYWORDS

childhood asthma, coronavirus, COVID-19



GRAPHICAL ABSTRACT

This study evaluates the frequency of acute respiratory and febrile presentations during the first wave of COVID-19 pandemic in childhood asthma. Data from the multinational PeARL cohort reveal improved health and asthma activity during the first wave of the COVID-19 pandemic, probably attributed to decreased exposure to asthma triggers and increased treatment adherence. During that period, children with asthma experienced fewer URTIs, episodes of pyrexia, emergency visits, hospital admissions, asthma attacks and hospitalizations due to asthma, in comparison to the preceding year.

1 | INTRODUCTION

A series of studies have demonstrated that the morbidity from Coronavirus Disease 2019 (COVID-19) is lower in children compared to adults.¹⁻³ Risk factors for severe disease include older age, male sex, chronic respiratory diseases, diabetes, coronary artery disease, obesity, and ethnicity (black, Asian, and mixed).⁴⁻⁶ Chronic respiratory diseases are among these high-risk pre-existing conditions, and asthma represents the majority of such patients.^{4,5,7} Initial clinical reports did not identify asthma to be over-represented among COVID-19 patients,⁸ but severe, uncontrolled asthma is included in most guidance documents among conditions which may increase the risk for severe COVID-19.⁹ Analysis in more than 17 million adults and ~11,000 COVID-19-related deaths identified severe asthma (defined as asthma with recent oral corticosteroid use) as a significant associate of COVID-19 death.⁶ It is, however, unclear what is the impact of asthma on the risk of SARS-CoV-2 infection and severe COVID-19 in children, and what is the impact of COVID-19 pandemic on asthma-related outcomes in children. Survey data among pediatric asthma specialists suggest that there is no apparent increase in asthma-related morbidity in children with asthma¹⁰; it is even possible that due to increased adherence and reduced exposures due to confinement, such children may have improved outcomes.¹⁰ Furthermore, it is also possible that allergic sensitization can have some protective effect against COVID-19.¹¹ However, this needs to be further explored.^{12,13}

For the above reasons, Pediatric Asthma in Real Life (PeARL), a think tank initiated by the Respiratory Effectiveness Group (REG), comprising of pediatric asthma experts globally,¹⁴ opted to evaluate the interplay between childhood asthma and the pandemic due

to COVID-19 infection in a multinational cohort of children with asthma and non-asthmatic controls. We aimed at assessing asthma activity (asthma control, respiratory infections, asthma attacks, and lung function) during the first months of the COVID-19 pandemic and exploring whether children with asthma had excess morbidity during this period, in comparison with prerecorded historical data.

The primary study objective was to assess differences in the impact of the pandemic on the frequency of upper (URTIs), lower respiratory tract infections (LRTIs), episodes of fever, emergency visits, and hospital admissions between asthmatic and non-asthmatic children. Secondary objectives to evaluate were as follows: (i) the impact of the pandemic on the frequency of asthma attacks, as well as the previously mentioned events among asthmatic children, compared to the baseline frequency of these events, during the preceding year (2019); (ii) the impact of the pandemic on disease control, evaluated using validated asthma clinical questionnaires, among children with asthma, compared to the baseline asthma control, during the preceding year (2019).

2 | METHODS

2.1 | Study design, setting, and participants

The impact of the COVID-19 pandemic on disease activity in children with asthma was evaluated in data collected as part of a multinational audit. Ethics review was not required for this audit, in most participating countries. When required, an ethics approval was acquired. The cross-sectional case-control study was designed and managed by

the PeARL Steering Committee, was conducted in accordance with the Good Clinical Practice Guidelines and reported following the Strengthening the reporting of observational studies in epidemiology (STROBE) statement.¹⁵ Participating centers were identified among members and collaborators of the PeARL think tank.

2.2 | Eligibility criteria, sources, and methods of selection of participants

Eligible subjects were children aged between 4 and 18 years, diagnosed with asthma and monitored in one of the participating asthma clinics. Non-asthmatic controls included children of the same age range, monitored at the same healthcare setting for a non-respiratory condition, who did not clinically suffer from asthma. Children with other chronic respiratory conditions, diabetes, hypertension, immunodeficiency, or any other chronic disease deemed by the responsible clinician that could impact the main outcomes of this study, were excluded. Each participating center was asked to contribute data from at least 45 participants, including twice as many children with asthma, compared to controls.

