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The effects of the COVID-19 pandemic on PICU admissions for severe asthma exacerbations: A single-center experience

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Abstract

Background: The incidence of severe asthma exacerbations (SAE) requiring a pediatric intensive care unit (PICU) admission during the coronavirus disease 2019 (COVID-19) pandemic (and its association with public restrictions) is largely unknown. We examined the trend of SAE requiring PICU admission before, during, and after COVID-19 restrictions in Amsterdam, the Netherlands, and its relationship with features such as environmental triggers and changes in COVID-19 restriction measures.

Methods: In this single-center, retrospective cohort study, all PICU admissions of children aged ≥2 years for severe asthma at the Amsterdam UMC between 2018 and 2022 were included. The concentrations of ambient fine particulate matter ($PM_{2.5}$) and pollen were obtained from official monitoring stations.

Results: Between January 2018 and December 2022, 228 children were admitted to the PICU of the Amsterdam UMC for SAE. While we observed a decrease in admissions during periods of more stringent restriction, there was an increase in the PICU admission rate for SAE in some periods following the lifting of restrictions. In particular, following the COVID-19 restrictions in 2021, we observed a peak incidence of admissions from August to November, which was higher than any other peak during the indicated years. No association with air pollution or pollen was observed.

Conclusion: We hypothesize that an increase in clinically diagnosed viral infections after lockdown periods was the reason for the altered incidence of SAE at the PICU in late 2021, rather than air pollution and pollen concentrations.

Abbreviations: COVID-19, coronavirus disease 2019; ED, emergency department; PICU, pediatric intensive care unit; $PM_{2.5}$, fine particulate matter; SAE, severe asthma exacerbation; UMC, University Medical Center.

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1 | INTRODUCTION

Pediatric asthma is the most common chronic lung disease in children worldwide and may cause serious morbidity and mortality.[1,2] The main focus of optimal asthma management is symptom control and prevention of exacerbations of disease. However, 5% of children suffer from uncontrolled asthma despite maximal therapy, substantially contributing to disease burden in this patient group.[3,4] Asthma exacerbations, defined as an acute deterioration requiring a prompt change in treatment, can be so severe that they require an emergency department (ED) visit, a hospital admission, or even a pediatric intensive care unit (PICU) admission.[5,6] A severe asthma exacerbation (SAE) is characterized by unresponsiveness to conventional therapy that requires PICU admission for intravenous therapy and potentially intubation and invasive ventilation.[7]

Usually, an asthma exacerbation is triggered by a viral respiratory tract infection, mediated through increased T2 inflammation.[8] However, external/environmental features such as pollen or air pollution are also common contributors,[5,9] influencing not only the occurrence of exacerbations but also, potentially, the pathobiology of asthma.[10,11] The coronavirus disease 2019 (COVID-19) pandemic is another example of an external factor influencing the risk of asthma exacerbations, especially during periods of major daily disruptions, such as public restrictions (i.e., lockdowns) intended to slow the spread of the disease.[12] It has been suggested that the societal changes experienced during the COVID-19 pandemic, in terms of the environment, medical practice and medication usage, have significantly influenced asthma management and outcomes.[13] The results of a study on Korean children between 12 and 18 years old showed that the prevalence of allergic diseases such as asthma and allergic rhinitis decreased during the COVID-19 pandemic years, while the number increased following periods when social gatherings were allowed. However, in this study, the severity of allergic disease and specific types of that were not investigated.[14] While the incidence of asthma exacerbations in children during the COVID-19 pandemic has been evaluated,[12,15–18] the incidence of SAE, specifically those requiring PICU admission and treatment, during the pandemic is, to our knowledge, not known. The aim of this study was therefore to examine the trend of admissions for SAE to the PICU before, during, and after COVID restrictions and to evaluate whether this trend could be linked to a variety of features including environmental triggers and the COVID-19 restrictions themselves.

2 | MATERIALS AND METHODS

2.1 | Study design

This study is a single-center, retrospective cohort study performed at the Amsterdam University Medical Center (UMC), a tertiary medical center. The PICU has a 12-bed facility providing intensive care treatment for the northwestern part of the Netherlands.

2.2 | Study subjects

The electronic hospital records of all children admitted to the PICU of the Amsterdam UMC between 2018 and 2022 were examined and the details of those admitted with a diagnosis of severe asthma were extracted for closer analysis. The diagnosis of SAE was made by a pediatrician and based on the following definition: "An exacerbation of asthma which is not improving after at least three doses of bronchodilator by nebulization, corticosteroids systemically and one dose of intravenously given Magnesium-sulphate." Wheezing children aged less than 2 years were excluded as these children will more likely present with bronchiolitis, and differentiation between bronchiolitis and asthma is extremely difficult. Furthermore, between the ages of 2 and 5 years, wheezing illnesses seem to be more related to the subsequent development of asthma.[19,20] Therefore, only children above the age of 2 years were included in this study.

2.3 | Institutional Review Board (IRB) approval

The study design was reviewed by the ethical committee of the Amsterdam UMC. Owing to the retrospective and anonymous nature of the current study it was deemed that informed consent was not necessary.

2.4 | Data collection

Demographic, social, and clinical data were extracted from electronic medical records. Additionally, the total number of children admitted to the PICU of the Amsterdam UMC was also extracted from the electronic patient file database. The exact dates and levels of governmental COVID-19 restrictions in the Netherlands, such as workplace restrictions, lockdowns, and school closures, were obtained from the Oxford COVID response tracker.[21] The key stringency criteria examined within the current paper were the complete closure of schools, a complete working from home order, or both being in effect. A Spearman correlation analysis was performed to determine the relationship between monthly SAE admission numbers and COVID-19 restriction maneuvers. The analysis used Oxford COVID response tracker daily restrictions scores for school closure and workplace closure, each of them ranging from 0 to 3.[21] To calculate the "stringency score," for the entire pandemic period having this information available (beginning of March 2020 to the end of February 2022), the monthly score of both indices were calculated and then added up together.

