

## Susceptibility of Patients with Airway Disease to SARS-CoV-2 Infection

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged at the end of 2019 and has resulted in a global pandemic. Viral infections are a known trigger of exacerbations in patients with underlying airway disease. The exact pathophysiology and mechanism of infectivity of SARS-CoV-2 in people with airway disease is not fully understood.

At the time of writing, there were over 1,500 publications on asthma and coronavirus disease (COVID-19), at least 20 systematic reviews on asthma and COVID-19, over 1,000 publications on chronic obstructive pulmonary disease (COPD) and COVID-19, and multiple systematic reviews on COPD and COVID-19. The aim of this global overview was to consider early concerns around susceptibility in airway disease, the key mechanistic and observational studies that changed our understanding regarding susceptibility, and to discuss the most recent large studies that are changing perceptions on the influence of asthma phenotypes on susceptibility to COVID-19.

## Molecular Mechanisms of Susceptibility to SARS-CoV-2

### Immune Modulation in Airway Disease

People with airway disease are at higher risk of respiratory infection; for example, patients with COPD and asthma are more susceptible to influenza (1–3). A major factor may be an altered immune response. Some features of this potential immune dysregulation are relevant to the risk of infection from all respiratory pathogens, including severe

acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

The first barrier of defense against environmental insults and pathogens is the airway epithelium. In patients with airway disease (and smokers), the airway epithelial barrier is often dysfunctional, thus facilitating the entry of viruses into the airways (4, 5). A breach of this barrier is likely to be relevant to SARS-CoV-2, as it is to influenza and other respiratory viruses. Studies addressing human rhinovirus infection found higher viral loads in patients with COPD compared with control subjects, supporting the concept of a deficient innate viral immune response (6). Chronic lung inflammation is common in COPD and can cause an altered adaptive immune response, reducing the antiviral defense of patients.

### Protein Receptors Facilitating Viral Infection of Cells Are at Altered Concentrations in Airway Disease

A key mechanism proposed to alter viral susceptibility in airway disease is the increased expression of protein receptors which viruses use to enter and thus infect cells. For example, ICAM-1, the receptor for rhinovirus entry, is upregulated in patients with COPD (7), asthma (8), and bronchiectasis (9). DPP4 is a transmembrane protein that serves as the receptor for Middle East respiratory syndrome coronavirus (MERS-CoV) and is upregulated in COPD (10). Upregulation of such receptors and proteins partly explains differing host tropism and the potential pathogenicity of the different viruses.

SARS-CoV-2 uses the host protein receptor ACE2 (angiotensin-converting

enzyme 2) to attach itself to the cell (11). The ACE2 receptor is expressed throughout the body, including in the lungs (12). After attachment, there is a cleavage of the SARS-CoV-2 spike protein allowing fusion of the viral and cell membranes, permitting entry of the virus into the cell. This is facilitated by TMPRSS2 (transmembrane protease serine 2), the protease furin, and cathepsins (13). Peters and colleagues studied ACE2 and TMPRSS2 gene expression in sputum cells from 330 patients with asthma and 79 healthy control subjects; they found similar degrees of expression in the two groups (14). However, they did find that male sex, African American ethnicity, and a history of diabetes mellitus were associated with an elevated ACE2 and TMPRSS2 mRNA expression in sputum. They also measured ICAM-1 and found this differed by age and sex, but did not differ in those of African American ethnicity or with diabetes. Interestingly, ICAM-1 was elevated in patients with asthma. They also reported that the use of inhaled corticosteroids (ICS) in subjects with asthma was dose-dependently associated with reduced ACE2 and TMPRSS2 mRNA expression. Bradding and colleagues also assessed ACE2, TMPRSS2, and furin concentrations in people with asthma, but they measured mRNA expression on human bronchial brushes and biopsies (15). Again, they found no difference in ACE2, TMPRSS2, or furin mRNA expression between people with asthma and healthy control subjects.

Several studies have also investigated ACE2 concentrations in people with COPD. Jacobs and colleagues examined lung tissue specimens from 134 subjects and found

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ACE2 mRNA expression was higher in current smokers without airflow limitation and current smokers with COPD (GOLD [Global Initiative for Chronic Obstructive Lung Disease] stages II and III–IV) compared with never-smokers (16). Maes and colleagues studied the mRNA expression of ACE2 in lung resection samples in people with and without asthma, COPD, and asthma/COPD overlap (17). They found ACE2 mRNA expression was increased in current or former smokers with COPD but was unchanged in patients with asthma or asthma/COPD overlap compared with control subjects. Leung and colleagues used cytology from bronchial brushes to demonstrate increased concentrations of ACE2 expression in current (but not former) smokers and patients with COPD (18). Increased ACE2 protein expression in the lower airways of patients with COPD is also supported by a further study involving immunohistochemistry analyses of lobectomy specimens (19).