2.3 | Definition of variables

For the purposes of this study, the onset of the pandemic in each participating center was defined as the date of the first fatality due to COVID-19 in the respective country. For each participant, the duration of the pandemic period was defined as the period between the onset of the pandemic and the captured clinical visit. Historical data (before the pandemic) were captured during 2019 and the duration of observation before the onset of the pandemic was 1 year, for all participants.

We collected basic demographic data for all participants and data on the main outcomes of interest. The frequency of acute events (URTIs, LRTIs, asthma attacks, episodes of fever, emergency visits, for any reason, and hospital admissions, for any reason) during and before the pandemic was reported as recalled by the participants or their parents. URTIs included episodes of sore throat, pharyngitis, or rhino/sinusitis. LRTIs included episodes associated acute bronchitis or pneumonia and were differentiated from URTIs on the basis of the clinical presentation. Asthma attacks were defined as the need for systemic glucocorticoids administration for at least 48 h or an emergency visit or a hospitalization for asthma. Need for additional treatment was defined as any treatment escalation, including increased use of short-acting bronchodilators, increased dose of inhaled corticosteroids, or the administration of systemic corticosteroid courses. Asthma activity during and before the pandemic was measured using validated disease control questionnaires (asthma control test: ACT,¹⁶ childhood asthma control test: C-ACT,¹⁷ asthma control questionnaire: ACQ,¹⁸ or composite asthma severity index: CASI¹⁹). For each participant with asthma, at least one questionnaire was administered at least 2 months after the onset of the

pandemic in their country and at least once during 2019 (the same questionnaire in both occasions). Physiological measurements, including forced expiratory value in 1 second (FEV₁), before or after bronchodilation and the peak expiratory flow rate (PEFR), during and before the pandemic, were also captured when available.

2.4 | Statistical analysis

Statistical analyses were performed using R statistical software (version 3.4.3 or newer; R Foundation for Statistical Computing; Vienna; Austria). We did not perform power calculations, as this was an exploratory analysis. Shapiro-Wilk test was used to evaluate normality of the distribution of continuous data. Student's *t*-test and Mann-Whitney test were used for comparing means of normally or non-normally distributed variables, respectively. Chi-squared test was used for comparing dichotomous data. The level of significance was set at 0.05 for all analyses.

We used a generalized linear model for evaluating the impact of the pandemic on the frequency of acute events in asthmatic versus non-asthmatic participants. We assumed a negative binomial distribution, with the number of events during the pandemic as the response variable and the natural logarithm of the duration of the pandemic for each participant as an offset variable. We included as potential covariates the age, gender, and the number of acute events each participant experienced during 2019, race (if it was available, according to the participating countries' ethics regulations), passive smoking history (cigarettes smoked per day by the parents), concomitant known history of allergic rhinitis, clinically relevant IgE sensitization, food allergy and history of flu vaccination during the preceding year. These variables were considered the most pertinent by the study group.

For evaluating the impact of the pandemic on the frequency of each acute event in asthmatic and non-asthmatic children, we extrapolated an annualized event count based on the number of observed events during the pandemic ($365 \times \text{events/pandemic duration [in days]}$). We then compared this with the actual number of acute events observed during 2019 using the Wilcoxon signed-rank test. In addition, we present the number of participants who had at least one event during the pandemic and during the preceding year.

Wilcoxon signed-rank test was also used to assess the impact of the pandemic on asthma control. As previously described, different standardized measures of asthma control were used in each center, depending on the measures that were evaluated during 2019, to facilitate comparisons. Firstly, we compared asthma control during versus before the pandemic in subgroups of participants, depending on the available asthma control tools. Next, we used Z-scores to estimate standardized differences by dividing the differences in the values during versus before the pandemic, with the standard deviation of all differences, for every test. In a sensitivity analysis, we only included subjects with a previous asthma control assessment between March and June 2019, during the same period as the pandemic, to account for seasonal variation.