Environmental exposures were defined by the amount of ambient air pollution and pollen exposure in the Netherlands from 2018 to 2022. Ambient air pollution was represented by particulate material with an aerodynamic diameter of less than 2.5 microns ($PM_{2.5}$) which has previously been associated with respiratory (and other) diseases.[22] Also, high concentrations of $PM_{2.5}$ were associated with an increase in asthma exacerbations in children, and children with asthma were at a higher risk of requiring an ED visit.[23] Hourly concentrations of ambient $PM_{2.5}$ were measured at the official monitoring stations of the Dutch National Institute for Public Health and the Environment (RIVM) (https://data.rivm.nl/data/luchtmeetnet/).[24] As the residential addresses of the patients were not available, the "Stadhouderskade" station, which is the closest station to the Amsterdam UMC (distance 11 km), was considered the proxy for exposures in the area. The daily amount of total pollen in the Netherlands (pollen index) was obtained from the pollen monitoring station of the Leiden University Medical Center,[25] located approximately 35 km from the Amsterdam UMC. Pollen grains were collected at the roof-top level (approx. 20 m above ground level) and counted following the requirements of the European Aerobiology Society.[26] The total daily values of all pollen types (in pollen/m^3) were summed to give the pollen index used in this study. Daily exposures were collapsed to monthly and annual averages to enable more broad comparisons. We also assessed exposure to secondhand smoke, which we defined as children with frequent exposure to smokers (either their parents or anyone mostly living with them).

2.5 | Analysis

Statistical analysis was conducted using IBM SPSS Statistics for Windows version 28.0.1.1 (15) (SPSS). Because of the small study population, only descriptive analyses were performed. Subgroups, based on period of time/years, were described by means with standard deviation (for variables with a normal distribution) or median with 25th–75th percentiles (for variables not normally distributed) or by frequency with percentages for categorical variables. Moreover, in post-hoc analysis, the time periods between August and November 2021 and September and November 2022 were examined (as "peak" subgroups). Spearman correlation was employed to evaluate the relationship between admission numbers and $PM_{2.5}$ as well as pollen concentrations. Graphical representations of the collected data were generated using R version 4.2.2.[27]

3 | RESULTS

3.1 | Description of patient groups per year

Between January 2018 and December 2022, 228 children were admitted to the PICU of the Amsterdam UMC for SAE. In the prepandemic years (i.e., 2018 and 2019), admissions tended to peak in April, however, this was not observed for the pandemic years of 2020 or 2021 (Figure 1A). Instead, we observed a peak in admission in the months of September, October, and November of 2021. However, for 2022, which was partly a pandemic year, a peak, similar to that for prepandemic years, was observed in April. However, the highest peak for 2022 was observed in the fall, which was quite similar to the 2021 peak (Figure 1A).

In the study population, 90 (39.5%) were girls and the mean (SD) age of the participants was 7.7 (4.0) years (Table 1). The majority of the patients were school aged (81.1%). This percentage was higher in the pandemic years (2020 and 2021) (87.6%) than in prepandemic years (2018 and 2019) (78.0%), as well as 2022 as a postpandemic year (74.1%) ($p = 0.08$). However, 2022 had the highest mean age (8.4 years). In 2021, the gender of patients was more equally distributed (44.3% girls), while in 2018 the patients were predominantly boys (75%).

Results demonstrated that 27.2% of our study population was exposed to tobacco smoke, with the lowest percentage of exposure in 2022 (15.5%). While there were no missing data for age and sex, the percentage of missing data varied for the other variables. Other than secondhand smoke exposure (missing for 28.5% of the total population), the percentage of missing data for the remaining variables did not exceed 7%.

A clinical diagnosis of a viral infection was found in 67.1% of the patients (Table 1). This percentage was the highest in the year 2018 (87.5%), followed by 2021 (70.5%), 2020 (69.4%), and 2022 (60.3%). The year 2020 had the highest percentage of patients for whom a viral test was performed (83.3%), followed by 2022 (72.4%), 2021 (68.9%), 2019 (43.9%) and 2018 (37.5%).

3.2 | PICU admission numbers in total and for SAE

When comparing the trend of monthly PICU admission numbers for asthma exacerbation to the total PICU admission numbers of 2018–2022 in the Amsterdam UMC, it was observed that the peak of admissions for SAE in the fall of 2021 did not correspond to an increased overall admission rate at the PICU (Supporting Information: Figure S1). The ratio of PICU admissions due to an asthma

