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Asthma and COVID-19 in children: A systematic review and call for data

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Abstract

Rationale: Whether asthma constitutes a risk factor for coronavirus disease-2019 (COVID-19) is unclear. Here, we aimed to assess whether asthma, the most common chronic disease in children, is associated with higher COVID-19 risk or severity in pediatric populations.

Methods: We performed a systematic literature search in three stages: first, we reviewed PubMed, EMBASE, and CINAHL for systematic reviews of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and COVID-19 in pediatric populations, and reviewed their primary articles; second, we searched PubMed for studies on COVID-19 or SARS-CoV-2 and asthma/wheeze, and evaluated whether the resulting studies included pediatric populations; third, we repeated the second search in BioRxiv.org and MedRxiv.org to find pre-prints that may have information on pediatric asthma.

Results: In the first search, eight systematic reviews were found, of which five were done in pediatric populations; none of the 67 primary studies included data on pediatric asthma as a comorbidity for COVID-19. In the second search, we found 34 results in PubMed, of which five reported asthma in adults, but none included data on children. In the third search, 25 pre-prints in MedRxiv included data on asthma, but none on children. We found one report by the US Centers for Disease Control and Prevention stating that 40/345 (~11.5%) children with data on chronic conditions had "chronic lung diseases including asthma," and one from a tertiary hospital in New York that reported asthma in 11/46 (~23.9%) children hospitalized for COVID-19.

Conclusion: There is scarcely any data on whether childhood asthma (or other pediatric respiratory diseases) constitute risk factors for SARS-CoV-2 infection or COVID-19 severity. Studies are needed that go beyond counting the number of cases in the pediatric age range.

KEYWORDS
asthma & early wheeze, SARS-CoV-2, COVID-19

1 | INTRODUCTION

The current outbreak of coronavirus disease-2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), started in or around December 2019, in Wuhan.[1] On 30th January 2020, the World Health Organization (WHO) declared COVID-19 a pandemic health emergency.[2] Since then, COVID-19 has continued to spread quickly

and has now become the most dangerous pandemic in over 100 years.

An interactive real-time COVID-19 reporting system set up by the Center for Systemic Science and Engineering at Johns Hopkins University[3] shows, as of the time of this writing, more than 5.8 million confirmed cases and over 361 000 deaths worldwide (led by the United States, with ~30% of all cases and ~28% of all deaths). Globally, this corresponds to a ~6% case fatality rate, although rates vary widely among countries and subpopulations and it is difficult to ascertain both the true numerator (active unresolved cases may eventually become deaths) and the true denominator (many true cases may go untested or undetected).

The first pediatric case in the literature was reported on January 2020 in 10-year-old boy from Shenzhen, China, whose family had visited Wuhan.[4] All epidemiological evidence to date suggests that SARS-CoV-2 infection is less severe in children than in adults. In the latest and largest study in the UK, including 16 749 patients hospitalized for COVID-19, only 239 (2%) were less than 18 years of age (including 139 who were <5 years old).[5] Large studies in Italy and China have also shown very low case-fatality rates in children and adolescents.[6] Understandably, most studies have focused on adult populations, with very few studies and reviews in children. Moreover, accumulating data points to risk factors for severity and mortality in adults (eg, older age, cardiovascular disease, diabetes, cancer, immunosuppression, obesity, tobacco smoking, etc),[5,6] but there is very scarce evidence on whether or which risk factors exist in children. While COVID-19 is a multisystem disease, it predominantly effects the lungs, and thus it is critically important to understand whether chronic lung diseases place children at higher risk.

The main objective of this study was to identify whether asthma, the most common chronic respiratory disease in children, is a risk factor for SARS-CoV-2 infection or COVID-19 severity in the pediatric population.

2 | METHODS

We performed a systematic literature research in three stages (see Figure 1): first, we searched PubMed, EMBASE, and CINAHL using the following terms: "(((SARS-CoV-2) OR (COVID-19)) AND ((systematic review)) AND ((children 0-18 years of age)))" to find systemic reviews on the topic, and then reviewed the primary studies included in those reviews. Second, we searched PubMed for "(((COVID-19) OR (SARS-CoV-2)) AND ((asthma) OR (wheezing)))," to directly find any studies on asthma/wheezing and COVID-19 (without an age filter), and evaluated whether they included pediatric populations. Third, we repeated search #2 in BioRxiv.org and MedRxiv.org to evaluate whether existing preprints may have relevant pediatric asthma information. The last update of the searches was on 6 May 2020 (see Figure 1).