**Type 2 Inflammation Predisposition Characterizes Response to Infection**

Type 2 inflammation is present in around 50% of patients with asthma and is characterized by the production of proinflammatory mediators, including IL-4, IL-5, and IL-13, with patients displaying raised IgE and eosinophils (20). These cytokines appear to affect the expressions of the protein receptors and cleaving proteins involved in viral cell entry.

Kimura and colleagues showed that IL-13 suppressed ACE2 expression and

increased TMPRSS2 expression in airway epithelial cells from patients with type 2 asthma and atopy (21). ACE2 was found to be negatively associated with type 2 cytokines; conversely, TMPRSS2 was positively associated (21). Work from Jackson and colleagues demonstrated that bronchial allergen challenge in adults with mild asthma led to decreases in ACE2 expression (22). They found that respiratory allergy and controlled allergen exposures were each associated with significant reductions in ACE2 expression, whereas nonatopic asthma was not. Song and colleagues also demonstrated a reduction of mRNA expression for ACE2 in bronchial epithelial cells from patients with allergic asthma (19). Altogether, these findings may suggest a potential mechanism for reduced severity of COVID-19 infection in those with allergic asthma.

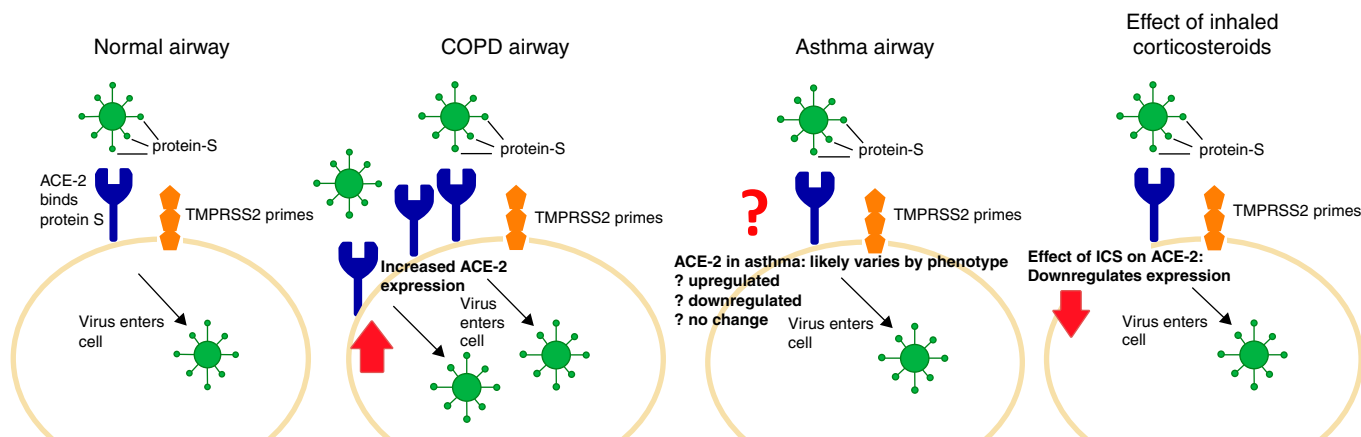
To summarize the data on receptor expression from the above studies, it appears that ACE2 concentrations are upregulated in people with COPD and smokers (16–19) but not in people with asthma (14, 15, 17). However, ACE2 concentrations in asthma vary by phenotype, in which patients with type 2 inflammation and atopy potentially have reduced ACE2 concentrations (19, 21, 22). The mechanism of viral cell entry and difference in receptor expression in airway disease are illustrated in Figure 1.

**ICS May Modulate the Inflammatory Response to SARS-CoV-2**

The immunomodulatory effects of corticosteroids have been the subject of interest

during the COVID-19 pandemic because of the aberrant inflammation caused by the virus. A survival benefit was demonstrated in severe disease in patients receiving intravenous or oral dexamethasone (23). In the early days of the pandemic, there was limited evidence on the use of ICS, and this posed a challenge to clinicians in considering whether to continue patients with airway disease already established on ICS with this therapy. Subsequently, the use of ICS was postulated as a potential mechanism for why patients with airway disease initially appeared to have reduced susceptibility to SARS-CoV-2.

The effects of ICS in patients with airway disease have been studied *in vitro* and *in vivo* for other respiratory viruses, including rhinovirus, in which inhaled budesonide has been shown *in vitro* to reduce replication of rhinovirus and reduce inflammation (24). Coronavirus 229E (HCoV-229E) is a cause of the common cold. Yamaya and colleagues infected human tracheal and nasal epithelial cells with HCoV-229E (25). Pretreatment of cells with budesonide, glycopyrronium, and formoterol reduced the replication of the virus and the production of cytokines (including IL-6, IL-8, and IFN-β) (25). Jeon and colleagues looked into repurposing existing drugs for use in COVID-19 disease and found that inhaled ciclesonide had *in vitro* antiviral activity against SARS-CoV-2 infection (26). A second group also proposes a potentially broad-spectrum antiviral effect of ciclesonide against different members of the coronavirus family; in cultured cells, it blocked the replication of SARS-CoV-2 viral RNA, as