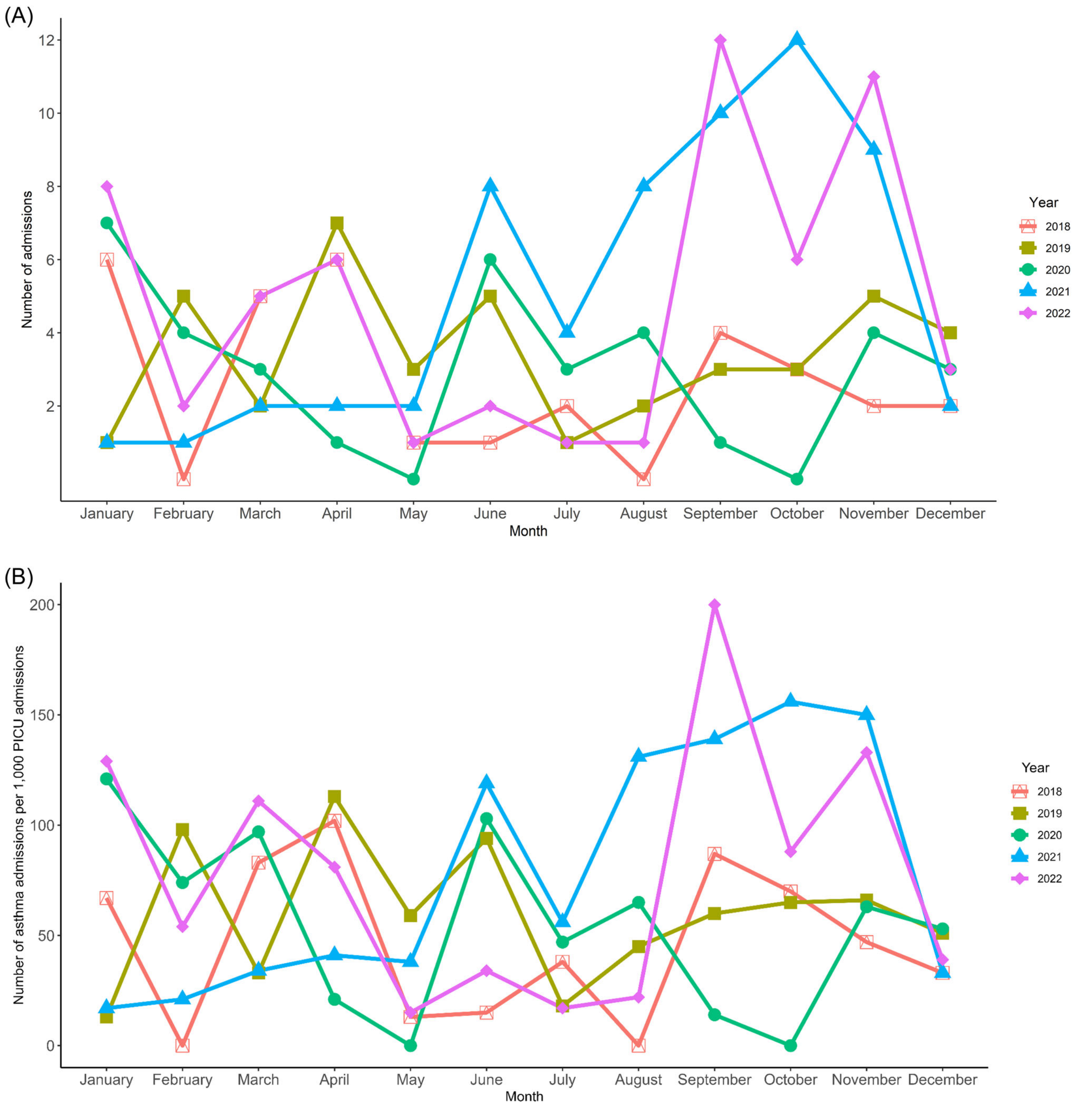

FIGURE 1 (A) The number of PICU admissions for severe asthma exacerbations in the Amsterdam UMC per month in 2018–2022. (B) The number of PICU admissions for severe asthma exacerbations per 1000 total PICU admissions in the Amsterdam UMC per month in 2018–2022. PICU, pediatric intensive care unit; UMC, University Medical Center.

exacerbation relative to the total number of PICU admissions for the August to November peak (13% in August, 14% in September, 16% in October, and 15% in November) was higher than that typically observed, including the peak month of April in the prepandemic years (10% in 2018 and 11% in 2019). This ratio was even higher in September 2022 (20%) (Figure 1B). Moreover, the percentage of annual PICU admissions due to asthma exacerbation was highest in 2021 and 2022 with 8%, followed by 2019 with 6% and 2020, and 2018 both with 5% of the total PICU admissions (Table 2).

3.3 | Effects of lockdown measures and environmental factors on admission rates

Figure 2A illustrates the relationship between lockdown measures (a complete working from home obligation and/or school closures) during the pandemic and admission numbers. In this graph, a relationship is observed between the application of lockdown measures and a decrease in the admission numbers of children with SAE. Specifically, for the three time periods during

TABLE 1 Patient characteristics, including environmental triggers.

Time of admission	Year 2018	Year 2019	Year 2020	Year 2021	Peak 2021[f]	Year 2022	Peak 2022[g]	Total 2018–2022
Number of admissions	32	41	36	61	39	58	29	228
Girls	8 (25%)	16 (39%)	14 (38.9%)	27 (44.3%)	19 (48.7%)	25 (43.1%)	18 (62.1%)	90 (39.5%)
School age participants®	25 (78.1%)	32 (78%)	31 (86.1%)	54 (88.5%)	34 (87.2%)	43 (74.%)	22 (75.9%)	185 (81.1%)
Age in years, mean ± SD	7.0 ± 3.6	7.1 ± 3.7	7.9 ± 3.6	7.6 ± 3.7	7.1 ± 3.6	8.4 ± 4.6	8.5 ± 4.7	7.7 ± 4.0
Divorced parents	12 (37.5%)	12 (29.3%)	8 (22.2%)	17 (27.9%)	12 (30.8%)	8 (13.8%)	5 (17.2%)	57 (25.2%)
Living with a single parent	8 (25%)	8 (19.5%)	1 (2.8%)	8 (13.1%)	4 (10.3%)	4 (6.9%)	0	29 (12.7%)
Tobacco smoke exposure (TSE)[a]	12 (37.5%)	14 (34.1%)	12 (33.3%)	15 (24.6.%)	8 (20.5%)	9 (15.5%)	6 (20.7%)	62 (27.2%)
Ambient $PM_{2.5}$[b] $_{(\mu g\ per\ cubic\ meter\ of\ air)}$, median (25th–75th percentiles)	10.4 (6.5–17.5)	7.4 (4.4–12.63)	7.6 (4.7–11.7)	9.5 (6.4–13.8)	9.9 (6.9–14)	8.6 (5.8–12.8)	7.2 (4.7–11.0)	8.6 (5.5–13.5)
Pollen$_{(grains\ per\ cubic\ meter\ of\ air)}$, median (25th–75th percentiles)	7 (1–28)	14.5 (2–60.7)	7 (1–22)	4 (1–25.7)	1 (1–8.5)	8 (2–35)	3 (2–6)	8 (1–32)
Clinical diagnosis of viral infection[c]	28 (87.5%)	22 (53.7%)	25 (69.4%)	43 (70.5%)	29 (74.4%)	35 (60.3%)	19 (65.5%)	153 (67.1%)
Performing virology laboratory tests[d]	12 (37.5%)	18 (43.9%)	30 (83.3%)	42 (68.9%)	24 (61.5%)	42 (72.4%)	23 (79.3%)	144 (63.2%)
Allergy history	18 (56.3%)	19 (46.3%)	19 (52.8%)	32 (52.5%)	19 (48.7%)	30 (51.7%)	14 (48.3%)	121 (53.1%)
Previously diagnosed asthma[e]	19 (59.4%)	21 (51.2%)	15 (41.7%)	22 (36.1%)	13 (33.3%)	22 (37.9%)	13 (44.8%)	99 (43.4%)