Both authors (JCR and EF) independently screened and retrieved articles. The same investigators independently assessed full texts of those primary studies included in the systematic review identified. Any discrepancies were resolved by discussion and consensus.

If sufficient studies with relevant data were found, the plan was to perform a meta-analysis by asthma status. The review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[7]

3 | RESULTS

After removing duplicates, the first search yielded eight systematic reviews.[5,8-14] Three of them were eliminated because they did include information on clinical characteristics in children.[8-10] Therefore, we evaluated five systematic reviews done at different periods during the pandemic and thus including somewhat different primary studies.[11-14] Castagnoli et al[11] included 18 articles, 17 from China and one from Singapore (444 patients < 10 years old and 553 aged 10-19 years), published up to 3 March 2020. Choi et al[12] included seven articles from China (225 pediatric patients) up to 12 March 2020. Chang et al[13] included nine studies from China (93 pediatric patients) up to 15 March 2020. The review by Ludvigsson[14] included 45 studies from China (the total number of patients was not described) up to 19 March 2020. And Streng et al[15] included eight studies from China (ranging from 6 to 2143 patients) and one survey from Germany (33 patients) in hospitalized children, up to 31 March 2020. After excluding duplicates, we identified and reviewed 67 primary studies included in those five reviews (see Table S1).

None of the primary studies reviewed reported asthma or recurrent wheezing as a comorbidity or risk factor for COVID-19. Instead, some of those studies reported young age (especially children <1 year of age) as a group with more severe COVID-19. One large Chinese study[16] reported nonrespiratory chronic conditions (hydronephrosis, leukemia receiving chemotherapy, and intussusception) among three children who required intensive care unit (ICU) support and mechanical ventilation. Among them, one death occurred in a 10-month old child with intussusception. Another study reported a patient who developed shock with metabolic acidosis requiring ICU.[17] Yet another report from China[18] described one patient aged 10 to 19 years who died, without other clinical information; that death probably represents the same 14-year-old boy described by Dong et al[19] Unfortunately, the two larger studies in Chinese pediatric patients, Dong et al[19] (2413 children) and Wu and McGoogan[20] (965 children) did not report enough clinical data to identify comorbidities or risk factors for COVID-19 severity. In the German survey of 33 hospitalized children, four out of 22 (18%) children with clinical information had "respiratory comorbidities" without further details.[15]

