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Environmental contributions to the interactions of COVID-19 and asthma: A secondary publication and update

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ABSTRACT

An outbreak of coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) started in Wuhan, Hubei Province, China and quickly spread around the world. Current evidence is contradictory on the association of asthma with COVID-19 and associated severe outcomes. Type 2 inflammation may reduce the risk for severe COVID-19. Whether asthma diagnosis may be a risk factor for severe COVID-19, especially for those with severe disease or non-allergic phenotypes, deserves further attention and clarification. In addition, COVID-19 does not appear to provoke asthma exacerbations, and asthma therapeutics should be continued for patients with exposure to COVID-19. Changes in the intensity of pollinization, an earlier start and extension of the pollinating season, and the increase in production and allergenicity of pollen are known direct effects that air pollution has on physical, chemical, and biological properties of the pollen grains. They are influenced and triggered by meteorological variables that could partially explain the effect on COVID-19. SARS-CoV-2 is capable of persisting in the environment and can be transported by bioaerosols which can further influence its transmission rate and seasonality. The COVID-19 pandemic has changed the behavior of adults and children globally. A general trend during the pandemic has been human isolation indoors due to school lockdowns and loss of job or implementation of virtual work at home. A consequence of this behavior change would presumably be changes in indoor allergen exposures and reduction of inhaled outdoor allergens. Therefore, lockdowns during the pandemic might have improved some specific allergies, while worsening others, depending on the housing conditions.

Keywords: Asthma, Allergic rhinitis, COVID-19

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INTRODUCTION

In December 2019, an outbreak of coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) occurred in Wuhan, Hubei Province, China. Several underlying conditions have been associated with the virus, and whether underlying asthma is associated with worse COVID-19 outcomes has been extensively analyzed.[1]

ASTHMA AND ALLERGIES

Epidemiology

Patients with chronic inflammatory airway disease such as asthma are proposed as a high-risk group for severe COVID-19 by different international health authorities[2] due to the fact that many respiratory viral infections increase the risk of asthma exacerbations. However, current evidence is contradictory on the association of asthma with COVID-19 and associated severe outcomes. In the beginning of the pandemic, several observational studies in China indicated that asthma prevalence among COVID-19 hospitalized patients was low or close to the expectancy for the general population.[3,4] However, subsequent studies have shown contrasting results. Broadhurst et al found a 12% prevalence of asthma among 436 COVID-19 hospitalized patients admitted to the University of Colorado Hospital in the United States.[5] Asthma was not found as an independent risk factor for intubation among hospitalized patients with COVID-19, even after adjusting for well-known risk factors for severity.[3] In the United Kingdom, data from 75 463 patients and 258 participating health-care facilities (ISARIC study) led to conclude that asthma patients were more at risk of needing intensive care unit (ICU) admission. Of note, only those with severe asthma had increased mortality compared to those without an underlying respiratory condition. Patients with asthma and older than 50 years had a lower mortality risk if they had used inhaled corticosteroids within 2 weeks of admission. In a Korean nationwide cohort, allergic rhinitis, and asthma, especially nonallergic asthma, confers a greater risk of susceptibility to SARS-CoV-2 infection and severe clinical outcomes of COVID-19.[6] Also, in Korea, asthma comorbidity was associated with poor prognosis of coronavirus disease.[7]

A systematic review from all reports on COVID-19 published since its emergence in December 2019 to June 30, 2020 looked into the description of asthma as a premorbid condition, which could indicate its potential involvement in disease progression. The authors found 372 articles describing the underlying diseases of 161 271 patients diagnosed with COVID-19. Asthma was reported as a premorbid condition in only 2623 patients accounting for 1.6% of all patients. As the global prevalence of asthma was 4.4%, they concluded that either asthma was not a premorbid condition that contributes to the development of COVID-19 or clinicians/researchers were not accurately describing the premorbidities in COVID-19 patients.[8]

The systematic review of Liu et al included 131 studies (410 382 patients) and concluded that prevalence of asthma was highly variable among COVID-19 patients, ranging from 1.1% to 16.9%. Patients with asthma have a lower risk of death compared with patients without asthma (RR, 0.65; 95% CI, 0.43–0.98). Asthma was not associated with a higher risk of intubation or mechanical ventilation (RR, 1.03; 95% CI, 0.72–1.46).[9] Moreover, a recent metanalysis indicated that subjects with asthma and COVID-19 had a marginally higher risk of hospitalization (pooled relative risk 1.13, 95% CI 1.03–1.24) but not for severe disease, ICU admission or mortality.[10]

In another systematic review and meta-analysis to explore the literature and collate data comparing the mortality of COVID-19, mortality data from patients with and without asthma were summarized in using a random-effects model. A meta-analysis of data from 744 asthmatic patients and 8151 non-asthmatic patients from the 5 retrospective studies meeting the inclusion criteria indicated that the presence of asthma had no significant effect on mortality (OR = 0.96; 95% CI 0.70–1.30; $p = 0.79$).