Note: ®School age participants; participants aged ≥4 years old.

Abbreviations: $PM_{2.5}$, fine particulate matter; URTI, upper respiratory tract infection.

[a]Missing for 28.5% of the total population.

[b]Concentration of fine particles or particulate matter ($PM_{2.5}$).

[c]As per physician diagnosis.

[d]There were two types of virology test kits used in the study period; a small one (only checks influenza virus type A and B, coronavirus, rhinovirus), and the complete kit (checking 12 respiratory viruses including respiratory syncytial virus, influenza virus type A and B, human metapneumovirus, parainfluenza virus types 1, 2, 3, and 4, adenoviruses, coronaviruses, rhinoviruses, and human bocavirus). During the pandemic years, the small kit was mostly used.

[e]Only children above 4 years old can be diagnosed with asthma, as the official diagnostic tool is a pulmonary function test, this cannot be properly performed in younger children.

[f]Peak 2021 was the time period from the beginning of August 2021 until the end of November 2021, during which the highest admission rates were observed.

[g]Peak 2022 was the time period from the beginning of September 2022 until the end of November 2022, during which the highest admission rates were observed.

TABLE 2 The total number of PICU admission, SAE incidence in 1000, and ratio of PICU admission due to SAE per each month.

	2018				2019				2020				2021				2022			
	SAE	Total	Ratio	Incidence ×1000[a]	SAE	Total	Ratio	Incidence ×1000	SAE	Total	Ratio	Incidence ×1000	SAE	Total	Ratio	Incidence ×1000	SAE	Total	Ratio	Incidence ×1000
January	6	90	0.07	67	1	78	0.01	13	7	58	0.12	121	1	58	0.02	17	8	62	0.13	129
February	0	48	0.00	0	5	51	0.10	98	4	54	0.07	74	1	48	0.02	21	2	37	0.05	54
March	5	60	0.08	83	2	61	0.03	33	3	31	0.10	97	2	58	0.03	34	5	45	0.11	111
April	6	59	0.10	102	7	62	0.11	113	1	48	0.02	21	2	49	0.04	41	6	74	0.08	81
May	1	75	0.01	13	3	51	0.06	59	0	47	0.00	0	2	53	0.04	38	1	66	0.01	15
June	1	65	0.02	15	5	53	0.09	94	6	58	0.10	103	8	67	0.12	119	2	58	0.03	34
July	2	53	0.04	38	1	57	0.02	18	3	64	0.05	47	4	71	0.06	56	1	60	0.02	17
August	0	38	0.00	0	2	44	0.05	45	4	62	0.06	65	8	61	0.13	131	1	46	0.02	22
September	4	46	0.09	87	3	50	0.06	60	1	72	0.01	14	10	72	0.14	139	12	60	0.20	200
October	3	43	0.07	70	3	46	0.07	65	0	52	0.00	0	12	77	0.16	156	6	68	0.09	88
November	2	43	0.05	47	5	76	0.07	66	4	63	0.06	63	9	60	0.15	150	11	83	0.13	133
December	2	61	0.03	33	4	79	0.05	51	3	57	0.05	53	2	61	0.03	33	3	76	0.04	39
Total annual	32	681	0.05	47	41	708	0.06	58	36	666	0.05	54	61	735	0.08	83	58	735	0.08	79

Abbreviations: PICU, pediatric intensive care unit; SAE, severe asthma exacerbation.

[a]Number of the SAE admissions per 1000 total PICU admissions.