Paired *t* test was used to compare pulmonary function measurements during versus before the pandemic. As previously, we conducted a sensitivity analysis only including subjects with a previous pulmonary function test, between March and June, 2019.

Finally, in a subgroup analysis, we repeated all previously described analyses only including data from participating centers that are in countries that were more severely hit by the pandemic (>200 deaths per million of inhabitants by 13/07/2020).

3 | RESULTS

3.1 | Participants and descriptive data

The study included 1,054 children with asthma and 505 control subjects, from 25 pediatric departments from 15 countries globally (Table S1). The baseline characteristics of the participants were generally balanced between the groups with a few, anticipated exceptions (Tables 1 and 2). A higher proportion of males (62.8% versus 51.9%) was observed in the asthma group compared to the controls, which is consistent with epidemiological characteristics of the disease in this age group. Allergic diseases such as allergic rhinitis (79.4% vs 39.4%) and food allergy (22.8% vs 15.6%) were also more prevalent in the asthma group. A higher proportion of children with asthma had a

confirmed IgE sensitization and was vaccinated for the flu in the preceding year. Finally, children with asthma suffered a higher number of episodes of URTIs, LRTIs, emergency visits, or hospital admissions during 2019, compared to the control group (Tables 3 and 4).

National lockdowns were imposed in all participating countries apart from Finland and Hong Kong. Lockdown measures were in place for a median of 54.5% (quantiles 27.8%-76.7%) of the study period days. Moreover, schools were closed for the duration of the study period in over half of the participating centers (median 100%, quantiles: 57.7%-100%).

3.2 | Outcome data

3.2.1 | Acute events frequency among asthmatic versus non-asthmatic controls during the pandemic

Using generalized linear regression analysis, we evaluated between-group differences in the frequency of acute events during COVID-19 pandemic (Tables 3 and 4). Children with asthma were not found to be at increased risk of LRTIs, episodes of pyrexia, emergency visits, or hospitalizations during the pandemic. However, our analyses revealed an increased risk of URTI among children with asthma, compared to the control group, during the pandemic ($p = 0.005$).

TABLE 1 Main characteristics of the participants. Continuous data are presented as median [percentiles 25–75], total number of participants with available data for this variable, and dichotomous data as number of events/ total numbers (percentage)

	Cases	Controls	<i>p</i> -value
Number of participants, <i>N</i>	1054	505	
Observation during the pandemic (days)	102 [77–123]	102 [79–122]	0.68
Age (years)	10 [8–12]	10 [8–13]	0.42
Sex (female)	392 (37.2%)	243 (48.1%)	<0.001
Race			
Asian	111 (10.5%)	53 (10.5%)	0.1
Black	22 (2.1%)	8 (1.6%)	
Caucasian	486 (46.1%)	264 (52.3%)	
Hispanic	147 (14.0%)	65 (12.9%)	
Other	271 (25.7%)	123 (24.4%)	
Missing data	164 (15.6%)	57 (11.3%)	
Passive smoking exposure			
Number exposed	166 (15.7%)	67 (13.3%)	0.22
Cigarettes per day	0 [0–0]	0 [0–0]	0.23
Weight (kilograms)	35 [25.1–50]	35 [21.2–50]	0.89
Height (centimeters)	140 [126–154]	140 [128–157]	0.17
Allergic rhinitis diagnosis	837 (79.4%)	199 (39.4%)	<0.001
Food allergy diagnosis	240 (22.8%)	79 (15.6%)	0.002
IgE sensitization	792 (75.1%)	201 (39.8%)	<0.001
Other chronic disease	176 (16.7%)	76 (15.1%)	0.45
Had flu vaccine in the previous year	402 (38.1%)	135 (26.7%)	<0.001

Note: Bold: Statistically significant between-group differences.