A descriptive analysis of other clinical outcomes indicated no difference in the duration of hospitalization and the risk of intensive care unit (ICU) transfer between asthmatic and nonasthmatic patients. In conclusion, preliminary data indicate that asthma as a comorbidity may not increase the mortality of COVID-19.[11]

As observed in the ISARIC study, corticosteroid treatment of asthmatic patients may reduce the risk of COVID-19 severe symptoms, and this has been proposed as a possible explanation for a protective effect of asthma to suffer COVID-19. In a Phase II randomized controlled trial (RCT), it was found that irrespective of being asthmatic, treatment of recently diagnosed asthmatic adults with COVID-19, was associated with lower rates of hospitalization or emergency care attendance (3% vs 15%).[12] Then, a Phase III RCT also found benefit on adding inhaled corticosteroids to conventional treatment for mild COVID-19 in high-risk groups because it shortened time to recovery.[13] In their review, Liu et al suggested that in addition to the conventional therapeutics for asthma, including inhaled corticosteroids, allergen immunotherapy and anti-IgE monoclonal antibody may reduce the risk of asthmatics suffering from COVID 19 through alleviating inflammation or enhancing antiviral defense.[9]

Effect of viruses including SARS-CoV-2 infection on asthma pathogenesis

SARS-CoV-2 infection results in a multi-organ inflammatory response where the tropism of the virus is barely known. The interaction of virus proteins such as spike protein (S protein) with angiotensin-converting enzyme 2 (ACE2) as its host cell entry receptor has been clearly described.[10] Also, ACE2 distribution in different organs could explain its multi-organ affinity. ACE2 has been observed in the lung, trachea, small intestine, kidney, pancreas, and heart,[11] but it is rarely expressed in immune cells.[12,13] Similarly, TMPRSS, CD147 (BSG), cyclophilins (PPIA and PPIB), CD26 (DPP4) have also been described as molecules related to the interaction of SARS-CoV-2 with organs or cells.[14] It is known that the respiratory system is a major target of SARS-CoV-2 and its has been identified in different lung cells (ie, basal, ciliated, club, and AT2) and trachea (epithelial goblet and ciliated cells).[11] However, it has been reported that the response to SARS-CoV-2 occurs with a significant component of immune-mediated disease (virus-independent immunopathologic process) as a primary mechanism in severe disease.[15] Therefore, it is important to know the interaction of SARS-CoV-2 with the components of the immune system related to asthma.

Different respiratory viral infections (rhinovirus, respiratory syncytial virus, and influenza), but not coronaviruses, are common triggers of asthma exacerbations in children and adults and are the main cause of recurrent wheezing in children which is considered as a risk factor for asthma development.[16-19]

However, an original report of more than 72 000 COVID-19 cases from the Chinese Center of Disease Control and Prevention did not identify asthma and respiratory allergy as significant risk factors for severe COVID-19 illness.[20] Poor clinical outcomes were associated with older age and underlying health conditions. In Japan, the prevalence of asthma among COVID-19 patients was not higher than that for the general population.[21] In Israel, a lower COVID-19 susceptibility in patients with pre-existing asthma has been reported.[22]

Although epidemiological relationships between asthma and COVID-19 disease severity are still contradictory, it has been hypothesized that some asthma especially the type-2 phenotype immune signatures may be protective on SARS-CoV-2 pathogenesis.

A possible hypothesis for these unexpected observations is a reduced expression of the cellular receptor for SARS-CoV-2, the ACE2,[10,23] in airway cells, and therefore a decreased susceptibility to infection. This hypothesis was explored by Jackson et al by examining if reduced ACE2 expression in airway cells was associated with asthma and allergy in 3 different cohorts of children and adults:[24] 1) in the Urban Environment and Childhood Asthma (URECA) Cohort they found that allergic sensitization, as well as type 2 biomarkers, were inversely associated to ACE2 expression in the nasal epithelium regardless of asthma status; 2) in adults with allergic rhinitis to cats, they found that allergen exposure by both nasal allergen challenge and environmental chamber exposure were associated to significant reductions in ACE2 expression; and finally, 3) adults with mild asthma not treated with controller therapy underwent allergen bronchoprovocation with dust mite,

ragweed, or cat, which resulted in a significantly reduced ACE2 expression in lower airway epithelium. In contrast, an upregulation of ACE2 expression has been observed in response to infection with HRV-16 in airway epithelial cells obtained from children with asthma and healthy control children.[25] These findings suggested a potential mechanism of reduced COVID-19 severity in patients with respiratory allergies although other factors might modulate the response to COVID-19 in allergic subjects.[24]

Reduced levels of ACE2 transcripts have been associated with allergy and allergen exposure, and high IgE levels, and IL-13 has been shown to downregulate the expression ACE2 on airway epithelial cells.[24,26] Type 2 biomarkers such as allergen specific IgE and fractional exhaled nitric oxide (FeNO) negatively correlates with ACE2 gene expression.[27] Radzikowska et al reported increased expression of the viral activator TMPRSS2, but not ACE2, which increases the possibility of SARS-CoV-2 cleavage in asthmatic bronchi.[14] ACE2 and TMPRSS2 co-expression is inversely related and depends on Type 2 and interferon mediated inflammation, respectively.[28] On the contrary, Peters et al found no differences in ACE2 and TMPRSS gene expression in sputum samples from asthmatics and healthy controls; however, among asthma patients, higher expression of these molecules was associated with male gender, African American race, and history of diabetes mellitus. As expected, the use of inhaled corticosteroids (ICS) was related with lower ACE2 and TMPRSS2 expression.[29]

