



Coronavirus disease 2019 and asthma, allergic rhinitis: molecular mechanisms and host–environmental interactions

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Purpose of review

Coronavirus disease 2019 (COVID-19), a respiratory infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 virus), is a pandemic in over 120 countries worldwide. Risk factors for severe COVID-19 include older age, ethnicity, sex, comorbidities, and living conditions. Although asthmatics and those with allergies are susceptible to more severe outcomes to viral infections, interestingly, asthma has not been reported to be a major comorbidity of COVID-19. However, there are some conflicting reports on the impact of asthma on COVID-19. The underlying immunological and molecular mechanisms may explain at least in part these observations. Furthermore, environmental factors like air pollution that have detrimental effects on asthma and respiratory illnesses also have an impact on COVID-19.

Recent findings

Angiotensin-converting enzyme 2 (ACE2) is the receptor for the attachment and entry of SARS-CoV-2 into the host cells that is upregulated by Th1-mediated responses. In asthmatics, ACE2 gene expression is generally reduced and recent studies have shown a negative correlation between the levels of Th2 cytokines including IL-4, IL-5, and IL-13 in airway epithelial cells and other type 2 biomarkers with ACE2 expression. This may explain in part the potential protective role of asthma on COVID-19. Here, we review the relation of respiratory viral illnesses and asthma, the immune-molecular mechanisms of SARS-CoV-2 infection, the impact of asthma on COVID-19 and that of SARS-CoV-2 on asthma and allergic rhinitis, and the impact of environmental factors like air pollution on COVID-19.

Summary

Expression of ACE2 in airway epithelial cells in SARS-COV-2 is influenced by inflammatory profile. Respiratory allergic diseases like asthma appear to have a protective effect against SARS-COV-2 infection. However, the clinical association between asthma and SARS-COV-2 is not fully established and the underlying immune-molecular mechanisms may explain these observations.

Keywords

air pollution, allergy, angiotensin-converting enzyme 2, asthma, coronavirus disease 2019, severe acute respiratory syndrome coronavirus 2

INTRODUCTION

COVID-19 is a respiratory disease caused by a highly infectious virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 virus), that was declared a pandemic by the WHO on 11 March 2020. SARS-CoV-2 infection can present as asymptomatic but most often manifests with acute respiratory illness which results in severe pneumonia and progresses to acute respiratory distress syndrome and even multiple organ failure. Abnormal, overactivated innate immunity and ‘cytokine storms’ are potential pathological mechanisms for the rapid COVID-19

progression. Conventionally, respiratory viral infections are known to exacerbate asthma and asthmatic patients should have increased susceptibility and severity for SARS-CoV-2 infection due to a deficient antiviral immune response. Therefore, asthma was

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KEY POINTS

- Asthma does not appear to be a major risk factor for COVID-19 overall; however, its actual risk may depend on the type and severity of asthma.
- The molecular mechanisms underlying allergic inflammation may have a protective effect against COVID-19.
- The environmental and behavioral changes associated with the COVID-19 pandemic have a substantial impact on asthma in terms of its control and triggers.
- Guidelines recommend to comply with the basic measures of protection against COVID-19 and to continue asthma therapies including inhaled corticosteroids and biologicals in asthmatic patients during the COVID-19 pandemic.

initially considered to be an important comorbidity for COVID-19. Furthermore, allergic sensitization is a risk factor for wheezing with rhinovirus (RV) infection, particularly in children. However, several early and subsequent reports have suggested that the prevalence of asthma in COVID-19 infection is low, and that asthma may not be a comorbidity of COVID-19 [1^a,2].

In reviewing the pathophysiology of both asthma and COVID-19, asthma may even have a protective effect against COVID-19 [3^a]. Certain aspects of the

type 2 inflammation seen in asthmatics like increased type 2 cytokines (IL-4, IL-13, etc.) and accumulation of eosinophils, might provide potential protective effects against COVID-19. Furthermore, asthma therapies, like inhaled corticosteroids, allergen immunotherapy, and anti-IgE mAb, might also reduce the risks of asthmatics to infection of the virus via alleviating inflammation or enhancing the antiviral defense. By contrast, some recent reports suggest the possibility of severe asthma being a risk factor in the more severe forms of COVID-19 [4] (<https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html>). In addition to these conflicting observations, it may be difficult to differentiate whether asthma exacerbations are due to COVID-19 or that asthma acts as a risk factor for COVID-19 given the similarity of symptoms in their severe forms (Fig. 1). In this context, it is important to discuss asthma as a comorbid condition of COVID-19.

