

Children with Asthma Exposed to COVID-19 Show a Decrease in Severity from Baseline: A Systematic Review from March 2020 to September 2022

Juel Chowdhury

Physician, Health Protection & Communicable Diseases Division
Ministry of Public Health, Qatar
ORCID: 0000-0003-4329-2392

Rejoice Puthuchira Ravi

Epidemiologist, Health Protection & Communicable Diseases Division
Ministry of Public Health, Qatar
ORCID: 0000-0001-7214-6488

Jesha Mohammed Ali Mundodan

Public Health Specialist, Vaccination
Health Protection & Communicable Diseases Division
Ministry of Public Health, Qatar

Hayat Mohamedbek

Supervisor, Vaccination
Health Protection & Communicable Diseases Division
Ministry of Public Health, Qatar

Soha Shawqi Albayat

Head of Vaccinations, Health Protection &
Communicable Diseases Division, Ministry of Public Health, Qatar

ABSTRACT

Introduction: During the COVID-19 pandemic, children have been affected by SARS-CoV-2 infection, primarily affecting the respiratory system. Children with chronic respiratory diseases such as asthma, emphysema, and chronic bronchitis can experience an exacerbation of the preexisting conditions. The study's primary aim was to identify the severity of asthma in COVID-19-exposed children aged 4-12 years. **Methods:** We extracted the data from the PubMed database between March 2020 and September 2022. During the COVID-19 pandemic, PubMed-published articles involving children living with asthma aged 4-12 years were identified. The study included children who had tested positive for SARS-CoV-2 and excluded children with any other comorbidities. **Results:** We identified 169 PubMed-published articles and filtered 28 articles. Seven articles met the inclusion criteria and were included in the study. The children with asthma hospitalized owing to COVID-19 worldwide was 1% to 2.7%. Incidence was 12.8 times less frequent in children than in adults. Increased expression of the angiotensin-converting

enzyme-2 gene in the bronchial epithelium of patients with type 2-low or T1-high asthma tended to have higher known risk factors for COVID-19. Among school-age children (N=277,285), 1.2% were hospitalized, 0.1% had intensive care unit admissions, and <0.1% died. Of those patients (hospitalized, ICU admissions, and those who died from COVID-19), all had at least one underlying medical condition, and 55% had chronic lung disease, including asthma. Conclusion: Most children with recurrent wheezing and asthma were well-controlled by their underlying asthma and did not require significant changes to their maintenance treatments. It concludes that children who tested positive for SARS-CoV-2 had fewer pediatric hospital admissions and attendance at urgent care settings. The reduction in asthma morbidities is due to improved adherence and decreased exposure to allergens and viral infections in children.

Keywords: Asthma, caregivers, children, health center, SARS-CoV-2.

INTRODUCTION

Asthma is a chronic lung disease requiring long-term medical monitoring, and individuals with asthma are particularly vulnerable to the changes resulting from COVID-19 infection [1]. Patients with asthma are highly susceptible to increased severity of SARS-CoV-2 infection due to their impaired immune response and the likelihood of respiratory exacerbation when infected with respiratory viruses [4]. The World Health Organization (WHO) and the Centers for Disease Control and Prevention CDC (Centers for Disease Control) have issued health alerts and prevention guidelines for people at increased risk of severe health outcomes and death due to COVID-19 [3,4]. Chronically ill patients are particularly vulnerable to severe complications of this disease, so they need special attention to help prevent increased morbidity and mortality [5]. Patients with asthma are hypothesized to be highly susceptible to SARS-CoV-2 infection due to their impaired immune response. The likelihood of respiratory exacerbation increases when infected with respiratory viruses. However, only limited evidence supports this theoretical risk [6]. It was reported that the risk of severe illness and death from COVID-19 was increased for people with severe asthma and those prescribed high-dose inhaled corticosteroids (ICS) [7-10]. As the COVID-19 virus spreads so easily and quickly, pediatric infections are inevitable. A reported case was encountered in January 2020 in a 10-year-old boy who contracted the virus in Wuhan [11]. Since then, a multitude of pediatric cases has been reported globally. To date, the data reveal that the course of the disease is milder in children than in adults.

Asthma patients may have experienced decreased access to healthcare due to restrictions on public movements during lockdowns and the diversion of healthcare resources to the care of patients affected by COVID-19 [12]. An online survey of caregivers of children with asthma from 27 countries and five continents revealed that during the COVID-19 pandemic, 47% of asthmatic children had limited access to healthcare services, and 20% experienced better disease control [13]. It was also reported that medication adherence among patients with asthma increased during this pandemic [13,14]. Furthermore, lockdown restrictions, school cancellations, and social distancing have significantly impacted movement and play behaviors, limiting children's physical activity (PA) and reducing exposure to environmental triggers [15,16]. These changes in health-seeking behaviors, medication management, and the environment may potentially impact asthma control [16].