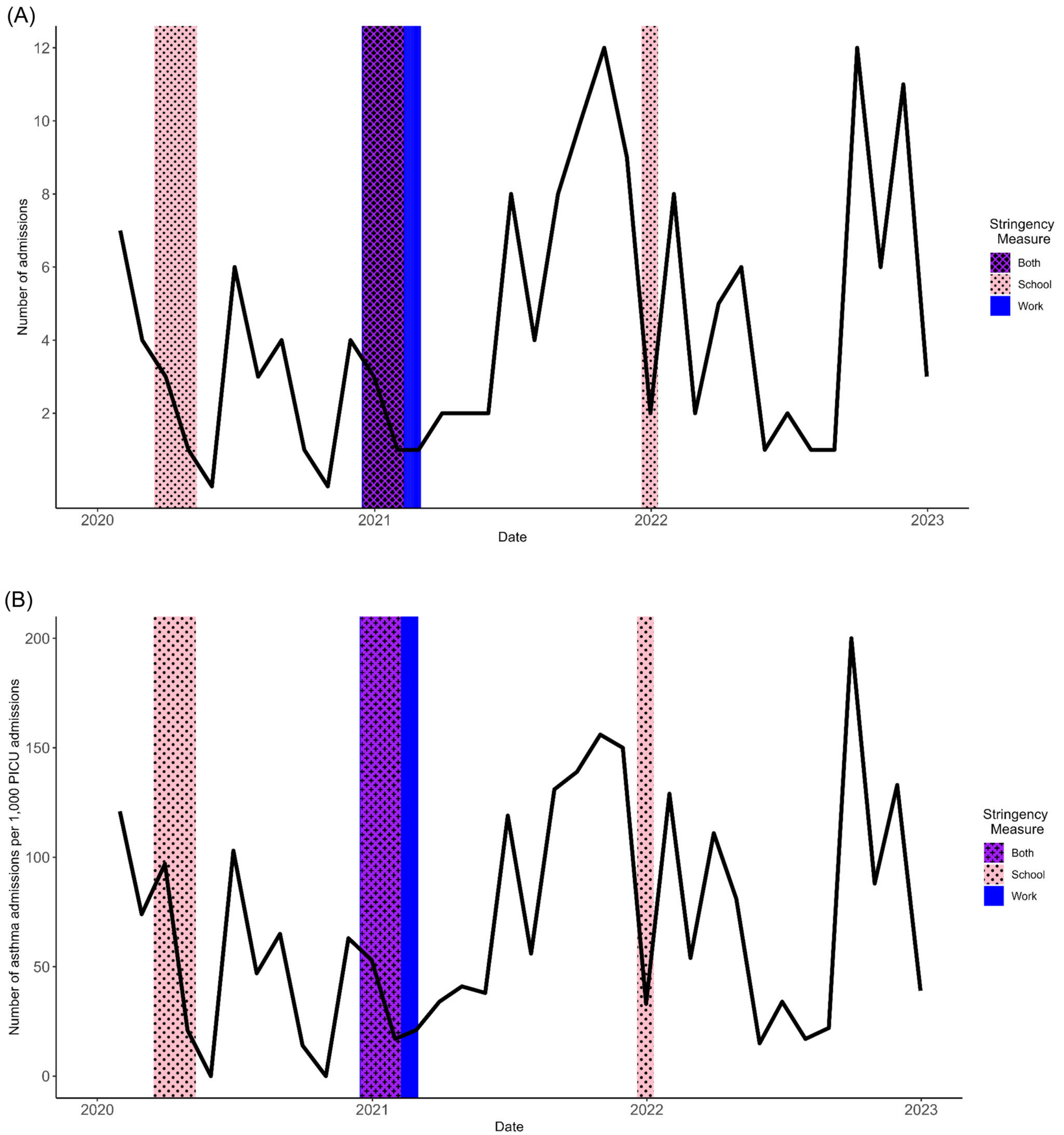

FIGURE 2 (A) The number of PICU admissions (per month) in 2020, 2021, and 2022 combined with the lockdown periods. (B) The number of PICU admissions per 1000 total PICU admissions (per month) in 2020, 2021, and 2022 combined with the lockdown periods. PICU, pediatric intensive care unit.

which schools were completely closed, a reduced number of PICU admissions was observed. This indicates that the stricter lockdown measures related to a decrease in admission numbers for SAE at the PICU (Figure 2A,B). After restrictions were lifted, the rate of admissions tended to increase. There was a statistically significant moderate negative correlation between the stringency score and both number of SAE admissions ($rs = -0.647$ with p value < 0.001) and SAE admission rate ($rs = -0.683$ with p value < 0.001). Finally, we found no correlations between the monthly PICU admission numbers and pollen or $PM_{2.5}$ concentrations ($rs = -0.06$ for pollen and $rs = 0.19$ for $PM_{2.5}$).

Most children (67.1%) showed signs of an airway infection as trigger for their SAE and a viral test was performed in 63.2% of children (Table 1). Infection through an unknown viral factor was the most frequent finding in both the total population (35.5%) and in each of the time-based subgroups. The Year 2018 had the highest percentage (53.1%) for unknown virology results, while 2019 (26.8%) had the lowest. After unknown viral species (cases with a clinical picture of viral infection whose virology was negative or not done at all), rhinovirus (22.4%) was the most common viral infection, followed by bocavirus (3.9%), and enterovirus (3.5%, Supporting Information: Table S1).

4 | DISCUSSION

The influence of the COVID-19 pandemic on pediatric asthma exacerbation leading to PICU admission remains an issue to be understood. This study assessed the pattern of admissions for SAE to the PICU before, during, and after COVID restrictions to see whether it could be attributed to a number of factors, such as environmental triggers or the COVID-19 restriction rules. Our findings demonstrated that the incidence of SAE in the PICU of Amsterdam UMC, the Netherlands was low in the first year of the COVID-19 pandemic with an increase in admissions observed after easing restrictions in 2020 and 2021, which is supported by our correlation analysis results. We observed a high peak incidence after all governmental restrictions had been lifted in the fall of 2021. However, in the Year 2022, more peaks were detected, with a pattern reflecting a combination of the prepandemic and pandemic years. This suggests that in 2022 the pattern had mostly normalized again, while the mechanisms causing the peak in fall 2021 still influenced that.