In this review, we summarize recently published studies of asthma and immune response to SARS-CoV-2 infection, the regulation of angiotensin-converting enzyme 2 (ACE2) and transmembrane peptidase serine 2 (TMPRSS2), in airway epithelial cells and its regulation by inflammatory markers, how SARS-CoV-2 may impact patients with upper airways disease like allergic rhinitis, an important comorbidity of asthma, the relation between air pollution and COVID-19, and the effect of asthma therapies including inhaled steroids on COVID-19.

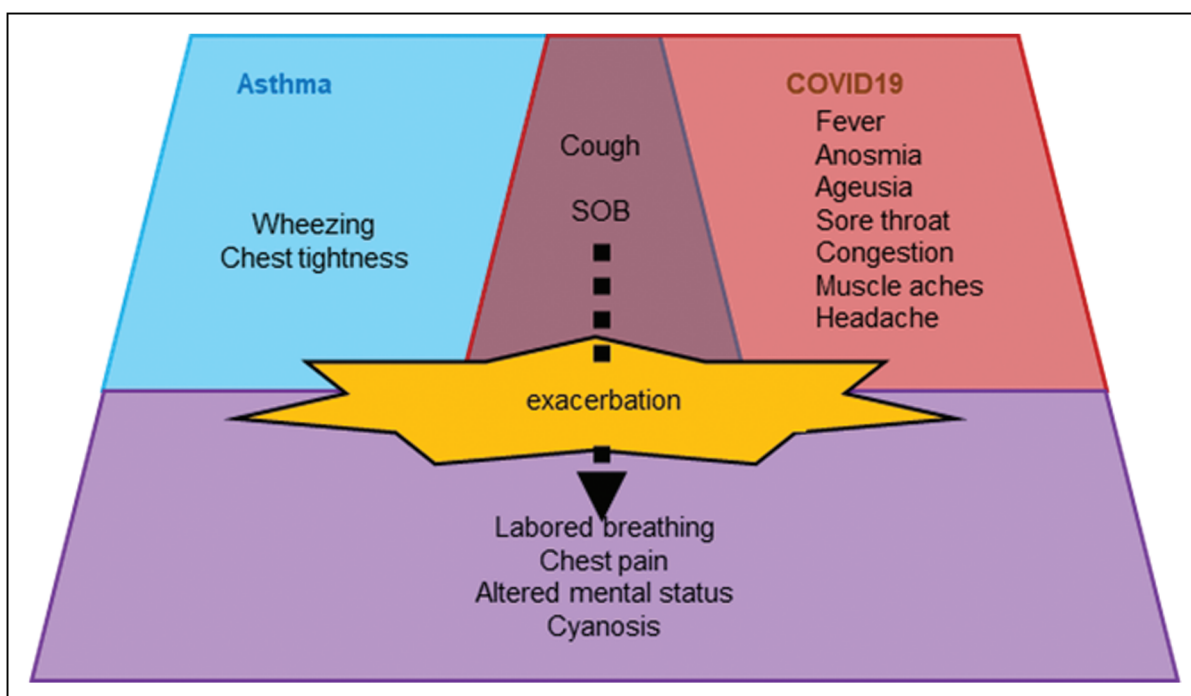


FIGURE 1. Overlapping symptom profile of asthma and coronavirus disease 2019.

VIRAL INFECTIONS AND ASTHMA

Respiratory viral infections, are regarded as a risk factor for asthma exacerbations. Upon exposure to certain viruses, the antiviral immunity which is the type 1 immunity is activated with the release of interferons. However, in asthmatics, the Th2 dominant microenvironment of increased IL-4, IL-5, and IL-13 results in a delayed and insufficient response to viruses [5]. One of the underlying mechanisms suggested is that IgE cross-linking in allergic immune response reduces viral toll-like receptor7 and toll-like receptor9-induced IFN- α production and secretion from plasma dendritic cells [6,7]. Indeed, the bronchial mucosa in asthmatics produces lower level of IFN- γ [5]. On the other hand, despite well defined mechanisms on the impact of viral infections on asthma, the multifactorial aspects may vary in part from virus to virus [8,9]. In fact, in children, RV is the only virus which has been shown to induce asthma exacerbations [5]. Significantly, in one study conducted in Philadelphia, reduced asthma-related admissions and systemic steroid prescriptions were observed along with reduced RV infection during the COVID-19 pandemic [10].

SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 AND ASTHMA

Asthmatics and patients with respiratory allergies are known to be at a greater risk of more severe outcomes with viral infections. Therefore, in the early stages of the COVID-19 pandemic, asthma

was considered as a major risk factor for COVID-19. However, recent reports highlight the low prevalence of asthma and allergic diseases in patients with COVID-19 as compared with other comorbidities of COVID-19 like diabetes, hypertension, etc [11¹²]. This raises the question of whether asthma could therefore have a potential protective role on COVID-19.

ACE2 is the receptor binding domain of SARS-CoV-2 [12], and is essential for docking the spike protein of SARS-CoV-2, while TMPRSS2 is essential to cleave the docked spike protein for the virus entry into the cell by membrane fusion [13,14] (Fig. 2). The expression of ACE2 and TMPRSS2 in the respiratory epithelial cells during SARS-CoV-2 infection is determined by the age, sex, comorbidity, and type 2 allergic inflammation [14]. In asthmatics, *ACE2* gene expression is generally reduced, which may result in preventing the SARS-CoV-2 virus from entering into the epithelium of the airways [15]. Others have reported that the gene expression for ACE2 and TMPRSS2 in the cells obtained from induced sputum did not differ between healthy individuals and asthmatics [14]. Studies have shown a negative correlation between the expression of ACE2 and the levels of Th2 cytokines including IL-4, IL-5, and IL-13 in airway epithelial cells, the number of positive allergen-specific cells, total IgE and fractional exhaled nitric oxide [15,16¹⁷]. On the other hand, some other statistics have shown that in contrast to allergic asthma, nonallergic asthma was a significant risk factor for severe COVID-19 [17]. These findings may explain the inconsistent evidence on *ACE2* gene expression in all asthmatics

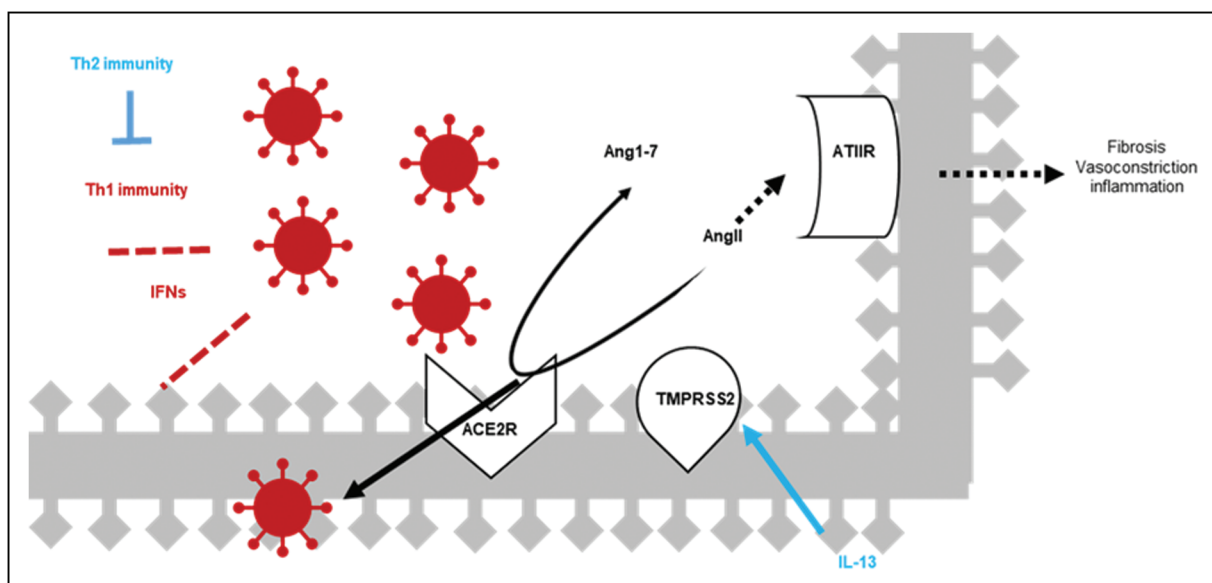


FIGURE 2. Allergic inflammation and severe acute respiratory syndrome coronavirus 2.