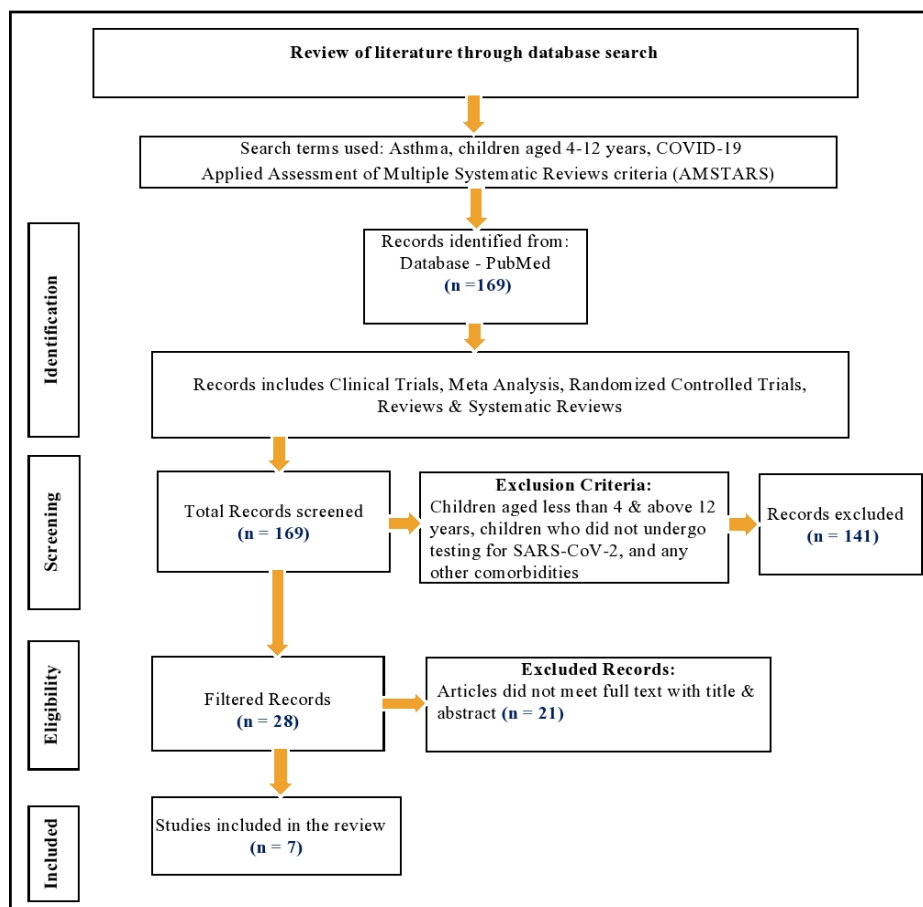
METHODS

Study design and setting

A systematic review of the literature was performed per the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to identify the severity of asthma in COVID-19-exposed children aged 4-12 years. In the first phase, we searched and identified 169 PubMed articles, including Clinical Trials, Meta-Analysis, Randomized Controlled Trials, Reviews, and Systematic Reviews. An analysis of PubMed data was performed between March 2020 and September 2022. According to PubMed, 42 articles were published in 2020, 72 in 2021, and 55 as of September 2022, a total of 169. (Figure 1.1: PRISMA flow diagram of the study selection process). Secondly, we filtered 28 articles out of 169 PubMed articles. In this phase, we applied inclusion criteria for filtering the data. Inclusion criteria were children living with asthma aged 4-12 years, children who underwent testing for SARS-CoV-2, and positive test results were included and excluded children with any other comorbidities in the study. Out of 28 full-text articles, seven met the inclusion criteria and were included in the study.

Flow diagram

Figure 1.1: PRISMA Flow diagram of the study selection process



A combination of search terms related to COVID-19 infection and asthma in children aged 4 to 12 years was used. The quality of the review was assessed using the modified Assessment of Multiple Systematic Reviews (AMSTARS) criteria. Enrollment criteria included children in the age group of 4-12 years who had experienced asthma and children who had undergone testing

for SARS-CoV-2 with positive test result. The study excluded children with cardiovascular disease, diabetes, cancer, immunosuppression, or obesity before they were infected with COVID-19. The study included both hospitalized and community settings. Asthma children were categorized according to their Clinical Asthma Scores (CAS): mild (0-4), moderate (5-8), and severe (9-12) [17,18].