TABLE 2 Asthma severity and asthma treatment adherence in the asthma group

Asthma severity	
Intermittent	296 (28.1%)
Mild persistent	351 (33.3%)
Moderate persistent	291 (27.6%)
Severe persistent	111 (10.5%)
Unknown	5 (0.5%)
Treatment adherence	
Always as prescribed	551 (52.3%)
Sometimes not taken	282 (26.8%)
Often not taken	41 (3.9%)
Never taken	106 (10.1%)
Unknown	74 (7.0%)

TABLE 3 Change in the frequency of acute events during the pandemic, compared to 2019 among children with asthma and controls

Acute event	Change in frequency from 2019		Between-group difference
	Asthma	Control	
URTI	↓	↓	More pronounced decrease in control
LRTI	-	↑	-
Pyrexia	↓	↓	-
Emergency visit	↓	-	-
Hospital admission	↓	-	-
Need for additional asthma treatment	↑	NR	NR
Acute asthma	↓	NR	NR
Hospitalization for acute asthma	↓	NR	NR

Note: Between-group differences in the frequency of events were assessed using generalized linear regression analysis.

The strongest predictor for each type of acute events was the number of such events experienced by the participants during the preceding year ($p < 0.001$ for all analyses). In addition, older age was associated with a decreased risk of pyrexia ($p = 0.025$), while the race of the participants was also associated with the frequency of these events.

3.2.2 | Impact of the pandemic on the frequency of the acute events, compared to the preceding year

Next, using paired statistics, we compared the frequency of each acute event during the pandemic, compared to the preceding year (Tables 3 and 4). Children with asthma experienced fewer URTIs,

episodes of pyrexia, emergency visits, hospital admissions, asthma attacks, and hospitalizations due to asthma during the pandemic, compared to the preceding year. No differences were observed in the frequency of LRTIs during versus before the pandemic.

On the other hand, the pandemic did not appear to impact the frequency of emergency visits or hospital admissions of non-asthmatic controls. In this group, we observed a decreased frequency of URTIs and episodes of pyrexia, but also a significantly increased risk of LRTIs during the pandemic.

3.2.3 | Asthma control during the pandemic

We then compared asthma control during versus before the pandemic (Table 5). A validated asthma control tool was used, following the local practice in every participating center, to ensure the availability of a measurement of the same tool during the pandemic and one during 2019. At least two asthma control measures (during and before the pandemic) were available for 90.9% of participants in the asthma group. ACT was used in 756 (78.9%) of these children, while cACT, ACQ, or CASI was used in the remaining cases.

Improved or unchanged asthma control during pandemic was reported by 90.2% of the participants, while only 9.8% reported worse asthma control. Moreover, 65.9% experienced an improvement. Importantly, one in three children with asthma (33.2%) reported an improvement in control that exceeded the minimal clinically important difference of the test used.

Given the seasonal differences in asthma control, we conducted a sensitivity analysis where we only included historical asthma control measurements conducted during the same months with the first months of the pandemic (March-June 2019), with consistent findings (Table 5).

3.3 | Analyses of subgroups

3.3.1 | Pulmonary function during the pandemic

Pulmonary function during the pandemic compared to 2019 was evaluated in a subgroup of asthma children with available data (Table 6). Adequate measurements of pre-bronchodilatation FEV₁, post-bronchodilatation FEV₁, and PFR were available in 155, 90, and 106 children, respectively. Paired analyses suggested pre-bronchodilatation FEV₁ and PFR were significantly improved during the pandemic, while there was also a non-significant trend for improved post-bronchodilatation FEV₁.

In a sensitivity analysis only including historical pulmonary function evaluated during the same months with the pandemic (March-June 2019), pre-bronchodilatation FEV₁ was significantly improved during the pandemic, while the remaining measures showed non-significant, numerical improvements.