and suggest that the allergic inflammatory mechanisms in asthma rather than asthma itself may be related to a reduced *ACE2* gene expression and the protective effect of asthma on COVID-19. In the context, in viral infections like respiratory syncytial virus (RSV), intracellular adhesion molecule (ICAM-1) [18], the receptor for rhinovirus, facilitates RSV entry and infection of human epithelial cells by binding to its F protein, a key factor for viral replication and infection. Given that the levels of ICAM-1, a possible reduced expression of *ACE2* in asthmatics may at least in part explain the observations that asthmatics may not be at increased risk of COVID-19. The Th2 dominant environment in asthmatics can downregulate the viral-induced release of interferons, resulting in dampening of the inflammatory response in SARS-CoV-2 infection, which is considered to be a major aspect in the pathophysiology of severe COVID-19 [5].

On the other hand, there are also conflicting reports that go against the protective effect of asthma on COVID-19. Some epidemiological data support the conventional understanding that asthma is a risk factor for severe COVID-19. First, the lower expression of *ACE2* in asthmatic patients can result in augmenting inflammation as *ACE2* reduces the inflammatory effect caused by angiotensin II once SARS-CoV-2 enters the epithelium. This can be explained by the suppression of

inflammation, fibrosis and vasoconstriction by angiotensin II as *ACE2* cleaves angiotensin II to angiotensin 1–7 [16^{***}]. What's more important is that the expression of *TMPRSS2* which allows for *ACE2*-mediated cell membrane fusion and endocytosis of the virus and subsequent viral replication by cleaving SARS-CoV-2 S protein [15,16^{***}] is highly upregulated in type 2 allergic inflammation mainly by IL-13 [13] in asthmatics. In the presence of a reduced expression of *ACE2*, *TMPRSS2* can play a key role for virus entry into the respiratory system, resulting in offsetting the protective aspect of asthma on COVID-19 as described above (Fig. 2).

SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 AND ALLERGIC RHINITIS

The nasal epithelium is the first barrier for the entry for viruses, bacteria or allergens and protects the lower respiratory tract [19]. SARS-CoV-2 likely binds to nasal epithelial cells prior to it replicating [20] (Fig. 3). Several studies have shown the link between allergic rhinitis and asthma and that allergic rhinitis is a risk factor for asthma [21]. In RSV, the levels of ICAM-1 is increased in the nasal and bronchial epithelium in patients with allergic rhinitis as well as asthma suggesting their susceptibility to RSV infections [18]. With SARS-CoV-2, significantly