Study selection and inclusion criteria

Study types considered were Clinical Trials, Meta-Analysis, Randomized Controlled Trials, Reviews, and Systematic Reviews that reported on COVID-19 among children with asthma. We analyzed studies that reported COVID-19 among children with asthma. In the analysis, we excluded studies that incorporated empirical data that was not original, asthma exacerbations in children, COVID-19 comorbidities such as diabetes, cancer, immunosuppression, obesity, and those that had not been confirmed as COVID-19 positive. We included studies that describe or apply severity scores to measure asthma conditions in patients between the ages of 4 and 12. To assess variation in severity, each parameter was assigned a numerical value. Studies that assessed dyspnea with other conditions, such as bronchiolitis and rhinitis, and articles that used a predictive score (looked at the need for hospitalization) were excluded. The title, the abstract, and the full-text screening process were systematically followed for the final selection of the study. Duplicate records were excluded, and misunderstandings regarding the inclusion of this study were resolved through discussions with colleagues in the same department.

Data extraction

A systematic review was conducted based on the required data, and inconsistencies were rectified. An analysis of data was conducted concerning the date of publication, the type of study, the age group, the gender, and children with asthma of mild or moderate severity (0-4), moderate or severe (9-12), as well as children with asthma exacerbations. Data has been extracted for COVID-19-related clinical symptoms and other comorbidities. The severity of COVID-19 disease was classified as mild (i.e., non-pneumonia and mild pneumonia), severe (i.e., dyspnea, respiratory frequency ≥ 30 /min, blood oxygen saturation $\leq 93\%$, and/or lung infiltrates $>50\%$ within 24-48 h), and critical (i.e., respiratory failure, septic shock, and/or multiple organ dysfunction or failure) [19]. ICU admission and recovery status (cured, died, still in hospital) were also extracted.

RESULTS

COVID-19 and Prevalence, Incidence, and Risk of Asthma among children

The number of children with asthma hospitalized owing to COVID-19 worldwide is low, with incidence reported from 1% to 2.7% [20]. An online questionnaire sent to 91 pediatric practitioners in 27 countries attempted to estimate the incidence of clinically relevant COVID-19 in pediatric patients with asthma. They noted that incidence was 12.8 times less frequent in children than in adults [13]. A retrospective study of a large cohort showed that patients with asthma have a lower susceptibility to COVID-19 in pediatric and adult patients. The study did not find any difference in the hospitalization rate in patients with COVID-19 with or without asthma [21]. A nationwide survey in Japan examining asthma during the COVID-19 outbreak found decreased asthma admissions in 2020 compared with previous years for children and adults [22].

Similarly, in Spain, 212 children with allergic asthma reported no significant difference in asthma severity between patients with and without COVID-19 [23]. The early data from Wuhan regarding hospitalized pediatric patients and those with severe COVID-19 do not list asthma as a risk factor [24,25]. Papadopoulos NG et al, conducted a study entitled 'childhood asthma outcomes during the COVID-19 pandemic', which included 1,054 children with asthma and 505 control subjects from 25 pediatric departments in 15 countries globally. A higher proportion of males (62.8%) in the asthma group compared to the controls is consistent with epidemiological characteristics of the disease in this age group [26]. A total of 297 parents/caregivers participated, and their response rate was 79%. Three age groups were defined: 4-6, 7-12, and 13-17 years, with 50% aged 7-12. 104 (35%) of the majority were diagnosed with asthma between 6 and 12 years [27]. In another study conducted in Turkey among children with asthma during the COVID-19 pandemic, 39 (65.0%) out of 60 patients with asthma were male [28]. Daoud Pérez Zet.al; conducted a study in Spain on the impact of the COVID-19 lockdown on children's treatment and asthma control. Data from 475 child participants were analyzed from 18 May to 15 June 2020. The median age was 5.6 years, and 60.6% were males [29].

Effect of the COVID-19 pandemic on adherence and asthma control

Numerous studies from around the world, including China, Brazil, Italy, Switzerland, and the United States, reveal that asthma is not associated with increased mortality risk in adult patients with COVID-19 [20]. The Morbidity and Mortality Weekly Report from October 2020 that evaluated COVID-19 trends among school-age children (N= 2,77285) noted that 1.2% were hospitalized, 0.1% had intensive care unit (ICU) admissions, and less than 0.1% died. Amongst them (hospitalized, ICU admissions, and deaths due to COVID-19), each had at least one underlying medical condition, and 55% of the underlying conditions were accounted for by chronic lung disease, including asthma and emphysema [30].