TABLE 4 Acute events observed during 2019 and during the pandemic

Acute events	Children with asthma			Controls			Between-group differences
	2019	Pandemic	Frequency change during pandemic	2019	Pandemic	Frequency change during pandemic	
URTI	2 [1–4], 81.6%	0 [0–1], 30.9%	<i>p</i> < 0.001 73 fewer*	2 [0–3], 71.3%	0 [0–1], 26.1%	<i>p</i> < 0.001 35 fewer*	<i>p</i> = 0.005 , favoring control
LRTI	0 [0–1], 28.8%	0 [0–0], 12.1%	<i>p</i> = 0.12	0 [0–0], 16.8%	0 [0–0], 9.1%	<i>p</i> < 0.001 18 more*	<i>p</i> = 0.09
Pyrexia	0 [0–2], 52.4%	0 [0–0], 17.2%	<i>p</i> < 0.001 24 fewer*	0 [0–2], 51.5%	0 [0–0], 15.8%	<i>p</i> < 0.001 20 fewer*	<i>p</i> = 0.08
Emergency visit	0 [0–1], 34.4%	0 [0–0], 11.0%	<i>p</i> < 0.001 9 fewer*	0 [0–0], 20.0%	0 [0–0], 8.5%	<i>p</i> = 0.79	<i>p</i> = 0.31
Hospital admission	0 [0–0], 13.1%	0 [0–0], 2.0%	<i>p</i> < 0.001 17 fewer*	0 [0–0], 5.5%	0 [0–0], 1.8%	<i>p</i> = 0.29	<i>p</i> = 0.08
Need for additional treatment	2 [0–4], 74.0%	0 [0–1], 29.5%	<0.001 165 more*				
Acute asthma	0 [0–1], 40.7%	0 [0–0], 9.6%	<i>p</i> < 0.001 31 fewer*				
Hospitalization for acute asthma	0 [0–0], 9.8%	0 [0–0], 1.2%	<i>p</i> < 0.001 9 fewer*				

Note: Presented as median [percentiles 25–75], and the percentage of participants experiencing at least one event in the respective observation period. Between-group differences assessed using generalized linear regression analysis.

*Events per 100 participants per year.

Bold: Statistically significant differences.

TABLE 5 Change in asthma control during the pandemic, compared to 2019

	N	2019	Pandemic	% improved or unchanged	% improved	% exceeding MCID	<i>p</i>
(A) Main analysis							
ACQ (↓ = better)	34	0.14 [0–0.74]	0 [0–0]	100%	56.7%	26.7% (MCID: 0.5)	<0.001
ACT (↑ = better)	756	20 [16–23]	23 [19–25]	89.9%	67.4%	32.1% (MCID: 3)	<0.001
cACT (↑ = better)	108	22 [19–24]	25 [23–26] ↑ in 66.7% of subjects	87.2%	66.7%		0.002
CASI (↓ = better)	60	2 [1–5]	1 [1–2]	93.3%	50%	50% (MCID: 0.9)	<0.001
z-scores (↑ = better)	958			90.2%	65.9%		<0.001
(B) Sensitivity analysis only including historical asthma control evaluations between March–June 2019							
ACQ (↓ = better)	15	0.14 [0–1.01]	0 [0–0]	100%	53.3%	33.3% (MCID: 0.5)	0.013
ACT (↑ = better)	284	22 [18–24]	24 [22–25]	88.7%	61.6%	28.5% (MCID: 3)	<0.001
cACT (↑ = better)	11	24 [23–25]	25 [23–25]	81.8%	45.5%		NS
CASI (↓ = better)	21	3 [2–5]	2 [1–3]	95.2%	57.1%	57.1%	0.003
Standardized (↑ = better)	331			89.4%	60.4%		0.001

Note: Presented as median [percentiles 25–75]. MCID: Minimal Clinically Important Difference. (A) Main analysis. (B) Sensitivity analysis only including historical asthma control evaluations between March–June 2019.

3.3.2 | Subgroup analysis only including countries that were more severely hit by the pandemic

In this subgroup analysis, all previously described analyses were repeated, including data from participating centers from countries that

were more severely hit by the pandemic (>200 deaths per million of inhabitants by 13/07/2020). More specifically, we included data from France, Italy, Mexico, Spain, UK, and the USA. This subgroup analyses, which involved 597 children with asthma and 298 non-asthmatic controls, yielded consistent results with the main analyses (Tables S2–S6).