T cell responses against SARS-CoV-2 have been more related with a cytotoxic response and T helper (Th) 1 or 17 profiles;[30] but most recent evidence supports changes in Th2 responses with contrasting results. Kim et al found that severe COVID-19 is associated with enhanced eosinophil-mediated inflammation when compared to non-critical disease. In addition, analyzing cytokine and chemokine markers, they found that Th2-biased immune responses were more common in the critically ill group. Retrieving scRNA-seq datasets from leukocytes led to know that M2 phenotype and hallmark genes of Th2 responses were significantly raised in the critical group.[31] On the contrary, by measuring T cell responses to viral peptide pools, Shahbaz et al reported that Th2 phenotype was associated with asymptomatic/mild disease, whereas a robust Th17 was associated with severe disease.[32] Accordingly, the authors interpret that Th2 responses may play a protective role in COVID-19 patient.[32] On the other hand, Ward et al found that critically-ill COVID-19 patients have at least a 6-fold reduction of interferon gamma (IFN-γ) levels compared to the control group. In spite that levels of IL-4 and IL-13 were not detectable in these patients, they argue critical outcomes may be connected to Th2 polarization due to the increase of IL-6 and IL-10,[33] 2 cytokines associated with this profile.[34] However, this finding should be interpreted with caution because they are not hallmarks of type 2 responses.

Besides their role on asthma, eosinophils also play a direct role in fighting RNA viruses, as demonstrated by the presence of RNAses inside their granules and endosomal Toll-like receptors (TLRs), including TLR3, TLR7, and TLR9, that detect viral microbe–associated molecular patterns.[35–37] On the contrary, eosinopenia has been a predominant feature in the COVID-19 disease, observed in more than half of the patients at the time of admission to the hospital[3] and in fatal cases.[38] In addition, no eosinophil enrichment into the pulmonary tissue was observed in samples from patients with COVID-19 at early stages of disease[39] or in autopsies.[40] However, particularly in the study by Kim et al, a kinetic pattern of these cells was shown in mild patients and a rapid eosinophilic infiltration into infected lungs was observed within 10 days after symptom onset, in contrast with a delayed but prolonged eosinophil infiltration and a significantly increased eosinophil-mediated inflammation observed in respiratory tracts of severe pneumonic cases. From this, they conclude that during the early stage of viral infection antiviral responses to respiratory viruses by producing reactive oxygen species and eosinophil-derived RNAses could have a role in the progression of the disease.[31] The pathophysiology for eosinopenia in COVID-19 remains unclear but is likely multifactorial.

Carli et al considered the possibility that Th2-predominant eosinophilic asthma might be protective against severe COVID-19.[41] The study carried out by Ferastroanu et al noted that

hospitalization in patients with asthma who arrived at the emergency room with asthma depended on a previous high eosinophil count (≥150 cells/μL). In addition, in case of being hospitalized, development of eosinophilia was associated with decreased mortality.[42] Consistently, in a stratified cohort of asthmatics the expression of the ACE2 in the bronchial epithelium was inversely correlated with peripheral blood eosinophil counts.[43]

ACE2 receptor expression is linked to upregulation of viral response genes in a subset of type 2–low patients with asthma with characteristics resembling known risk factors for severe coronavirus disease 2019 (1). In asthmatics, pre-existing eosinophilia (AEC≥150 cells/μL) was protective from COVID-19-associated admission, and development of eosinophilia (AEC≥150 cells/μL) during hospitalization was associated with decreased mortality. Preadmission AEC influenced the AEC trend during hospitalization. Having a Th2-asthma phenotype might be an important predictor for reduced COVID-19 morbidity and mortality that should be further explored in prospective and mechanistic studies.[43]

Taken together, although the current data are limited, there is little indication that eosinophils have a protective or exacerbating role during SARS-CoV-2 infection. Eosinopenia, however, may serve as a prognostic indicator for more severe COVID-19. The precise mechanisms underlying eosinopenia associated with COVID-19 remain unclear at this time; however, its severity indicator role makes us think that eosinophils may be playing a role in the regulation of the immune response in COVID-19.

Trying to solve whether COVID-19 disease could predispose to asthma exacerbations, there are currently no data to suggest a role for SARS-CoV-2 in the pathogenesis of allergic asthma, since prospective cohort studies are needed for a longer time than leading to the COVID-19 pandemic in order to determine its causation. In COVID-19, IL-6 plays a fundamental role in the development of the systemic inflammatory response[44] and is a factor that should be studied. IL-6 is a multifunctional pleiotropic cytokine involved in regulation of immune responses, acute-phase responses, hematopoiesis, and inflammation.[45]

In allergic response models, allergen-induced IL-6 promotes type 2 and type 17 airway inflammation[28] and it cannot be excluded taking into account the possible antigenic presentation in the inflammatory context or the possible cross-reactivity of the SARS-CoV-2 epitopes with allergens, a potential role of SARS-CoV-2 in asthma.

Comorbidities such as obesity, hypertension, diabetes, cardiovascular disease, and chronic obstructive pulmonary disease have been identified as risk factors for severe COVID-19 illness.[28]

In addition, regarding vaccination, this could also be a risk factor for allergic disease. Nucleocapsid protein vaccination was implicated as a major driver of vaccine-associated pulmonary eosinophilia, although passive transfer of anti-nucleocapsid protein antibody was not sufficient to drive enhanced TH2 disease, suggesting a possible role for anti-nucleocapsid protein-specific T cells. However, so far, no allergic or Th2 reaction induced by vaccination has been reported.