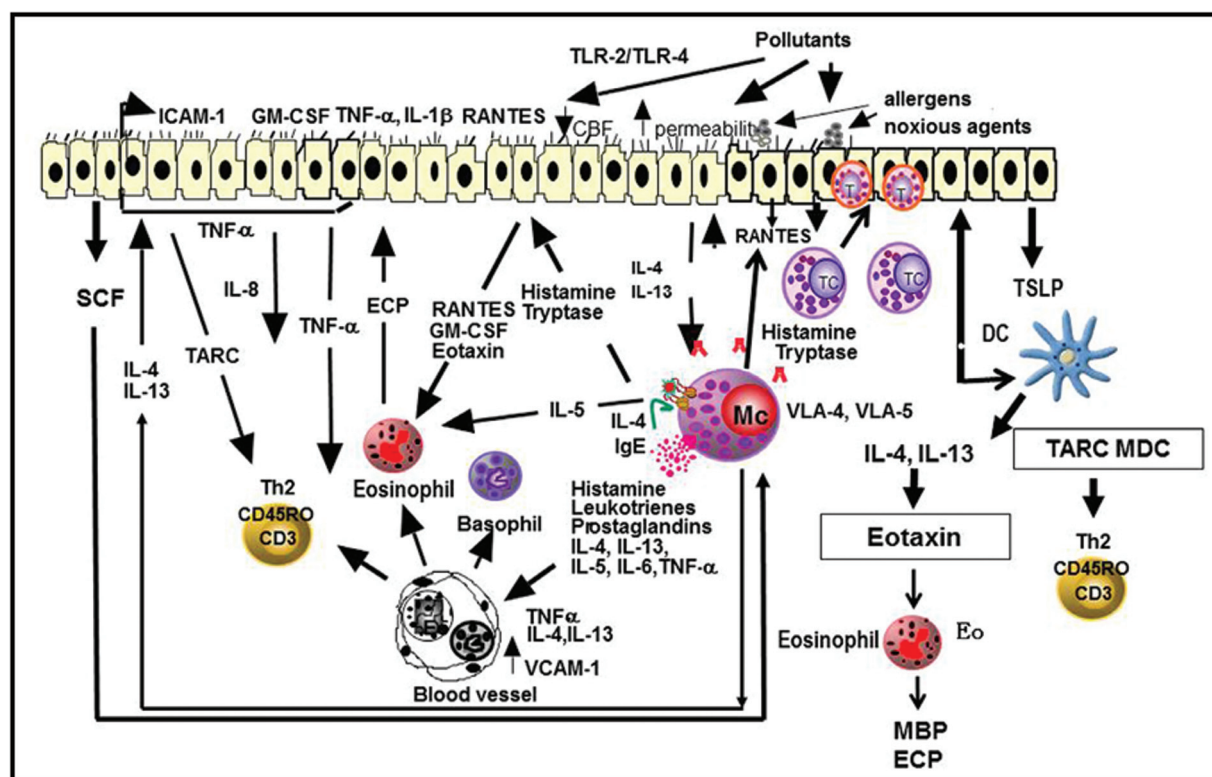


FIGURE 3. The epithelial cell barrier function and allergic inflammation [19].

reduced ACE2 and increased TMPRSS2 expression were observed not only in the lower airway epithelial cells but also in the nasal epithelial cells both in patients with asthma and with allergic rhinitis [15]. In the light of these observations, the reduced ACE2 expression in patients with allergic rhinitis can also have a protective effect against COVID-19, and so far, allergic rhinitis is not considered as a comorbidity of COVID-19 [22], although there are only limited data on the relationship between allergic rhinitis and COVID-19. On the other hand, another report suggests that ACE2 expression in nasal tissues is not altered in allergic rhinitis since ACE2 expression correlates with interferon response but not with type 2 response in nasal tissues and epithelial cells [22]. It also would be worth noting that the ACE2 expression in the upper airways may play a crucial role in infection with COVID-19 given that the anosmia seen in COVID-19 appears to be caused by primary infection of nonneuronal cell types including stem and support cells in the olfactory epithelium and vascular pericytes in olfactory bulb rather than through sensory or bulb neuron [23]. Given that 40% of patients with allergic rhinitis have comorbid asthma, and that 94% of asthmatics have comorbid allergic rhinitis [24], it would be interesting to compare the presence and severity of COVID-19 in asthmatics with and without allergic rhinitis.

HOST-ENVIRONMENTAL FACTORS IN CORONAVIRUS DISEASE 2019

The COVID-19 pandemic has changed patient behavior in relation to asthma treatment, which is also an important host factor. One aspect is the implementation of preventive strategies [25] and a better adherence to asthma treatment, thereby making them less susceptible to environmental insults. Kaye *et al.* [26] demonstrated that there was a 14.5% increase in mean daily controller medication adherence from January to March this year. Although the precise mechanisms are unclear, it may be attributed to COVID-19 pandemic given that the similar improvement in adherence to medications has been reported in autumn when other respiratory viral infections are prevalent [26].

The second aspect is the impact of environmental factors. In the general population, Scafetta [27] concluded that temperature is a major contributing environmental factor for COVID-19 based on the relatively low COVID-19 diffusion, mortality rates, and larger proportion of mild cases observed in warmer countries and the higher mortality levels observed in colder countries. While previous studies have suggested that ambient air pollutants are risk

factors for respiratory infection in general, the relationship between air pollution and COVID-19 appears to be controversial. Scafetta [27] did not find any significant association between air pollutants and COVID-19 in the general population. Taquechel *et al.* [10] did not find a significant association as well, but considered this lack of significance in asthmatics most likely to be due to the limited assessment or due to the reduction of exposure to outdoor environmental pollutants and allergens resulting in better asthma control. On the other hand, Zhu *et al.* [28^{*}] reported a significantly positive associations between PM_{2.5}, PM₁₀, NO₂ and O₃ within a 2 week period with COVID-19 confirmed cases. A 10-μg/m³ increase in PM_{2.5}, PM₁₀, NO₂, and O₃ was associated with a 2.24, 1.76, 6.94, and 4.76% increase in the daily counts of confirmed cases, respectively, suggesting a significant relationship between air pollution and COVID-19 infection. We summarize this association in selected countries including in the United States of America, Italy and the United Kingdom especially since April, although the significance of this association is unclear (Fig. 4).