Pulmonary function test	N	Mean 2019	Mean pandemic	p-value
Main analysis				
FEV1 pre-bronchodilatation	155	94.5% (15.1%)	98.4% (16.6%)	<0.001
FEV1 post-bronchodilatation	90	100.6% (14.6%)	104.0% (19.2%)	0.055
PFR	106	121.4% (94.7%)	129.4% (99.4%)	0.003
Sensitivity analysis only including historical asthma control evaluations between March-June 2019				
FEV1 pre-bronchodilatation	63	93.2% (12.0%)	97.4% (15.2%)	0.046
FEV1 post-bronchodilatation	38	98.3% (12.8%)	103.5% (22.5%)	0.167
PFR	39	121.8% (106.5%)	128.7% (106.6%)	0.141

TABLE 6 Change in pulmonary function during the pandemic, compared to 2019. Presented as mean (SD)

4 | DISCUSSION

4.1 | Key results

In the multinational PeARL childhood asthma cohort, we evaluated the impact of the COVID-19 pandemic on asthma activity. During the pandemic, children with asthma experienced improved disease control (two thirds of the patients), as evidenced by improved scores in validated asthma control measures (>MCID in one third), fewer asthma attacks, fewer hospitalizations, and improved pulmonary function. The multifaceted etiology of this observation may include the avoidance of major asthma triggers including outdoor allergens, viral infections, physical exercise, and air pollution, due to social distancing, home sheltering, and reduced school days.^{1,12,20-23} Increased treatment adherence during the pandemic²⁴ could have also contributed. While our compliance data were self-reported and not objectively observed, we did find high adherence levels during the pandemic in our cohort. However, along with these “protective” effects of the pandemic, children were also more exposed to indoor allergens and pollutants and possibly adverse psychological factors and there is a chance this could have precipitated worse asthma control, nevertheless, in a minority of children (1/10 children in our cohort). Finally, during the pandemic we observed an increase in the frequency of URTIs among asthmatic children, compared to controls. While this could be considered consistent with previous findings suggesting COVID-19 infection may only be associated with limited upper respiratory symptoms in children,²⁵ it is more likely to reflect an increased attention given to minor symptoms or heightened awareness due to the COVID-19 pandemic.

4.2 | Interpretation

The interplay between asthma and COVID-19 infection is being extensively investigated. Several studies explored the prevalence of asthma among children and adults with confirmed COVID-19 infection and failed to find an increased risk of contracting the infection or

of adverse outcomes among asthmatic patients.^{26,27} A recent review with meta-analysis done in adults with COVID-19 (744 asthmatic and 8151 non-asthmatic) showed that the presence of asthma had no significant effect on mortality (OR = 0.96 [0.70–1.30], $I^2 = 0\%$, $p = 0.79$), duration of hospitalization, or the risk of ICU admission.²⁸ However, COVID-19 infection was significantly underdiagnosed during the initial months of the pandemic due to limited availability of diagnostic tests that led most countries to recommend home isolation without testing in case of non-severe symptoms consistent with COVID-19. The PeARL asthma cohort is the first large, multinational cohort to demonstrate that children with asthma do not experience more frequent events of disease deterioration during this period, including in countries with an increased COVID-19 burden. In contrast, most outcomes were improved. These findings strongly reinforce the need and potential of compliance to treatment,^{29,30} as well as the prospect of improved outcomes with environmental control in asthma, an area of some discrepancy.³¹

The role of different viruses as asthma attack triggers has been investigated extensively. While rhinoviruses represent the main viral trigger of attacks, coronaviruses also trigger asthma attacks, albeit less frequently.³² However, and in line with our findings, the outbreak of SARS in Singapore and Hong Kong was not associated with increased asthma attacks in children.^{33,34} On the contrary, and in line with our results, the incidence of acute respiratory tract infections and acute asthma attacks declined dramatically, likely due to the closure of schools for a period of time, stepped-up public hygiene measures and the use of facemasks.^{33,34}

Despite that we did not have access to serology or exposure data, the improved outcomes among asthmatic children during SARS/COVID-19 epidemics are not incompatible with the hypothesis of a protective effect of asthma against COVID-19. This hypothesis is based on several observations, including changed in the immune response or decreased risk secondary to chronic medications such as inhaled corticosteroids (ICS). In vitro models have shown that ICS may suppress both coronavirus replication and cytokine production.^{35,36} Analysis of induced sputum samples in a well-characterized cohort of adults with severe asthma found reduced