Metbulut AP. et.al conducted a study among asthmatic children with SARS-CoV-2 infection in Turkey; cough, shortness of breath, vomiting, and diarrhea were significantly more common in the asthma group than in the control group. Hospitalization was significantly higher in the asthma group, and hospitalization duration was significantly longer in the control group. There were no statistically significant differences between the asthmatic and control groups regarding the need for oxygen treatment and laboratory findings [31]. Among respondents, 181(61%) (95% CI (Confidence Interval) 55.1% to 66.5%) reported improved compliance with medications during the lockdown, with most respondents, 194(65%) (95% CI 59.6% to 70.7%) reporting ongoing use of preventers at prescribed doses. More than 75% of the children used their bronchodilator <2 days/week, 227 (76%) (95% CI 71.2% to 81.1%). Only 23(8%) patients required a reliever inhaler ≤5 days/week. Around one-third of 103 (35%) parents or caregivers reported reduced controller dosing during the lockdown. The majority, 81(79%), indicated this was due to their children's asthma stability, and 22% of parents decreased the dose of inhalers because of fear of drug shortages. A small number mentioned their inability to reach the hospital [27].

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 than the preceding year. 66% of asthmatic children had improved asthma control, while in 33%, the improvement exceeded the minimal clinically relevant difference. Pre-bronchodilatation forced expiratory volume in 1 second (FEV1), and

the peak expiratory flow rate was improved during the pandemic. Compared to non-asthmatic controls, children with asthma were not at increased risk of Lower Respiratory Tract Infections (LRTIs), episodes of pyrexia, emergency visits, or hospitalizations during the pandemic. However, there was an increased risk of Upper Respiratory Tract Infections (URTIs) [26]. According to this study, these 14 children tended to escalate their treatment (11.8% vs. 4.2%), but the difference was not statistically significant. Eleven children (64.7%) received reliever treatment, and two (11.8%) required further escalation. Two of these children needed relief and escalation treatment. Seven patients were assisted in the emergency department. Two of these children needed relief and escalation treatment, requiring hospital admission for supplementary oxygen therapy; one was admitted to the pediatric intensive care unit (PICU). Regarding the symptoms they presented, the most frequent was cough/respiratory distress (41.2%), followed by fever (29.4%), headache (17.6%), gastrointestinal problems (17.6%), sore throat (5.9%) and (35.3%) were asymptomatic. No significant differences were observed in the frequency of symptoms compared to children with negative IgG SARSCoV-2 [20].

Decreased willingness and inability to seek medical care

All caregivers reported being reluctant to seek healthcare if their children had mild asthma symptoms. In addition, they only visited the asthma clinic occasionally, only if symptoms persisted and worsened. The caregivers expressed that they were unwilling to put themselves and their children at higher risk of exposure to the virus and feared being quarantined, which led to delayed hospital visits during the COVID-19 outbreak [32]. Almost one-third, 103 (35% of parents/caregivers), reported reduced controller dosing during the lockdown. The majority, 81 (79%), indicated this was due to their children's asthma stability [27].

Use of telemedicine during the COVID-19 lockdown

During the pandemic, caregivers/parents and children were isolated at home and feared being admitted to the hospital for diagnosis and treatment. They sought healthcare through virtual online or telephone consultations with doctors who had previously treated their children and were familiar with their condition, which enabled them to continue their treatment. According to the 64 parents who called their doctor's office, 87 percent found it convenient and easy to reach. 76 (26%) contacted the child's medical team at least once. Methods were most commonly WhatsApp 45(15%) and phone 45(15%) [27]. Nevertheless, several caregivers had concerns about virtual consultation and regarded it as a suboptimal clinical encounter in which doctors could not comprehensively assess their children's situations [31]. Most parents (91.6%) preferred not to be away from their children during the COVID-19 pandemic. More than half of the parents (66.6%) seemed to have adapted to the new normal and adjusted their lives to the changing conditions [28].

DISCUSSION

We performed a systematic review in children with asthma exposed to COVID-19, suggesting a decrease in severity from its baseline during the pandemic period. The primary aim of the study was to provide updated evidence that high-risk children require medical care and support from their families when vulnerable groups like those with COVID-19 are infected. To ensure that children with asthma can attend school safely, asthma control, risk stratification, and medication compliance should be considered [33]. However, during the pandemic period, the treatment of chronic diseases may be interrupted for several reasons. Parental anxiety is one of them [34]. The pandemic disrupted the treatment of one in five asthma patients. Despite

having complaints, some of them decided not to enter the hospital due to the risk of COVID-19 [35].

During the pandemic, children with asthma experienced improved disease control (two-thirds of the patients), as evidenced by enhanced scores. Validated asthma control measures include fewer asthma attacks, hospitalizations, and better pulmonary function. This observation's multifaceted etiology may include avoiding primary asthma triggers, including outdoor allergens, viral infections, physical exercise, and air pollution, due to social distancing, home sheltering, and reduced school days [36-41]. It shows that the childhood asthma cohort improved asthma activity and health during the COVID-19 pandemic, due to decreased exposure to asthma triggers and increased adherence to treatment. Atopic asthmatic children with mild to moderate symptoms did not exhibit an increase in the frequency of acute episodes, which should not be confused with COVID-19 infection [26].