Other studies have also reported a reduction in asthma exacerbations during the COVID-19 pandemic. A similar study conducted in Italy reported a decrease in the incidence of pediatric asthma exacerbations visiting the ED during the first and second waves of the COVID-19 pandemic in 2020. They attributed this to the closing of daycare and schools, less air pollution due to reduced travel and fear of visiting hospitals during the peak of the pandemic that in turn led to avoidance or delays in seeking medical care. They also attributed this observation to reduced exposure to viruses, although they were unable to quantify this in their evaluation.[12] Also a narrative review stated that COVID-19 pandemic led to a decrease in hospital admissions for pediatric asthma exacerbation due to improved hygienic standards reducing the risk of infection-related asthma attacks. Lockdown measures and school closures were also found to decrease asthma symptoms by reducing exposure to environmental allergens.[28]

We found that during the peak period in 2021, respiratory viruses were the most frequent trigger for SAE. It is well known that viral respiratory tract infections are a major trigger of SAE, which typically induce a chemokine-mediated neutrophil pattern.[5] Due to the COVID-19-related restrictions, including increased hygienic measures, wearing face masks and social distancing, the spread of infectious agents was reduced and thereby asthma attacks diminished.[15,16] We hypothesize that when the restrictions were lifted, children were exposed to these viruses again, explaining the high rate in the peak of 2021. This was exactly the same as Chelabi et al.'s hypothesis about the increase in asthma exacerbation rates in Quebec following the general easing of public health COVID-19 regulations. Also, during their peak period, positive tests for common respiratory viruses increased, suggesting weak public health regulations contributed to the spread of these viruses, subsequently increasing asthma exacerbations.[29]

Another reason for the rise in the number of acute asthma patients that were admitted to the PICU in late 2021 can be related to the "Hygiene Theory," which was introduced by Strachan in 1989. This theory states that the trend of allergic diseases can be related to infectious diseases and an unhygienic contact in early childhood could prevent allergic disorders.[30] An extension of hygiene theory is "biodiversity hypothesis," which states that shifting to the urban lifestyle causes microbial deprivation in human, which in turn leads to immune dysfunction and developing inflammatory conditions such as asthma.[31]

In another study conducted by Braun-Fahrländer et al., it was found that environmental exposure to microbial products decreased the likelihood of developing diseases such as hay fever, atopic sensitization, atopic asthma, and atopic wheeze in children. It is unknown what mechanism(s) may prevent the atopic immune responses after exposure to microbial products.[32] Furthermore, the reduction of infectious contacts because of hygiene measures during the pandemic may have decreased children's immune training, which in turn makes them more susceptible to infection.[33] Immunity debt, implies the lack of protective immunity caused by prolonged low exposure to a specific pathogen. This makes children susceptible to viral disease, which is particularly of concern for viruses whose transient immunity is acquired through virus contact. For example, respiratory syncytial virus maternal antibodies soon diminish and without seasonal exposure, immunity declines and susceptibility to subsequent, and possibly more severe, infection increases.[34] There is also evidence that induction of trained immunity leads to enhancing the potency of the immune system against viral infections.[35] Therefore, as a supplemental hypothesis to the hygiene theory, we hypothesize that staying at home during the lockdown periods of the pandemic may have reduced exposure to a wider range of infectious agents, resulting in a more vulnerable immune system against viral infections as well as an increased risk for exacerbation in asthmatic diseases, which may have contributed to the increase in SAE admissions observed in late 2021. However, as this observation is based on a single hospital, a wider perspective, including an evaluation of the immunological aspect of asthma exacerbations during the COVID pandemic is required. Furthermore, if this hypothesis is supported elsewhere, any increased risk of postlockdown infections will need to be evaluated against reduced COVID-19 infections (and mortality) provided as a result of lockdown measures.

The COVID-19 pandemic also led to an increased rate of viral testing at the PICU, as the updated infection control measures required an active SARS-CoV-2 infection to be confirmed or ruled out by a rapid test before admission. However, more extensive viral testing for respiratory viruses was limited because of decreased laboratory capacity during the pandemic. Thus, while there is an increased frequency of performing viral tests in the pandemic years, it was usually unknown what viral agent had caused the respiratory symptoms in our cases. Among the detected viral agents, rhinovirus was the most commonly detected virus. This finding was the same as the results that were found in a similar study in Hong Kong, from the beginning of 2015 to the end of 2020.[36]

In a study conducted by Ulrich et al. in Ohio, USA, a drastic decline in the number of ED visits due to asthma exacerbations in 2020 was reported. This decline was proportionately more than the decrease observed in the number of total ED visits. The authors attributed better air quality as a result of staying home as the reason for this decrease in asthma exacerbation rate.[17] In another study by Papadopoulos et al., (February 2021), it was found that the rate of asthma attacks in children decreased during the pandemic in comparison with the Year 2019. They also hypothesized that this might be the effect of decreased exposure to asthma triggers and increased treatment adherence.[18] During lockdown, ambient $PM_{2.5}$ concentrations were reported to be lower, although this was variable in different areas, depending on factors such as local meteorological conditions and intensity of lockdown rules. In some areas, up to 159% reduction in the $PM_{2.5}$ concentration was reported during the lockdown in comparison to nonlockdown months.[37] While there is some prior evidence supporting the association between pollen, $PM_{2.5}$ concentration and asthma exacerbation,[23,38] we found no correlation between these two environmental factors and admission numbers. This might be explained by the more prominent role of viral infection as a trigger for an asthma exacerbation rather than other triggers such as air pollution and pollen. Furthermore, the relationship between air pollution and diseases during COVID-19 pandemic is complex as the reduced traveling during lockdown also reduced air pollution. However, as the findings of the current paper were based on a single monitoring site, a wider sampling would be required before drawing firmer conclusions.

A strength of this study is that it utilized a well-defined population with detailed observations and personal histories covering a wide range of variables at very clearly defined time points. There are also some limitations to this study being restricted to a single population and hospital it is limited in how externally applicable its findings are in the wider context. Moreover, as we did not have information on the residential addresses of the participants, we used data from one air quality monitoring station as a proxy for personal exposure to $PM_{2.5}$. A further limitation is that we did not have the confirmed virology tests for all participants, so that we could not determine the exact viral agents for all patients. Thus, viral infections were clinically diagnosed. Also, given the retrospective nature of this study, we were not able to obtain more detailed information on secondhand smoke exposure, for example, whether the parents of the children smoke on a daily basis or not.