In allergic response models, allergen-induced IL-6 promotes type 2 and type 17 airway inflammation[28] and taking into account the possible antigenic presentation in this inflammatory context or the possible cross-reactivity of the SARS-CoV-2 epitopes with allergens, the appearance of COVID-19 asthma is not impossible. In addition, regarding vaccination, this could also be a risk factor for allergic disease. Nucleocapsid protein vaccination was implicated as a major driver of vaccine-associated pulmonary eosinophilia, although passive transfer of anti– nucleocapsid protein antibody was not sufficient to drive enhanced TH2 disease, suggesting a possible role for anti-nucleocapsid protein-specific T cells. However, so far, no allergic or Th2 reaction measured by vaccination has been reported.

However, from another point of view such as heterologous immunity (HI) where previous infections can alter the immune response to other infections or subsequent antigenic presentations, Balz et al hypothesized that SARS-CoV-2 may show protein sequence homology to allergens, which may generate cross-reactive T-cell epitopes. Their *in silico* analysis revealed numerous candidate

epitopes.[46] Memory T and B cells that recognize allergens could help the immune response against SARS-CoV-2 epitopes. This would provide a significant advantage for patients with allergic asthma over other patients with asthma in combating SARS-CoV-2 infections; however, it cannot be ruled out that this exacerbates the inflammatory response. Further experimental studies are underway to provide supporting functional data and confirm this concept.

In conclusion, the risk of severe COVID-19 could be reduced by type 2 immune mechanisms associated with allergic inflammation. However, the diagnosis of asthma, especially the non-allergic phenotype, may be a risk factor for severe COVID-19. Currently there is limited evidence to support the role of SARS-CoV-2 infection in the pathogenesis of asthma; studies in this field need to be carried out.

These mechanisms associated with type 2 inflammation may reduce the risk for severe COVID-19. Whether asthma diagnosis may be a risk factor for severe COVID-19 especially for those with severe disease or non-allergic phenotypes deserve further attention and clarification. In addition, COVID-19 does not appear to provoke asthma exacerbations and asthma therapeutics should be continued for patients with exposure to COVID-19.

ENVIRONMENTAL EXPOSURES

COVID-19 and pollen allergy

The COVID-19 pandemic has posed a positive impact on the air pollution level, wildlife, and nature. As all human activities came to a halt, a reduction in the air dispersion of particulate matter, and lower NO2 and CO2 emissions have been reported.[47,48]

Ambient air pollution has been associated with susceptibility to respiratory viral infection. It is estimated that a 10 μg/m3 increase of PM2.5 concentration leads to a 3% increase of mortality from nonmalignant respiratory disease.[49,50]

Neutrophil infiltration, monocyte differentiation, and increase Th1 response may contribute to the severity of viral infection and subsequent respiratory disease.[51] Exposure to ozone increases sputum production and modifies cell surface phenotypes of antigen presenting cells in healthy subjects. There is a reduction in lung function (FEV1) of healthy subjects and increased neutrophilic airway inflammation following exposure to ozone.[52,53]

ACE-2 receptor involved in the coronavirus entrance of respiratory epithelial cells is overexpressed under chronic exposure to air pollutants. In fact, air pollution damages the respiratory tract and increases the activity of ACE-2 enzyme, which in turn leads to enhanced uptake of virus.[54,55]

Few studies focused on the impact of airborne pollen on COVID-19, which could be useful to advance future research. One recent paper has studied the relationship between SARS-CoV-2 infection rates and pollen concentrations under different weather conditions in 130 sites in the world. The hypothesis was that high airborne pollen concentrations could promote viral infections because they weaken the immunity system and diminish the antiviral interferon response. Results have shown that infection increased in some places after higher pollen exposition during the 4 previous days.[56]

On the other hand, airborne pollen probably acts as a potent carrier for SARS-CoV-2 transport, dispersal, and proliferation; for example, it has been demonstrated that *Artemisia* pollen is the main vector for airborne endotoxin.[57] These studies are very interesting and require multidisciplinary research.

Further, a clear conclusion cannot be drawn due to limited evidence and hence more research is needed to show how pollen bioaerosols could affect virus survival and spread in communities.[58]

A COVID-19 infected person talking, sneezing, or coughing at distance of 1.8 m can generate a bioaerosol with particles that remain viable in air for up to 3 h which may expose healthy persons near and far the source in a stagnant environment. The bioaerosol contaminates surfaces, which if touched can introduce the virus by, nose, eyes, or mouth and cause disease.[59]

Pollen bioaerosols were recognized as one of the independent factors involved in reducing,

waning, or inhibiting flu-like illness incidence in the Netherlands over the time-period of 2016–2019. The authors found a highly inverse correlation of flu-like incidence every week with solar radiation, total pollen dispersion, and allergenic pollens. However, this is not evidence of cause/effect relationship.[60]

The seasonality of previous flu-like pandemics and studies indicating that airborne pollen has an anti-viral effect could likely impact COVID-19 but this remains to be further explored.[61–63]