ACE2 (angiotensin-converting enzyme 2) and TMPRSS2 (transmembrane protease serine 2) gene expression among patients taking ICS, and especially among those on higher doses³⁷; and we know ACE2 and TMPRSS2 mediate SARS-CoV-2 cell infection. Similarly, a recent study done in children and adults showed that patients with asthma and respiratory allergies had reduced ACE2 gene expression in airway cells, suggesting a potential mechanism of reduced COVID-19 risk.¹¹

4.3 | Limitations and strengths

This study was based on an audit and, therefore, we did not have access to COVID-19 serology or details on the exposure history of the children or their parents, which would have been informative.

Evaluation of the frequency of acute events during the pandemic is challenging, but we believe our methodology was rigorous. Firstly, the accuracy of parent-reported frequency of acute events has been previously validated.³⁸ We assumed a potential under-reporting of acute events during 2019, due to recall bias; however, we do not anticipate between-group differences in this bias. In addition, potential under-reporting of acute events prior to the pandemic would have led to an overestimation of the relative risk during the pandemic. Since we did not find an increased risk, we suggest the impact of recall bias was minimal.

During the first wave of the pandemic, many patients hesitated to attend face-to-face follow-up visits, suggesting that potential participants may have been missed.¹⁰ However, all participating centers offered alternative follow-up options, including phone call or teleconference facilities. Moreover, we would anticipate that patients with less controlled asthma, or those experiencing acute events are more likely to adhere to their follow-up visits or phone calls. However, study participants in the PeARL cohort reported in general better asthma control and less acute events during the pandemic. Therefore, it is unlikely that potential bias from missing well-controlled patients had a significant impact in our findings.

For estimating the duration of the pandemic, we considered the onset of the pandemic to coincide with the first fatality in each respective country. This usually followed a few days to weeks after the identification of the first case. We chose this time point as an objective marker that could better identify the onset of the impact of the pandemic in each community. Since we were inquiring for acute episodes during the epidemic, we wanted to avoid a potential underestimation of the frequency of the events that could have been caused by accounting for a wider time period of the epidemic.

Extrapolating an annualized asthma attack rate based on the events that were observed during the pandemic is complicated by the seasonal variability of asthma attacks.^{39,40} However, numerous high-quality studies demonstrate a peak in childhood asthma attack during autumn and schools reopening, which is counterbalanced by a low frequency during summer.^{32,41} Interestingly, these studies consistently show that the frequency of asthma attacks and asthma hospitalizations during spring and early summer

levels with the median frequency of asthma attacks throughout the year.^{19,20} The study period coincided with these months, suggesting that the frequency of acute events equals to their frequency throughout the year. This observation enhances our confidence on the accuracy of our annualized estimates and our findings, however, the limited observation period during the pandemic remains a limitation of this study.

The over-representation of atopic diseases in the control group shall be mentioned as a potential limitation, but it has been accounted for in our analyses. Finally, different validated questionnaires were used for assessing asthma control across the study centers, depending on the availability of historic measurements, to allow for paired comparisons. While the results of different tools are not directly comparable, our study revealed consistent results in the subgroups evaluated with different tools. On the other hand, the extensive, multinational study population with a good geographic balance across 4 continents, was a major strength of our study, increasing our confidence in our findings.

5 | CONCLUSION

Overall, this analysis of the PeARL childhood asthma cohort revealed improved health and asthma activity during the COVID-19 pandemic, probably associated with decreased exposure to asthma triggers and increased treatment adherence. It also demonstrated that during the pandemic, children with predominantly mild to moderate atopic asthma did not suffer from an increase in the frequency of acute episodes that could represent COVID-19 infection.

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CONFLICT OF INTEREST


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AUTHOR CONTRIBUTIONS

NGP: Study conception and study design. AGM and NGP: Data analysis. All authors: Data collection, interpretation of the findings, and critical revision of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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APPENDIX 1

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