In asthmatics, several studies have demonstrated a reduction in air pollution-induced asthma exacerbations. Indeed, studies have shown a marked reduction in the levels of air pollution namely levels of PM_{2.5}, CO₂, and NO₂ which are important risk factors for asthma exacerbations, since the implementation of lockdown [29,30]. This tendency is observed in most of the countries (Fig. 4). Socioeconomic status and race are also suggested risk factors of COVID-19 due to the crowded living conditions, multigenerational homes, limited access to health-care, lack of healthy foods and clean water and chronic exposure to air pollution [31]. While the lockdown may have a positive effect in host-environmental interactions by protecting asthmatics from exposure to outdoor air pollutants, as mentioned by Taquechel *et al.* [10]. By contrast, there is an increased risk of exposure to indoor air pollutants.

IMPACT OF ASTHMA TREATMENT ON CORONAVIRUS DISEASE 2019

Corticosteroids both inhaled and systemic play a significant role in asthma management. In other viral infections including Middle East respiratory syndrome (MERS) [32], SARS, and influenza [33], especially when the infection is severe, it has been suggested that systemic steroid therapy may lead to worsening of the clinical outcomes by inhibiting the production of the critical antiviral mediators including type I and III interferons [34]. Similarly, the corticosteroid use in asthmatic patients in a context