Airborne pollen constitutes a significant fraction of bioaerosols and serves as carriers for bacteria and virus.[64] Various bacterial pathogens and fungi transmitted through bioaerosols cause respiratory disease, hypersensitivity reactions and systemic infection. They are influenced and triggered by meteorological variables such as temperature, relative humidity, rainfall, and wind; acting jointly they could explain the effect on COVID-19. SARS-CoV-2 is capable of persisting in the environment and can be transported by bioaerosols which can further influence the transmission rate and seasonality of coronavirus.[65]

Climate change, urbanization, and loss of biodiversity affect sources, emissions, and concentrations of main aeroallergens and air pollutants and are among the most critical challenges facing the health and quality of life of the still increasing number of allergic patients today and in the coming decades.[66]

In addition to phenological changes the intensity of pollinization, earlier start and extension of pollinating season, and increase in allergenicity and pollen production, air pollution has direct effects on physical, chemical, and biological properties of the pollen grains. Changes in composition of inorganic ions are the most abundantly studied and documented chemical effect.

Further studies are required to demonstrate if all these changes could facilitate vírus carriage by airborne pollen and contribute to dissemination of infection.

Effect of changes in environmental allergen exposures on allergy during the pandemic

A general trend during the pandemic has been human isolation indoors due to school lockdowns and loss of job or implementation of virtual work at home. A consequence of this behavior change would presumably be changes in indoor allergen exposures and reduction of inhaled outdoor allergens. However, to properly assess the effects of these changes on allergy, and consequently on asthma, worldwide differences in indoor allergen exposures and the behavior of the inhabitants need to be considered. For example, some countries use wall-to-wall carpets to cover floors in homes (which is usually associated with mite exposure); whereas, others have mostly tiled floors indoors that can be easily kept free of allergens (eg, northern versus southern countries in Europe, respectively). Therefore, lockdowns during the pandemic might have improved some specific allergies, while worsening others, depending on the housing conditions. Also, considerable differences in outdoor exposures can be found worldwide.

For example, some Bedouin population in Southern Israel, of low socioeconomic status, live in large over-crowded families, with poor housing conditions and limited access to health care. Areas among them, the exposure to outdoor allergens was probably not significantly reduced, even during the lockdown.[67]

A Turkish study reported this effect on house dust mite–sensitized children with respiratory allergies during March to May 2020, a period that included a 75-days lockdown from April 3.[68] Mild to moderate asthmatic children with or without allergic rhinitis (n = 165) (from which 61.8% were sensitized to house dust mites), experienced significantly less upper respiratory tract infections and reduced asthma exacerbations compared with the same period in the previous year. On the other hand, nasal symptoms worsened in house dust mite-sensitized asthmatics with allergic rhinitis, which implies the importance of indoor hygiene measures for allergic rhinitis control. This study underlines that staying indoors, presumably with reduction in respiratory tract infections and outdoor pollution due to decrease in traffic-related air pollutants, seem to play a role in asthma control and prevent exacerbations despite continuous indoor allergen exposure.[68] However, house dust mite allergen levels, which correlate with symptoms, bronchial reactivity and pulmonary function,[69] might vary and were not measured. More studies about the effect of

changes in allergen exposures on allergy and asthma during the pandemic, including allergen measurements, are needed to fully assess the effect of isolation on allergy and allergic asthma.

Interactions among air pollution, asthma, and COVID-19

After the emergence of the SARS-CoV-2 respiratory virus (COVID-19), many scientists immediately recognized the potentially catastrophic public health ramifications when simultaneously considering infectious diseases and the influence of air pollution on SARS-CoV-2.[70]

Outdoor air pollution

Air pollution is a significant, yet manageable threat to human health and well-being, and to sustainable development. Air pollution is considered the main preventable health risk that affects all people, although those in more vulnerable situations – people of lower socioeconomic status, sick individuals, the elderly, women, and children – face disproportionate risks.[71]

Recent evidence suggests a positive association between long-term exposure to ambient air pollution and the severity of COVID-19 infection.[72,73] Deek et al consider that populations exposed to both indoor and outdoor environments with high levels of fine particulate matter (PM) show an increased risk for COVID-19 pathogenesis.[74]

The exposure to air pollutants can cause neutrophil infiltration and monocyte differentiation, and increase Th17 cells, which may contribute to the severity of viral infection and subsequent respiratory disease.[75]

Exposure to ozone increases sputum production and modifies cell surface phenotypes of antigen presenting cells in healthy subjects. There is a reduction in lung function (FEV1) of healthy subjects and increased neutrophilic airway inflammation following exposure to ozone.[52,53]

Pollution and respiratory virus exposure, in particular rhinovirus can worsen asthma symptoms and trigger exacerbations.[76]

Public health interventions to control coronavirus disease were accompanied by a reduction in pediatric asthma encounters and systemic steroid prescriptions. Decreased rhinovirus infections may have contributed to this apparent reduction in asthma exacerbations, although changes in criteria air pollutants were not significantly different than historical trends. The findings reinforce the value of preventative measures for asthma control, especially those designed to limit transmission of respiratory viruses.[77,78]