Our second search yielded 34 results in PubMed. Of those, five were primary studies that reported on asthma in adults[21-25]; one other was a guidance statement[26] that referenced a primary report that also included information on asthma in adults.[27] No studies from that search included information on asthma in children, although one case series reported two young children (ages 2 and 3 years) with history of atopic dermatitis and allergic rhinitis, who were hospitalized with COVID-19; both patients recovered.[28]
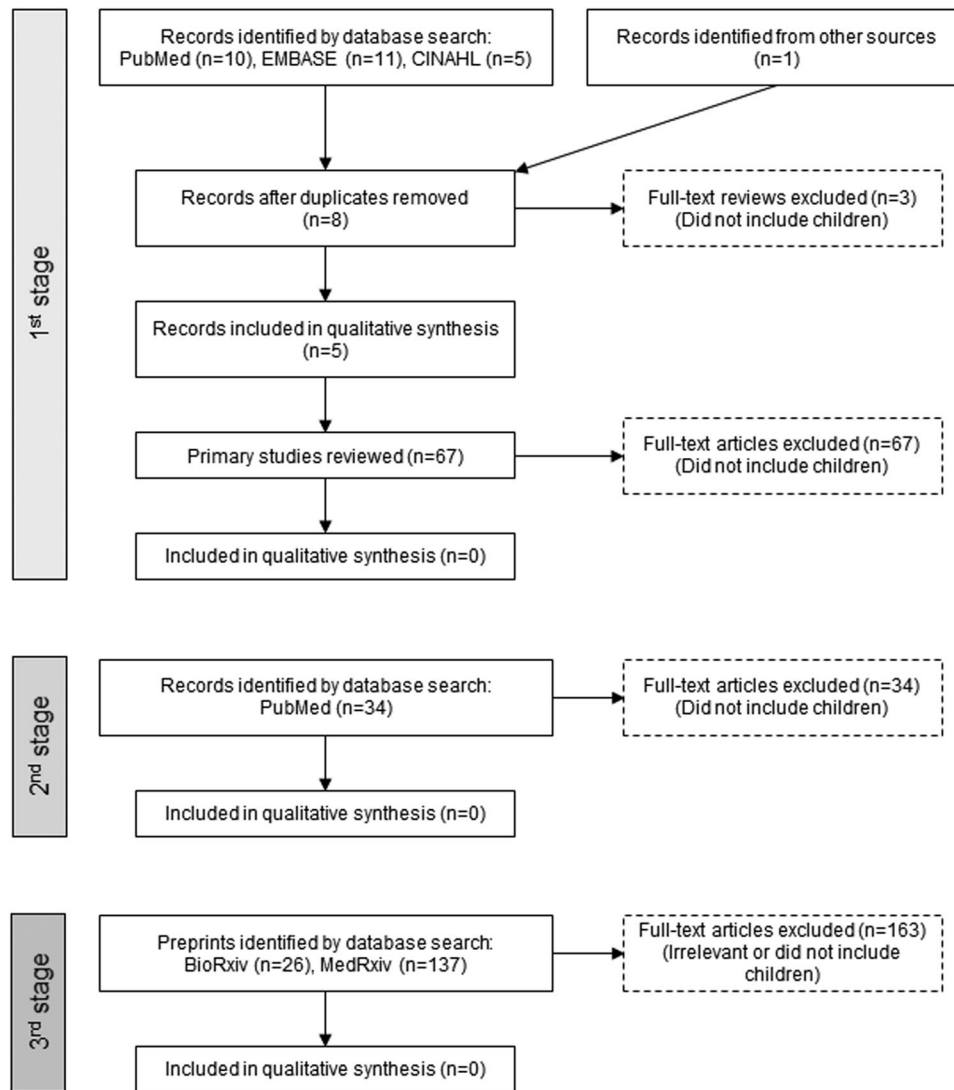
FIGURE 1 Process of study selection

Our third search yielded 26 pre-prints in BioRxiv and 137 in MedRxiv. None of the BioRxiv posts were relevant to our topic. Of the 137 pre-prints in MedRxiv, 23 nonduplicate studies included information on asthma,[29-51] but none of them included specific information in children.

A search of secondary sources and reference lists identified a Morbidity Mortality Weekly Report (MMWR),[52] published by the Centers for Disease Control and Prevention (CDC), that included information from 2572 US children aged less than 18 years. Of those cases, 345 had data on clinical and underlying conditions, and 80 of those children (23%) had at least one underlying condition. The most common underlying conditions were "chronic lung diseases (including asthma)" in 40 children, cardiovascular disease in 25, and immunosuppression in 10; separate information on asthma was not provided. Among the 295 cases for which data on both hospitalization status and underlying medical conditions was available, 28/37 (77%) hospitalized patients had one or more underlying medical condition (including all six patients admitted to an ICU); compared with 30/258

(12%) patients who were not hospitalized.[52] A recently published Italian study, including 100 children seen in 17 emergency departments, reported that 27% had comorbidities without more specifications, and no deaths occurred.[53] And most recently, a study of 46 children hospitalized for COVID-19 at a tertiary center in New York reported 11/46 (23.9%) had asthma, with no differences in the proportions admitted to the general floor (8/33 or 24.2%) vs PICU (3/13 or 23.1%).

4 | DISCUSSION

In a systematic review of the literature, we only found two reports that described asthma or recurrent wheezing as potential risk factors for COVID-19 in children. Importantly, none of the largest epidemiological studies including children with COVID-19 reported clinical findings or underlying characteristics to help assess whether asthma, or other chronic lung diseases, constitutes a risk factor for SARS-CoV-2 infection or COVID-19 severity.