Furthermore, as routine asthma diagnostic tests such as spirometry are not performed for preschool children due to unreliable results,[39] this group of participants has an uncertain diagnosis status. While all study participants between 2 and 5 years old were admitted and treated under the diagnosis of Status Asthmaticus or severe acute asthma it is unknown whether they will develop chronic asthma. Despite this limitation, their phenotype (eosinophils, sensitization to aeroallergens, atopic comorbidities, and positive family history of atopic disease) and/or response to treatment are often more in line with reversible bronchoconstriction/asthma, hence justifying their inclusion in the current study. On the other hand, as bronchiolitis is extremely common in children with wheezing below the age of 2 years and the therapeutic response to asthma treatment with albuterol and steroids is usually lacking, this group therefore does not sufficiently resemble asthmatic children to make them eligible for inclusion.

In conclusion, the total number of PICU admissions of children with SAE in the Amsterdam UMC was decreased in the first year of the COVID-19 pandemic, and increased considerable for SAE in the fall of 2021 and 2022, when COVID-19 restrictions were no longer present, compared with previous years. We hypothesize that an increase in clinically diagnosed viral infections due to viruses other than SARS-CoV-2 after lockdown periods was the reason for the altered incidence of SAE at the PICU in late 2021. Therefore, in future pandemic preparedness planning, it is important to consider changes in other infectious diseases in a postrestriction period. However, as this is a single-site study, these findings need to be studied further and replicated in a wider setting to better understand these observations.

AUTHOR CONTRIBUTIONS

AnkeH Maitlandvan der Zee was the principal investigator. All authors contributed to the study design. Somayeh Bazdar, George S. Downward, and Lizan D. Bloemsma contributed to statistical analysis. Berber Kapitein, Suzanne W. J. Terheggen-Lagro, and Niels W. Rutjes contributed to clinical analyses. Berber Kapitein contributed to patient recruitment. Sarah van den Berg, Somayeh Bazdar, and Letty A. De Weger contributed to data collection. Somayeh Bazdar prepared the initial manuscript draft with input from other authors, and all authors edited the manuscript. All authors approved the final version of the report.

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CONFLICT OF INTEREST STATEMENT

Prof. Dr. Anke-Hilse Maitland-van der Zee has received research grants outside the submitted work from GSK, Boehringer Ingelheim and Vertex, she is the PI of P4O2 (Precision Medicine for more Oxygen), a public-private partnership co-funded by Health~Holland involving many private partners that contribute in-cash and/or in-kind (Aparito, Boehringer Ingelheim, Breathomix, Clear, Danone Nutricia Research, Fluidda, MonitAir, Ncardia, Ortec Logiqcare, Philips, Quantib-U, RespiQ, Roche, Smartfish, SODAQ, Thirona, TopMD and Novartis), and she has served in advisory boards for AstraZeneca, GSK and Boehringer Ingelheim with money paid to her institution. Moreover, Dr. George Downward's, Y. van Wijck's and Dr. Lizan Bloemsma's conflicts of interest relate to the funding structure of P4O2 (public-private). The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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REFERENCES