In the case of long-term exposure, the angiotensin-converting enzyme 2 (ACE-2) receptor involved in the coronavirus infection of respiratory epithelial cells is over-expressed under chronic exposure to air pollutants. In fact, air pollution damages the respiratory tract and increases the activity of ACE-2 enzyme, which in turn leads to enhanced uptake of virus.[54,55]

Indoor air pollution

Household air pollution (HAP) affects approximately 2.45 billion people in low- and middle-income countries. Annually, 3.8 million people worldwide die prematurely from diseases attributable to household air pollution.[79]

Home isolation is known to be the most effective prevention method implemented in many countries to fight COVID-19 among healthy and infected individuals with mild symptoms.[80] Thus, poor indoor air quality in households, already an important public health problem, becomes even more relevant now that many individuals are spending more time at home.[71,81,82]

Household air pollution may result from fuel burning (coal, charcoal, wood, agricultural waste, animal manure and kerosene, among others) used for heating or cooking using campfires or stoves with limited ventilation which generates fine particulate matter (PM2.5), black carbon and carbon monoxide, harmful products for human health.[79]

Household cleaning products are also a particularly relevant source of indoor pollution at the present time. Many people are cleaning their homes more often and using stronger disinfectants to reduce viral infection rates, but overexposure to disinfectant chemicals can lead to unintended risks to human health.[83]

Home isolation may cause other health problems if the places used for isolation do not have adequate ventilation.[83,84] Exposure to internal

aerosols and fine particles emitted by a variety of human activities and sources, many with unique physio-chemical and aerodynamic properties, represents another route for airborne pathogens, including SARS-CoV-2.[85]

Understanding the functions of indoor aerosols and their influences on infection is an urgent task for the ongoing scrutiny of SARS-CoV-2 airborne indoor transmission, especially in enclosed public spaces. The bioaerosol contaminates surfaces, which if touched, can introduce the virus by, nose, eyes, or mouth and cause disease.[59] The risk of respiratory viral transmission via aerosols and droplets is influenced by 4 factors: (1) properties of the aerosols or droplets; (2) indoor air flow; (3) virus-specific factors; and (4) host-specific factors.[86] People infected with the virus that causes COVID-19 exhale infectious virus in their breath—and those infected with the Alpha variant (the dominant strain circulating at the time this study was conducted) put 43 to 100 times more virus into the air than people infected with the original strains of the virus. Virus from the nose and mouth might be transmitted by sprays of large droplets up close to an infected person. Loose-fitting cloth and surgical masks reduced the amount of virus that gets into the air around infected people by about half. The study shows that the virus in exhaled aerosols is increasing even more evolving to be better at traveling through the air.[65]

Many sources can generate or resuspend abundant amounts of aerosol particles in indoor air. These include activities involving combustion, such as smoking, cooking, and burning candles, incense, or mosquito coils, as well as non-burning sources such as vacuum cleaning and laser printing.[84–87]

Smoking is one of the most common sources of indoor aerosol emissions. Secondhand smoke represents an important risk factor for children, pregnant women, and other non-smokers. Without adequate natural ventilation, smoking can increase aerosol concentrations in indoor environments and buildings.[88,89]

Semple et al analyzed the levels of fine particles in 110 Scottish households. The median PM2.5 concentrations in households with smokers were 31 μg m^3, approximately 10 times higher than those in homes without smokers, suggesting that members of households with smokers were exposed to high concentrations of PM2.5, especially in houses with inadequate ventilation.[89]

Fuoco et al reported high particulate concentrations in the aerosol streams of electronic cigarettes—higher, in fact, than those measured in traditional cigarettes under the same conditions.[90] Mahabee-Gittens et al postulated that the particles generated by tobacco smoke and electronic cigarettes may facilitate indoor transmission of SARS-CoV-2.[91]

Recent studies have shown that exposure to cigarette smoke particles led to an increased expression of ACE2 and increased hosts' susceptibility to COVID-19 infection.[92]

In many indoor environments, cooking is also recognized as a dominant source of indoor aerosols in terms of exposure to particles.[85]

Wan et al measured PM2.5 levels during and after cooking activities in 12 non-smoking homes with natural ventilation in Hong Kong. The average concentration of PM2.5 increased to 160 μg m^3 in the kitchen, and the airborne particles generated by cooking dispersed quickly, resulting in a PM2.5 concentration of 60 μg m^3 in the living room.[93]

The characteristics of the particles emitted by cooking varied significantly depending on the fuel, oil, and cooking method used. See and Balasubramanian investigated particle emissions from 5 different cooking methods, including steaming, boiling, stir-frying, pan-frying, and deep-frying in a domestic kitchen environment, and found that cooking with oils generated far more particles than cooking with water.[94]

Torkmahalleh et al determined the emission flows of 7 cooking oils, namely: peanut, coconut, soybeans, corn, olive, and canola oils. The results showed that cooking with olive oil and peanut oil produced the highest PM2.5 emission.[95]

Vacuum cleaners can also become significant sources of airborne particles due to their ability to release or resuspend large amounts of small particles in the indoor air.[96]

Emissions by laser printers can also be a main source of aerosols in office environments or in homes where they are present. Koivisto et al compared the particle emissions of 2

monochrome laser printers and 1 color laser printer, finding that the geometric mean diameter of the particles emitted was larger for the color laser printer (79 nm) compared to the monochrome laser printers (32 and 40 nm).[97]