During the COVID-19 pandemic, children have been affected by the sudden withdrawal from school, social life, and outdoor activities. Several studies have shown that prolonged school closure and home confinement negatively affect children's psychological and mental states, cause behavioral problems, and increase stress in children [42-44]. It shows that high anxiety and depressive symptoms occur in children and adolescents due to the pandemic, social isolation, and parental stress [45]. Some children may also have experienced increased domestic violence during this period. Efforts can be made to reduce the damage caused by this pandemic to mental health with adequate and timely intervention [46]. Irregular sleep pattern is one of the most significant factors affecting mental health [47,48]. A study in Italy showed that children significantly delayed sleep timing and worsened sleep quality during the lockdown due to COVID-19 [49]. It showed that the COVID-19 pandemic affects mental health more in young people with asthma/allergies than those without asthma/allergies. Our study found that asthmatic patients with changes in their sleep patterns were more likely to fear COVID-19 infection [50].

Most caregivers perceived that their children's level of asthma control was maintained or even improved during the epidemic. The maintenance or improvement of asthma control was partly mediated by increased medication adherence, which is critical to optimal asthma control [51]. It was driven by enhanced awareness of asthma control and reduced exposure to asthma triggers [52-55]. These results indicated that children should continue good asthma management even under the pressure of lockdown. They should adhere to medication treatments and avoid environmental triggers to control and prevent asthma symptoms and attacks [56]. They conducted an online survey in 27 countries and five continents. They reported that 20% of children with asthma had improved asthma control with no apparent deterioration. Medication adherence among patients with asthma during the COVID-19 pandemic reported a 14.5% increase [57].

CONCLUSION

Respiratory viruses are the most common asthma triggers. Up to 90% of childhood exacerbations are estimated to be related to viral infections. SARS-CoV-2 infections commonly affect the respiratory tract. Children with SARS-CoV-2 infection were studied to determine whether asthma severity may be influenced by SARS-CoV-2 infection. COVID-19 has less incidence and severity in childhood compared with adults, usually asymptomatic or with mild

symptoms. During the pandemic, most children with asthma and recurrent wheezing maintained their preventive treatments unchanged, showing good therapeutic adherence. Factors that contributed included adherence to therapy such that the need for frequent bronchodilator use has dropped. Reduced exposure to outside allergens and respiratory viruses is another factor. The COVID-19 pandemic was associated with a significant decrease in emergency department presentations and hospitalizations among children with asthma.

Among asthmatics and chronic obstructive pulmonary disease patients, medication adherence increased. COVID-19 guidelines and patients' increased awareness of the importance of controlling their primary respiratory disease may have contributed to this improvement. During the pandemic, caregivers preferred to access healthcare through virtual online or telephone consultations and proactively attempted home remedies. The caregivers have changed their health-seeking behavior to provide more support for their children and managed new challenges, including increased financial burdens and difficulties in drug purchasing. We conclude that our findings will enlighten health promotion interventions to guide children and their caregivers to restore, maintain and promote effective asthma management, especially during the outbreak and pandemic.

ACKNOWLEDGMENT

I want to extend my sincere thanks to every author in this work that contributed to completing this research work and its publication.

References

- [1]. Oreskovic, N.M., Kinane, T.B., Aryee, E., et al., The unexpected risks of COVID-19 on asthma control in children. *J Allergy Clin Immunol Pract*, 2020. 8: p. 2489-91.
- [2]. Liu, S., Zhi, Y., Ying, S., COVID-19, and asthma: reflection during the pandemic. *Clin Rev Allergy Immunol*, 2020. 59: p. 78-88.
- [3]. CDC. coronavirus disease 2019 (COVID-19). <https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html>.
- [4]. WHO. Coronavirus disease (COVID-19) pandemic. <https://www.who.int/emergencies/diseases/novel-coronavirus-2019>.
- [5]. Saqib, M.A.N., Siddiqui, S., Qasim, M., et al., Effect of COVID-19 lockdown on patients with chronic diseases. *Diabetes Metab Syndr*. 2020. 14: p. 1621-3.
- [6]. Liu, S., Zhi, Y., Ying, S., COVID-19 and asthma: reflection during the pandemic. *Clin Rev Allergy Immunol*, 2020. 59: p. 78-88.
- [7]. National Institute for Clinical Excellence. COVID-19 rapid guideline: severe asthma, 2020. <https://www.nice.org.uk/guidance/ng166>.
- [8]. Bloom, C.I., Drake, T.M., Docherty, A.B., et al., Risk of adverse outcomes in patients with underlying respiratory conditions admitted to hospital with COVID-19: a national, multicentre prospective cohort study using the ISARIC who clinical characterisation protocol UK. *Lancet*, 2021. *Respir Med*. doi:10.1016/S2213-2600(21)00013-8.
- [9]. Schultze, A., Walker, A.J., MacKenna, B., et al., Risk of COVID-19-related death among patients with chronic obstructive pulmonary disease or asthma prescribed inhaled corticosteroids: an observational cohort study using the Open SAFELY platform. *Lancet Respir Med*, 2020. 8: p. 1106-20.
- [10]. Williamson, E.J., Walker, A.J., Bhaskaran, K., et al., Factors associated with COVID-19-related death using Open SAFELY. *Nature*, 2020. 584: p. 430-6.