1. Serebrisky D, Wiznia A. Pediatric asthma: a global epidemic. *Ann Glob Health*. 2019;85(1):6.
2. Zahran HS, Bailey CM, Damon SA, Garbe PL, Breysse PN. Vital signs: asthma in children - United States, 2001-2016. *MMWR Morb Mortal Wkly Rep*. 2018;67(5):149-155.
3. Andrenacci B, Ferrante G, Roberto G, et al. Challenges in uncontrolled asthma in pediatrics: important considerations for the clinician. *Expert Rev Clin Immunol*. 2022;18(8):807-821.
4. Beasley R, Braithwaite I, Semprini A, Kearns C, Weatherall M, Pavord ID. Optimal asthma control: time for a new target. *Am J Respir Crit Care Med*. 2020;201(12):1480-1487.
5. Wark PAB. Asthma exacerbations· 3: pathogenesis. *Thorax*. 2006;61(10):909-915.
6. Zhang X, Zhang L, Wang G, et al. Clinical phenotypes of patients hospitalized for an asthma exacerbation: prognostic implications. *J Allergy Clin Immunol Pract*. 2021;9(2):830-841.
7. van den Berg S, Hashimoto S, Golebski K, Vijverberg SJH, Kapitein B. Severe acute asthma at the pediatric intensive care unit: can we link the clinical phenotypes to immunological endotypes? *Expert Rev Respir Med*. 2022;16(1):25-34.
8. Menzies-Gow A, Busse WW, Castro M, Jackson DJ. Prevention and treatment of asthma exacerbations in adults. *J Allergy Clin Immunol Pract*. 2021;9(7):2578-2586.
9. Jartti T, Bønnelykke K, Elenius V, Feleszko W. Role of viruses in asthma. *Semin Immunopathol*. 2020;42(1):61-74.
10. Annesi-Maesano I, Maesano CN, Biagioni B, D'Amato G, Cecchi L. Call to action: air pollution, asthma, and allergy in the exposome era. *J Allergy Clin Immunol Pract*. 2021;148(1):70-72.
11. Subramanian A, Khatri SB. The exposome and asthma. *Clin Chest Med*. 2019;40(1):107-123.
12. Dondi A, Betti L, Carbone C, et al. Understanding the environmental factors related to the decrease in Pediatric Emergency Department referrals for acute asthma during the SARS-CoV-2 pandemic. *Pediatr Pulmonol*. 2022;57(1):66-74.
13. Oreskovic NM, Kinane TB, Aryee E, Kuhlthau KA, Perrin JM. The unexpected risks of COVID-19 on asthma control in children. *J Allergy Clin Immunol Pract*. 2020;8(8):2489-2491.
14. Koo MJ, Kwon R, Lee SW, et al. National trends in the prevalence of allergic diseases among Korean adolescents before and during COVID-19, 2009–2021: a serial analysis of the national representative study. *Allergy*. 2022;78:1665-1670.
15. Sayed S, Diwadkar AR, Dudley JW, et al. COVID-19 pandemic–related reductions in pediatric asthma exacerbations corresponded with an overall decrease in respiratory viral infections. *J Allergy Clin Immunol Pract*. 2022;10(1):91-99.
16. Liuzzo Scorpo M, Ferrante G, La Grutta S. An overview of asthma and COVID-19: protective factors against SARS-COV-2 in pediatric patients. *Front Pediatr*. 2021;9:661206.
17. Ulrich L, Macias C, George A, Bai S, Allen E. Unexpected decline in pediatric asthma morbidity during the coronavirus pandemic. *Pediatr Pulmonol*. 2021;56(7):1951-1956.
18. Papadopoulos NG, Mathioudakis AG, Custovic A, et al. Childhood asthma outcomes during the COVID-19 pandemic: findings from the PeARL multi-national cohort. *Allergy*. 2021;76(6):1765-1775.
19. Meissner HC. Viral bronchiolitis in children. *N Engl J Med*. 2016;374(1):62-72.
20. Boeschoten SA, Buysse CMP, Merkus PJFM, et al. Children with severe acute asthma admitted to Dutch PICUs: a changing landscape. *Pediatr Pulmonol*. 2018;53(7):857-865.
21. Hale T, Angrist N, Goldszmidt R, et al. A global panel database of pandemic policies (Oxford COVID-19 Government Response Tracker). *Nat Hum Behav*. 2021;5:529-538. doi:10.1038/s41562-021-01079-8
22. Martins NR, Carrilho da Graça G. Impact of PM2. 5 in indoor urban environments: a review. *Sustain Cities Soc*. 2018;42:259-275.
23. Fan J, Li S, Fan C, Bai Z, Yang K. The impact of PM2. 5 on asthma emergency department visits: a systematic review and meta-analysis. *Environ Sci Pollut Res*. 2016;23(1):843-850.
24. *Rijksinstituut voor Volksgezondheid en Milieu, "Luchtmeetnet dataset"*, data.rivm.nl. Accessed July 20, 2022. https://data.rivm.nl/data/luchtmeetnet.
25. de Weger LA, Bruffaerts N, Koenders MM, et al. Long-term pollen monitoring in the Benelux: evaluation of allergenic pollen levels and temporal variations of pollen seasons. *Front Allergy*. 2021;30:676176.
26. Galán C, Smith M, Thibaudon M, et al. Pollen monitoring: minimum requirements and reproducibility of analysis. *Aerobiologia*. 2014;30(4):385-395.
27. R Core Team. R: a language and environment for statistical computing. *R Foundation for Statistical Computing*. 2018. https://www.R-project.org/
28. Khojasteh-Kaffash S, Parhizkar Roudsari P, Ghaffari Jolfayi A, Samieefar N, Rezaei N. Pediatric asthma exacerbation and COVID-19 pandemic: impacts, challenges, and future considerations. *J Asthma*. 2023;1-11. https://doi.org/10.1080/02770903.2023.2251062
29. Chelabi K, Osmanlliu E, Gravel J, Drouin O, Tse SM. The effect of the COVID-19 pandemic on pediatric asthma-related emergency department visits and hospital admissions in Montréal, Quebec: a retrospective cohort study. *CMAJ Open*. 2023;11(1):E152-E159.
30. Strachan DP. Hay fever, hygiene, and household size. *BMJ*. 1989;299(6710):1259-1260.
31. Haahtela T, Holgate S, Pawankar R, et al. The biodiversity hypothesis and allergic disease: world allergy organization position statement. *World Allergy Organ J*. 2013;6:3.
32. Braun-Fahrländer C, Riedler J, Herz U, et al. Environmental exposure to endotoxin and its relation to asthma in school-age children. *N Engl J Med*. 2002;347(12):869-877.
33. Cohen R, Ashman M, Taha MK, et al. Pediatric Infectious Disease Group (GPIP) position paper on the immune debt of the COVID-19

pandemic in childhood, how can we fill the immunity gap? *Infect Dis Now*. 2021;51(5):418-423.
34. Hatter L, Eathorne A, Hills T, Bruce P, Beasley R. Respiratory syncytial virus: paying the immunity debt with interest. *Lancet Child Adolesc Health*. 2021;5(12):44.
35. Netea MG, Giamarellos-Bourboulis EJ, Domínguez-Andrés J, et al. Trained immunity: a tool for reducing susceptibility to and the severity of SARS-CoV-2 infection. *Cell*. 2020;181(5):969-977.
36. Wong KL, Wong WHS, Yau YS, LEE SL, Chiu SSS. Asthma admission among children in Hong Kong during the first year of COVID-19 pandemic. *Pediatr Pulmonol*. 2022;57:3104-3110.
37. Chauhan A, Singh RP. Decline in PM2. 5 concentrations over major cities around the world associated with COVID-19. *Environ Res*. 2020;187:109634.
38. De Roos AJ, Kenyon CC, Zhao Y, et al. Ambient daily pollen levels in association with asthma exacerbation among children in Philadelphia, Pennsylvania. *Environ Int*. 2020;145:106138.
39. Crenesse D, Berlioz M, Bourrier T, Albertini M. Spirometry in children aged 3 to 5 years: reliability of forced expiratory maneuvers. *Pediatr Pulmonol*. 2001;32(1):56-61.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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