In modern society, candles are used for aesthetic and religious purposes, such as meditation, memorials and ceremonies, usually indoors. Burning candles can be another substantial source of indoor particle emissions.[98]

Afshari et al have shown that burning pure wax candles generated a higher concentration of ultrafine particles (2.4 × 105 cm^3) than smoking, frying meat, cooking on an electric stove, and all other sources of particle emissions tested by the authors.[99]

Wallace et al measured the indoor ultrafine particles (2.3–64 nm) originating from lit candles in a residence. During the quasi-steady state burning period, the average emission rates of ultrafine particles were up to 7.2 × 10 12 particles/min^{-1}, while the total number of particles produced reached an order of magnitude of 10 13 particles/min^{-1} in the room.[100]

Ultrafine particles with sizes around 20 nm, consistent with the sizes of most particles released by burning candles, showed the highest deposition rate in the alveolar region (up to 50%).[101]

Mosquito coils are widely used as insect repellents in th summer. To achieve the desired effects, they are often burnt slowly and indoors, leaving their users exposed to high concentrations of particulate material smaller than 0.35 μm for several hours in unventilated indoor environments.[102]

As a visible source of particle emissions, indoor incense burning also leads to increases in airborne particle concentrations. Frequent indoor incense burning is a source of course (PM10; aerodynamic diameter <10 μm) and fine (PM2.5; aerodynamic diameter <2.5 μm) particles, which may facilitate the transmission of SARS-CoV-2 in indoor environments.[103]

The existence of several indoor sources of fine and ultrafine particles, which can remain suspended and accumulate in the air, and the widespread adoption of sedentary lifestyles in the population in recent years both significantly increase the likelihood of exposure to indoor aerosols, especially in closed spaces with inadequate ventilation.[104,105]

The underlying mechanisms of the adverse health effects of this exposure are believed to mainly involve oxidative stress and inflammation mechanisms. The oxidative stress mediated by airborne particles may be due to the direct generation of reactive oxygen species (ROS) on the surface of particles containing metals or polycyclic aromatic hydrocarbons (PAHs), but mitochondria, cell membranes, phagosomes, and the endoplasmic reticulum also produce ROS after exposure to airborne particles.[106]

ROS can impair the structure and function of bio-macromolecules, including lipids, proteins and DNA,[107] activate signaling pathways and even lead to cell apoptosis or necrosis.[108]

Regarding inflammation, alveolar macrophages and airway epithelial cells are the main sites where inhaled particles are processed, resulting in a synergistic increase in the production and secretion of pro-inflammatory mediators.[109]

Exposure to PM2.5 can lead to development and progression of acute and chronic lung diseases, such as tracheal and pulmonary inflammation, asthma and its exacerbations, and chronic obstructive pulmonary disease (COPD) and its acute exacerbations.[110]

The defense functions of the host's airway epithelium mainly include mucociliary clearance, epithelial barrier functions and the secretion of proteins and peptides with antimicrobial activities. Exposure to PM2.5 impairs these defenses, making the host more susceptible to infections due to defective defense functions, insufficiency and dysfunction of immune cells, and changes in respiratory microecology.[110]

The epithelial barrier can also be impaired by oxidative stress, increasing permeability and allowing invasion by pathogens, which can lead to increased susceptibility to infections.[111]

The expression of the angiotensin-converting enzyme 2 (ACE2), which is the receptor to which SARS-CoV-2 binds and is thus responsible for its entry in host cells.[23] Exposure to internal aerosols

can also worsen the symptoms of infection in COVID-19 patients. Mishra et al reported that exposure to particles can promote greater replication of RNA viruses by suppressing innate immune antiviral response.[112]

Chronic exposure to fine PM can also be a contributing variable interrupting the activation of the hypothalamic-pituitary-adrenal system (HPA) normally associated with altered regulation of circulating glucocorticoids, resulting in inefficient or delayed immune response to COVID-19 infection. This carries important implications for how environmental factors may bring about disproportionately severe COVID-19 infections in populations with low socioeconomic resources.[74]

Recent studies have shown that indoor air microbiomes are diverse and can also have significant impacts on human health. The recognition of airborne microorganisms and how the indoor air microbiome reacts to exposure to a variety of chemicals is also extremely important for building a more comprehensive understanding of indoor air quality.[47]

Exposure to particles also changes the normal microbiota of the respiratory tract, an important natural immune defense to prevent invasion by pathogens or foreign substances.[110,113]

Thus, long-term exposure to household air pollution (HAP), the presence of indoor aerosol particles and the high risk of transmission of respiratory pathogens in the indoor environments to which people are exposed during the pandemic require an urgent assessment, mainly regarding how this exposure may worsen situations related to COVID-19 and the reemerging outbreaks reported in some countries and regions.[114–116]

Dai et al warn about the synergistic effects of these multiple household variables on the development and progression of obstructive respiratory diseases and on deficits in lung function, when compared to individual exposures.[117]

Measures for better ventilation in homes can reduce the great influence of HAP.[112] Risk reduction measures related to indoor environments to prevent chronic respiratory diseases such as asthma and COPD are poorly identified in the current guidelines found for developed countries.[73,74] Although the GINA guidelines recognize HAP as a modifiable risk factor, they do not specify which adverse household sources may need to be addressed.[117]