- [11]. Chan, J.F., et al (2020) A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet*, 2020. p. 3957.
- [12]. Chudasama, Y.V., Gillies, C.L., Zaccardi, F., et al., Impact of COVID-19 on routine care for chronic diseases: a global survey of views from healthcare professionals. *Diabetes Metab Syndr*, 2020. 14: p. 965-7.
- [13]. Papadopoulos, N.G., Custovic, A., Deschildre, A., et al., Impact of COVID-19 on pediatric asthma: practice adjustments and disease burden. *J Allergy Clin Immunol Pract*, 2020. 8: p. 2592-9.
- [14]. Kaye, L., Theye, B., Smeenk, I., et al. Changes in medication adherence among patients with asthma and COPD during the COVID-19 pandemic. *J Allergy Clin Immunol Pract*, 2020.8: p. 2384-5.
- [15]. Moore, S.A., Faulkner, G., Rhodes, R.E., et al., Impact of the COVID-19 virus outbreak on movement and play behaviours of Canadian children and youth: a national survey. *Int J Behav Nutr Phys Act*, 2020.17: p. 85.
- [16]. Oreskovic, N.M., Kinane, T.B., Aryee, E., et al., The unexpected risks of COVID-19 on asthma control in children. *J Allergy Clin Immunol Pract*, 2020. 8: p. 2489-91.
- [17]. Wu, Z., McGoogan, J.M., Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese center for disease control and prevention. *JAMA*, 2020. 323(13): p. 1239-42.
- [18]. Parkin, P.C., Macarthur, C., Saunders, N.R., et al., Development of a clinical asthma score for use in hospitalized children between 1 and 5 years of age. *J Clin Epidemiol*, 1996. 49: p. 821-825.
- [19]. Liu, L.L., Gallaher, M.M., Davis, R.L., et al., Use of a respiratory clinical score among different providers. *Pediatr Pulmonol*, 2004. 37: p. 243-248.
- [20]. Skevaki, C., Karsonova, A., Karaulov, A., et al., Asthma-associated risk for COVID-19 development. *J Allergy Clin Immunol*, 2020. 146(6): p. 1295-301.
- [21]. Green, I., Merzon, E., Vinker, S., et al., Covid-19 susceptibility in bronchial asthma. *J Allergy Clin Immunol Pract*, 2021. 9(2): p. 684-92.
- [22]. Abe, K., Miyawaki, A., Nakamura, M., et al., Trends in hospitalizations for asthma during the COVID-19 outbreak in Japan. *J Allergy Clin Immunol Pract*, 2021. 9(1): p. 494-6.
- [23]. Ruano, F.J., Somoza, A'lvarez, M.L., Haroun-Dí'az, E., et al., Impact of the COVID-19 pandemic in children with allergic asthma. *J Allergy Clin Immunol Pract*, 2020. 8(9): p. 3172-4.
- [24]. Zheng, F., Liao, C., Fan, Q-H., et al., Clinical characteristics of children with coronavirus disease 2019 in Hubei, China. *Curr Med Sci*, 2020. 40(2): p. 275-80.
- [25]. Sun, D., Li, H., Lu, X-X., et al., Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: a single center's observational study. *World J Pediatr*, 2020. 16(3): p. 251-9.
- [26]. Papadopoulos, N.G., Mathioudakis, A.G., Custovic, A., Deschildre, A., Phipatanakul, W., Wong, G., Xepapadaki, P., Abou-Taam, R., Agache, I., Castro-Rodriguez, J.A., Chen, Z., Cros, P., Dubus, J.C., El-Sayed, Z.A., El-Owaidy, R., Feleszko, W., Fierro, V., Fiocchi, A., Garcia-Marcos, L., Goh, A., Hossny, E.M., Huerta, Villalobos, Y.R., Jartti, T., Le, Roux, P., Levina, J., López, García, A.I., Ramos, Á.M., Morais-Almeida, M., Murray, C., Nagaraju, K., Nagaraju, M.K., Navarrete, Rodriguez, E.M., Namazova-Baranova, L., Nieto, Garcia, A., Pozo Beltrán, C.F., Ratchataswan, T., Rivero, Yeverino, D., Rodríguez, Zagal, E., Schweitzer, C.E., Tulkki, M., Wasilczuk, K., Xu, D., PeARL collaborators, on behalf of the PeARL Think Tank. Childhood asthma outcomes during the COVID-19 pandemic: Findings from the PeARL multi-national cohort. *Allergy*, 2021. 76(6): p. 1765-1775. doi: 10.1111/all.14787. Epub 2021 Mar 24. PMID: 33608919; PMCID: PMC8013557.
- [27]. Al-Iede, M., Waters, K., Aleidi, S.M., Alqutawneh, B., Alnawaiseh, H., Alshraideh, A., Almaaitah, S., Mahmoud, R., Abualsoud, R., Kiswani, A., Al-Zayadneh, E., Yousef, A.M., Impact of COVID-19 lockdown on children with asthma in Jordan: a parental questionnaire. *BMJ Paediatr Open*, 2021. 5(1): p. e001136. doi: 10.1136/bmjpo-2021-001136. PMID: 34222681; PMCID: PMC8228568.
- [28]. Hepkaya, E., Kilinc, A.A., Cebi, M.N., Koyuncu, Z., Cokugras, H., General health status of children with asthma during the COVID-19 pandemic. *Pediatr Int*, 2021. 63(3): p. 331-337. doi: 10.1111/ped.14453. Epub 2021 Mar 2. PMID: 32881185.