COVID-19 affects primarily the lungs, and accordingly several international guidelines have designated some respiratory conditions as a potential risk factor for severe disease. Chinese guidelines[54] state that "children with a history of contact with severe 2019-nCoV infected cases, or with underlying conditions (such as congenital heart disease, bronchial pulmonary hypoplasia, respiratory tract anomaly, with abnormal hemoglobin level, and severe malnutrition), or with immune deficiency or immunocompromised status... may become severe cases." A recent statement from the EAACI Section on Pediatrics[26] declared that "patients with asthma (particularly severe or uncontrolled asthma) and immunodeficiency have also been classified to be at increased risk of developing severe COVID-19, based more on common sense rather than mounting evidence." The Global Initiative for Asthma (GINA) recommends avoiding the use of nebulizers due to the increased risk of disseminating COVID-19 to other patients and health care staff; they thus recommend the use of pressurized metered dose inhalers (pMDI) as the preferred delivery system during asthma attacks.[55] A recent randomized controlled trial[56] showed that even in children with severe asthma exacerbations, administration of albuterol/salbutamol, and ipratropium by MDI with valved-holding chamber and mask along with oxygen by nasal cannula was more effective than nebulized administration. GINA[55] and the British Thoracic Society[57] do not recommend stopping oral steroids in the patients already taking them for asthma management, and they do not recommend avoiding them for acute asthma attacks even if due to COVID-19. The US CDC, the Canadian Pediatric Society, and other professional associations have issued guidance for patients with asthma and/or allergies.[58-60] Other professional organizations, such as the American Academy of Pediatrics and the American Thoracic Society, have published interim guidelines that do not specifically address asthma, likely given a paucity of evidence.[61,62]

Rather than a risk factor, a recent review of data in adults reported that both asthma and chronic obstructive pulmonary disease appear to be underrepresented in the comorbidities reported for patients with COVID-19, compared with global estimates of prevalence for these conditions in the general population.[63] This is consistent with individual studies we found during our search, which have shown lower-than-expected prevalence of asthma among cases of COVID-19,[21-24,27] and in contrast to the prevalence of other chronic diseases such as diabetes, which occurred with higher frequency among patients with COVID-19 than the estimated national prevalence.[63] If asthma is indeed "protective," this could be due to several factors, including changes 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.[64,65] Analysis of induced sputum samples in a well-characterized cohort of adults with severe asthma found reduced angiotensin-converting enzyme 2 (*ACE2*) and transmembrane protease serine 2 (*TMPRSS2*) gene expression among patients taking ICS, and especially among those on higher doses[66]; *ACE2* and *TMPRSS2* mediate SARS-CoV-2 cell infection. Similarly, a recent study (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.[67] This is particularly noteworthy considering that one of the potential explanations for children being generally less affected than adults is the hypothesis that children have lower ACE2 receptor expression in alveolar type 2 cells.[68] However, the lower prevalence of asthma among COVID-19 cases could also stem from bias due to under diagnosis and underreporting, or because patients with chronic lung diseases may be especially cautious in practicing physical distancing and other measures to avoid infection. Finally, it is also conceivable that some milder cases of COVID-19 might be confused with exacerbations of respiratory disease, and/or that these patients may be reluctant to seek medical care even when sick and are thus never counted.

It is important to note that our understanding of the role of asthma, even in adults, is still incipient. In the largest and most recent analysis to date, UK investigators analyzed data from 17 million adults, including 5683 deaths due to COVID-19, and reported that both asthma (adjusted hazard ratio, aHR: 1.11 [95% confidence interval, 1.02-1.20]) and severe asthma (aHR: 1.25 [1.08-1.44]) were risk factors for COVID-19 mortality.[51] This study compared COVID-19 deaths with the general population (regardless of being SARS-CoV-2 positive or not), so the estimates combine both risk of infection and risk of death once infected. These results highlight how incomplete our understanding still is. As with most other studies, this large analysis did not include a pediatric population.

5 | CONCLUSIONS

After an extensive review of the current literature, only two reports included information on asthma as a potential risk factor for COVID-19 infection, but not severity or mortality, in children. However, the largest studies to date have been limited to a description of the number of cases by age group, and so it remains unclear whether childhood asthma, or other pediatric respiratory diseases, are associated with COVID-19 risk or severity.

We, hereby, ask the public health community to move beyond confirming what's already known that the disease affects children and young adults less frequently and severely than older groups, and to study affected pediatric populations in more detail. Does asthma constitute a risk factor for COVID-19 in children? Do asthma severity or control modify the course of the disease? Are asthma medications (particularly ICS and systemic steroids) or their doses protective or detrimental? Given the limited numbers of pediatric cases in any one given center/country, collaborative international efforts may be the only way to shed light on the topic. Initiatives such as the Pediatric Asthma in Real Life group[69] or a pediatric version of the International Severe Asthma Registry,[70] or efforts coordinated by large professional societies, may be best suited for the task. This will be true not just for childhood asthma but for pediatric diseases in general.

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SUPPORTING INFORMATION

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

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