BEHAVIOUR PATTERNS

Behavior changes during the COVID-19 pandemic

The COVID-19 pandemic has changed the behavior of adults and children globally. The implementation of in-home work for adults and school cancellations for children has forced them to spend more time indoors in the home environment. This had led to changes in physical activity, known to be beneficial in asthma, as well as in allergen and tobacco smoke exposures.[118]

Air quality has improved with the pandemic, although not consistently[119] and children might have less exposure to outdoor pollution that worsens asthma.[120] Also, changes in lifestyle during the COVID-19 pandemic (eg, school lockdowns) can reduce exposure to viruses that cause upper respiratory diseases and exacerbate asthma.[118] The pandemic has disrupted many well-established epidemiological and pathogenetic relationships. For example, the global influenza activity has been reduced; whereas, the spread of human rhinoviruses has not been substantially affected.[121]

In addition, medical care has had changes that impact asthma management control. An advantage of spending more time at home and keeping social distancing, has been a reduced exposure to viruses, which resulted in a reduction of asthma exacerbations.[75] A decrease in asthma-related emergency department visits was observed, presumably due to avoidance of health-care institutions for fear of contracting COVID-19, or due to improved asthma control and reduced exposure to viruses and environmental allergens because of isolation at home.[67,75,118,122,123]

Medication adherence potentially also improved, due to concerns about asthma control during a respiratory illness pandemic. Other changes in medication management, such as use of corticosteroids, might also affect asthma.[118,124] Use of intranasal corticosteroids have been associated with better outcomes in COVID-19.[125]

An Italian survey conducted in a pediatric population with allergic rhinitis and/or asthma assessed changes in symptoms and use of medications during the COVID-19 lockdown. The use of on-demand therapy (salbutamol for asthma and nasal steroids/antihistamine for rhinitis) and basal therapy was markedly lower during the lockdown compared to the same period in 2019. It was observed that 94.1% of asthmatic children with on-demand therapy used less salbutamol, 5.8% required the same use, while no one needed more of this drug compared to the previous year. Among patients with rhinitis, there was a reduction of 51.3% in nasal corticosteroid, 36.4% required the same use, and 12.1% used more nasal therapy than in the previous year. 47.8% of all the enrolled patients used oral antihistamines less frequently, 32.6% reported the same use, and 19.6% use them more frequently compared to the previous year.[126]

A study included 70 557 adult participants from the UK Biobank who were tested for SARS-CoV-2 between 16 March and 31 December 2020 evaluated the effects of AR and asthma on COVID-19 infection, hospitalization and mortality as well as the effects of long-term AR and asthma medications on the risk of COVID-19 hospitalization and mortality.[127]

AR patients of all ages had lower positive rates of SARS-Cov-2 tests (RR:0.75, 95% CI: 0.69–0.81, $p < 0.001$), with lower susceptibility in males (RR: 0.74, 95%CI: 0.65–0.85, $p < 0.001$) than females (RR: 0.8, 95% CI: 0.72–0.9, $p < 0.001$). However, similar effects of asthma against COVID-19 hospitalization were only major in participants aged <65 (RR:0.93, 95% CI: 0.86–1, $p = 0.044$) instead of elderlies.[127]

In contrast, asthma patients tested positive had higher risk of hospitalization (RR:1.42, 95% CI: 1.32–1.54, $p < 0.001$). Neither AR nor asthma had impact on COVID-19 mortality. None of conventional medications for AR or asthma, eg, antihistamines, corticosteroids or β2 adrenoceptor agonists showed association with COVID-19 infection or severity.[127]

The COVID-19 pandemic has also affected socio-economic, physical, and mental health conditions of individuals. A substantial increase in virtual interactions among subjects has occurred due to changes in work conditions, as well as to compensate for home isolation and lack of in-person social interactions.[130] A survey completed by 2683 people from around the globe reported a moderate to severe effect on an individual's social, financial, and mental health conditions during the COVID-19 disease outbreak.[128]

COVID-19 and the future

The current crisis is a fundamental, revolutionary moment of change, and what we do now to minimize and mitigate impacts on the climate by developing, investing, and implementing renewable energy technologies can and will make a difference in the years and decades to come.[129]

There has been a notable worldwide reduction in ambient air pollution during the COVID-19 crisis. The restrictions imposed by the pandemic prevented many deaths due to the impact of ambient pollution. But at the same time, COVID-19 taught us that mortality rates and the speed at which the disease spreads varied widely, being higher in less favored populations.[130]

The distortion of the exposome is directly responsible for the epidemic increase in the prevalence and severity of allergies, asthma, and infectious diseases.[131] Call for action at all levels of organizations, from international climate change agreements to actions by individuals are needed to meet the challenge of mitigating the effects of climate change.[132]

However, for long-term success and sustainability, governments need to be willing and able to prioritize COVID-19 rescue programs that simultaneously push forward the climate agenda, by setting ambitious policies that reflect the scale of the challenge posed by climate change, introducing significant socio-economic reforms in order to generate sustainable opportunities and skills for everyone.[130]

Abbreviations

ACE2, Angiotensin converting enzyme 2; COVID-19, Coronavirus disease 19; GINA, Global Initiative for Asthma; HAP, Household air pollution; PM 2.5, particulate matter 2.5; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2.

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