- [29]. Daoud, Pérez, Z., Rázquin, Arias, M., López-Escobar, A., Díaz-Conradi, A., Arce, A., Ruggeri, N., Romero, Blanco, I., Díaz-Delgado, B., Ventura, Wichner, P.S., The impact of COVID-19 lockdown on children with recurrent wheezing and asthma in Spain. *J Paediatr Child Health*, 2022. 58(9): p. 1635-1641. doi: 10.1111/jpc.16068. Epub 2022 Jun 24. PMID: 35748401; PMCID: PMC9350390.
- [30]. Leeb, R.T., Price, S., Sliwa, S., et al., Covid-19 trends among school-aged children - united states, March 1-September 19, 2020. *MMWR Morb Mortal Wkly Rep*, 2020. 69(39): p. 1410-5.
- [31]. Metbulut, A.P., Mustafaoğlu, Ö., Şen, G., et al., Evaluation of the clinical and laboratory findings of asthmatic children with SARS-CoV-2 infection. *Int Arch Allergy Immunol*, 2021. p. 1-8. doi:10.1159/000517153
- [32]. Jia, Y., Bao, J., Yi, M., Zhang, Z., Wang, J., Wang, H., Li, Y., Chen, O., Impact of the COVID-19 pandemic on asthma control among children: a qualitative study from caregivers' perspectives and experiences. *BMJ Open*, 2021. 11(5): p. e046525. doi: 10.1136/bmjopen-2020-046525. PMID: 33986062; PMCID: PMC8126436.
- [33]. Boechat, J.L., Wandalsen, G.F., Kuschnir, F.C., Delgado, L., COVID-19 and pediatric asthma: clinical and management challenges. *Int J Environ Res Public Health*, 2021. 18(3): p. 1093.
- [34]. Kulhas, Celik, I., Metbulut, A.P., Uneri, O.S., Senses, Dinc, G., Dibek, Misirlioglu, E., Effect of patient and parental anxiety on adherence to subcutaneous allergen immunotherapy during the coronavirus disease 2019 pandemic. *Ann Allergy Asthma Immunol*, 2021. 126(5): p. 595-7.
- [35]. Cekic, S., Karali, Z., Cicek, F., Canitez, Y., Sapan, N., The Impact of the COVID-19 Pandemic in Adolescents with Asthma. *J Korean Med Sci*, 2021. 36(49): p. e339. doi: 10.3346/jkms.2021.36.e339. PMID: 34931499; PMCID: PMC8688346.
- [36]. Wu, H., Zhu, H., Yuan, C., et al., Clinical and immune features of hospitalized pediatric patients with coronavirus disease 2019 (COVID-19) in Wuhan, China. *JAMA Netw Open*, 2020. 3(6): p. e2010895. <https://doi.org/10.1001/jamanetworkopen.2020.10895>
- [37]. Krivec, U., Kofol, Seliger, A., Tursic, J., COVID-19 lockdown dropped the rate of paediatric asthma admissions. *Arch Dis Child*, 2020. 105: p. 809-810.
- [38]. Niespodziana, K., Borochova, K., Pazderova, P., et al., Toward personalization of asthma treatment according to trigger factors. *J Allergy Clin Immunol*, 2020. 145: p. 1529-1534.
- [39]. Eguiluz-Gracia, I., Mathioudakis, A.G., Bartel, S., et al., The need for clean air: the way air pollution and climate change affect allergic rhinitis and asthma. *Allergy*, 2020. 75: p. 2170-2184.
- [40]. Taquechel, K., Diwadkar, A.R., Sayed, S., et al., Pediatric asthma healthcare utilization, viral testing, and air pollution changes during the COVID-19 Pandemic. *J Allergy Clin Immunol Pract*, 2020. 8(10): p. 3378. <https://doi.org/10.1016/j.jaip.2020.07.057>
- [41]. Chavasse, R., Almario, A., Christopher, A., Kappos, A., Shankar, A., The indirect impact of COVID-19 on children with asthma. *Arch Bronconeumol*, 2020. 56(11): p. 768-769. <https://doi.org/10.1016/j.arbres.2020.07.00>
- [42]. Brooks, S.K., Webster, R.K., Smith, L.E., Woodland, L., Wessely, S., Greenberg, N., et al., The psychological impact of quarantine and how to reduce it: rapid review of the evidence. *Lancet*, 2020. 395(10227): p. 912-20.
- [43]. Jiao, W.Y., Wang, L.N., Liu, J., Fang, S.F., Jiao, F.Y., Pettoello-Mantovani, M., et al., Behavioral and emotional disorders in children during the COVID-19 epidemic. *J Pediatr*, 2020. 221: p. 264-266.
- [44]. Sprang, G., Silman, M., Posttraumatic stress disorder in parents and youth after health-related disasters. *Disaster Med Public Health Prep*, 2013. 7(1): p. 105-10.
- [45]. Saraçlar, Y., Kuyucu, S., Tuncer, A., Sekerel, B., Saçkesen, C., Kocabaş, C., Prevalence of asthmatic phenotypes and bronchial hyperresponsiveness in Turkish schoolchildren: an International Study of Asthma and Allergies in Childhood (ISAAC) phase 2 study. *Ann Allergy Asthma Immunol*, 2003. 91(5): p. 477-84.
- [46]. Kulhas, Celik, I., Metbulut, A.P., Uneri, O.S., Senses, Dinc, G., Dibek, Misirlioglu, E., Effect of patient and parental anxiety on adherence to subcutaneous allergen immunotherapy during the coronavirus disease 2019 pandemic. *Ann Allergy Asthma Immunol*, 2021. 126(5): p. 595-7.