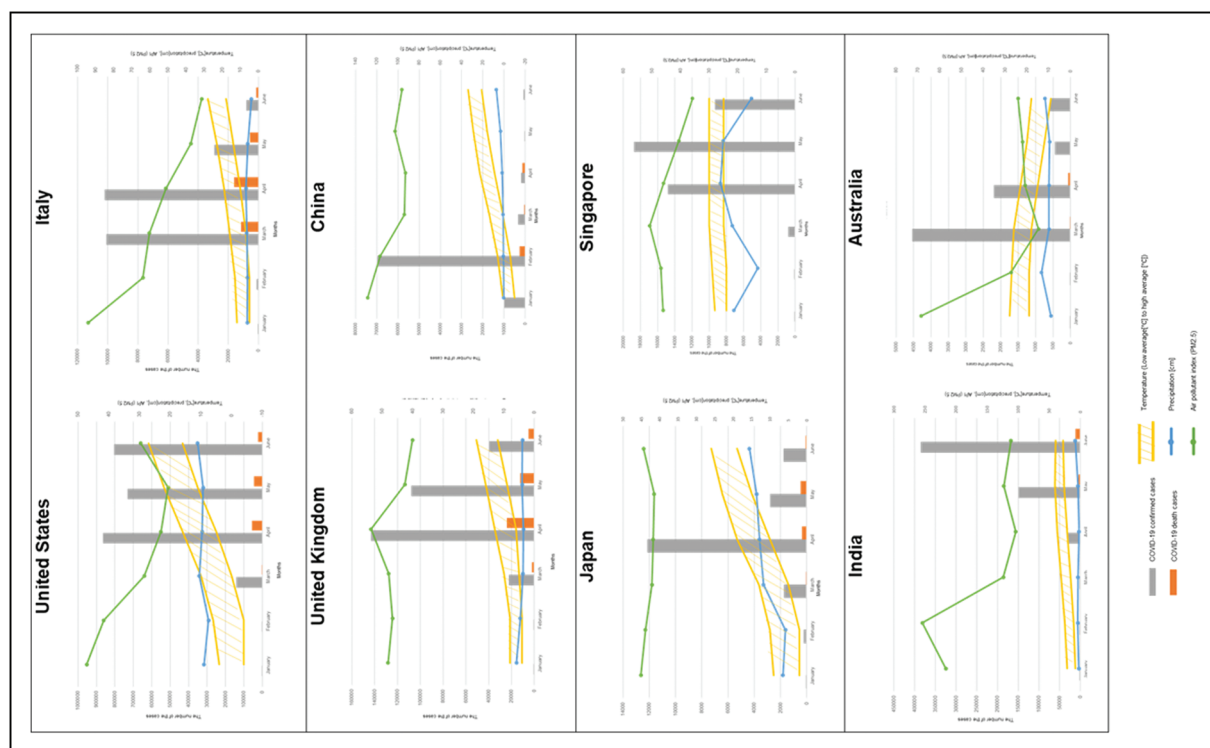


FIGURE 4. (a)–(h) The impact of environmental factors on severe acute respiratory syndrome coronavirus 2.

of COVID-19 may restore type 1 immunity against SARS-CoV-2 by suppressing over-activated type 2 immunity in asthmatics [34]. Recently, it has been suggested that the peak of the viral load of SARS-CoV-2 is observed within the first week from onset of symptoms while that of SARS-CoV and MERS-CoV was observed in the second week from onset of symptoms [35]. In the RECOVERY trial [36[■]], better outcomes were observed in hospitalized patients receiving respiratory support and treatment with systemic dexamethasone in the 2nd week from onset of symptoms, while non superior or possibly harmful outcomes were observed in hospitalized patients not receiving respiratory support but receiving the steroid in the first week since the onset of symptoms. These findings suggest the possible correlation between the viral load and the balance of risk–benefit of systemic steroids. Ciclesonide, an inhaled corticosteroid has been shown to have anti-viral properties against respiratory viruses including SARS-CoV-2, MERS-CoV, HCoV-229E, and SARS-CoV *in vitro* [37]. Its antiviral effect is likely exerted by blocking coronavirus RNA replication by targeting viral NSP15 [38[■]]. In addition, just like other corticosteroids in general, its anti-inflammatory effects suppress respiratory inflammation. Indeed, the clinical improvement of COVID-19 with Ciclesonide has been reported in the several case reports in which the Ciclesonide were used in patients with

COVID-19 but without asthma [39,40], suggesting a positive effect of Ciclesonide on COVID-19 infection. It could also suggest the possibility that these positive effects may potentially protect asthmatics on Ciclesonide from severe COVID-19. Globally, asthma guidelines advocate the continued use of inhaled steroids for asthmatics and intranasal steroids for patients with allergic rhinitis.

Severe asthma has been demonstrated to be a major risk factor of COVID-19-related death [41], and management of patients with severe asthma during the COVID-19 pandemic is a challenge. Several patients with severe asthma are also on biological therapies like anti-IL-5, anti-IL-4 and Omalizumab (anti-IgE). Some significant effects in the reduction of the duration of RV infection, viral shedding and risk of RV illnesses in children has been demonstrated with these biologics [42] but whether this is also seen in COVID-19 is unclear. Eosinophils have been implicated in antiviral immunity in preclinical studies, and eosinopaenia is reported in over half of the patients with COVID-19 leading to poor prognosis. [43,44] The implications during the pandemic are unknown but current recommendations is to continue the administration of these biological therapies during the COVID-19 pandemic. For patients with severe asthma who are infected by SARS-CoV-2, the decision to maintain or postpone biological therapy until the patient

recovers should be based on recommendations of the treating clinical team case by case.

CONCLUSION

With the continued spread of COVID-19 globally, it is crucial to better elucidate the potential risk factors for virus infection and for disease severity. COVID-19 has a mortality risk which is particularly high in the elderly, obese and those with underlying cardiovascular, respiratory, and metabolic comorbidities. It also seems to have greater adverse effects in certain ethnic populations, related to race, low socioeconomic status, comorbidities, or differences in susceptibility. Although asthmatics and those with allergies are more susceptible to viral infections, interestingly, asthma has not been found to be a major comorbidity of COVID-19. This can be partly explained by the molecular mechanisms of allergy that may have protective effects against COVID-19. On the other hand, it is still unclear whether the same holds true for nonallergic asthma. Further studies are needed to better understand the relationship between asthma and COVID-19 but also other respiratory allergic diseases and COVID-19. Further studies are warranted on the relation between COVID-19 and different phenotypes of asthma.

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Conflicts of interest

There are no conflicts of interest.

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