- [47]. De-Figueiredo, C.S., Sandre, P.C., Portugal, L.C., Mázala-de-Oliveira, T., da-Silva, Chagas, L., Raony, Í., et al., COVID-19 pandemic impact on children and adolescents' mental health: Biological, environmental, and social factors. *Prog Neuropsychopharmacol Biol Psychiatry*, 2021. 106: p. 110171.
- [48]. Mindell, J.A., Williamson, A.A., Benefits of a bedtime routine in young children: sleep, development, and beyond. *Sleep Med Rev*, 2018. 40: p. 93-108.
- [49]. Cellini, N., Di, Giorgio, E., Mioni, G., Di, Riso, D., Sleep and psychological difficulties in Italian school-age children during COVID-19 lockdown. *J Pediatr Psychol*, 2021. 46(2): p. 153-67.
- [50]. Hawke, L.D., Monga, S., Korczak, D., Hayes, E., Relihan, J., Darnay, K., et al., Impacts of the COVID-19 pandemic on youth mental health among youth with physical health challenges. *Early Interv Psychiatry*, 2021. 15(5): p. 1146-53.
- [51]. Horne, R., Price, D., Cleland, J., et al., Can asthma control be improved by understanding the patient's perspective? *BMC Pulm Med*. 2007. 7: p. 8.
- [52]. Gautier, C., Charpin, D., Environmental triggers and avoidance in the management of asthma. *J Asthma Allergy*, 2017. 10: p. 47-56.
- [53]. Pelaia, G., Vatrella, A., Gallelli, L., et al., Respiratory infections and asthma. *Respir Med*, 2006. 100: p. 775-84.
- [54]. Nnodum, B.N., McCormack, M.C., Putcha, N., et al., Impact of physical activity on reporting of childhood asthma symptoms. *Lung*, 2017. 195: p. 693-8.
- [55]. Dales, R., Chen, L., Frescura, A.M., et al., Acute effects of outdoor air pollution on forced expiratory volume in 1 S: a panel study of schoolchildren with asthma. *Eur Respir J*, 2009. 34: p. 316-23.
- [56]. Papadopoulos, N.G., Custovic, A., Deschildre, A., et al., Impact of COVID-19 on pediatric asthma: practice adjustments and disease burden. *J Allergy Clin Immunol Pract*, 2020. 8: p. 2592-9.
- [57]. Kaye, L., Theye, B., Smeenk, I., et al., Changes in medication adherence among patients with asthma and COPD during the COVID-19 pandemic. *J Allergy Clin Immunol Pract*, 2020. 8: p. 2384-5.