**Figure 1.** A simplified summary of the proposed mechanism of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) cell entry in airways disease. The spike protein on SARS-CoV-2 binds to ACE-2 as an entry receptor in airway epithelial cells and undergoes priming by TMPRSS2. This allows entry into the host cell. There are other proteins also involved not included in the diagram for simplicity. ACE-2 = angiotensin-converting enzyme-2; COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroids; protein-S = spike protein; TMPRSS2 = transmembrane protease serine 2.

well as other coronaviruses, including MERS-CoV (27). A third ICS, mometasone, has also been shown to suppress SARS-CoV-2 viral RNA replication; however, in the same study, dexamethasone and fluticasone did not (27). Interestingly, ciclesonide did not block the replication of respiratory syncytial virus or influenza (27).

Another potential impact of corticosteroids on susceptibility may be related to viral entry protein receptors. ICS have been shown to reduce ACE2 receptor expression *in vitro* and *in vivo* (28, 29). Pulmonary ACE2 expression was investigated *in vitro* in human airway epithelial cell cultures and *in vivo* in mouse models of ICS administration (28). ICS administration decreased ACE2 expression in mice, in epithelial cell cultures from patients with COPD, and in mouse models of elastase-induced COPD-like disease (28). In addition, patients with COPD who were taking ICS had reduced sputum expression of ACE2 compared with those not using ICS (28).

The DISARM randomized controlled trial evaluated 63 patients with COPD (of whom 43% were current smokers) and compared COVID-19–related gene expression in patients on 12 weeks of combined long-acting  $\beta$  agonists (LABAs) with ICS versus those on LABAs alone (29). The authors found that the ICS + LABA therapy downregulated bronchial epithelial ACE2 expression compared with LABAs alone (29), but there was no effect on the expression of TMPRSS2 or furin. Baker and colleagues evaluated the inflammatory response to SARS-CoV-2 in the nasal mucosa of patients in the STOIC1 (Steroids in COVID) trial and a cohort of SARS-CoV-2–negative individuals (30). Although most of these patients did not have airway disease, it is perhaps interesting to note that inhaled budesonide was used as a treatment for early SARS-CoV-2 infection and found to ameliorate the early and persistently elevated interferon response.

### RCTs of ICS in COVID-19

We searched PubMed between November and December 2021 to identify studies investigating the use of ICS in COVID-19 in patients with airway disease. We searched using the search terms “COVID-19,” “SARS-CoV-2,” “inhaled corticosteroids,” “inhaled glucocorticosteroids,” “asthma,” “COPD,” and “airway disease” published since Dec 1, 2019, in English or translated

into English. Randomized controlled trials on ICS in COVID-19 were mainly population-based studies, and patients with airway disease were often excluded from these trials as they were already using corticosteroids.

Two RCTs in the community treatment of early-stage COVID-19 infection have demonstrated a mild beneficial effect of inhaled budesonide compared with usual care. The PRINCIPLE trial found patients in the budesonide arm who were aged 65 years or older and those aged 50 years or older with comorbidities had a shorter time to self-reported recovery (11.8 d) than those in the control arm (14.7 d) (31). There was no significant reduction in hospital admissions or mortality. The STOIC trial was smaller than PRINCIPLE and had to be stopped early but also recorded a slight benefit; a reduction in urgent medical care visits and time to recovery (32). The study did include 21 patients with asthma, but patients who had had recent use of inhaled or systemic corticosteroids (within 7 d) were excluded. To our knowledge, they did not perform subgroup analyses related to preexisting airway disease.

The CONTAIN RCT evaluated inhaled and intranasal corticosteroids in an outpatient setting in COVID-19, this time studying ciclesonide (33). They also excluded patients who had already been prescribed an ICS. There was no significant difference between the ciclesonide group compared with the placebo group in symptom resolution on Day 7. The study had to end early and consisted of mainly young adults without comorbidities.

Therefore, the role of ICS in COVID-19 in people with or without airway disease remains unclear; influencing factors may include the type of ICS, timing of its use, and phenotype of any underlying conditions.

## Epidemiology of COVID-19 and Airways Disease

The intensity and volume of observational studies related to COVID-19 have been unprecedented. This review has only included those with the lowest risk of bias, large nationwide, population-based studies, and focussed only on adults with airway disease in the categories specified below. Key studies are summarised in Table 1.

### Measurable COVID-19 Outcomes

It has been postulated that patients with airway disease may have a different risk profile for their susceptibility to SARS-CoV-2 infection, development of COVID-19, and risk of adverse consequences. Although some studies have attempted to answer the first two outcomes, to date, these have been limited by the available observational data. To assess acquisition of SARS-CoV-2 infection and progression to COVID-19 would ideally require a population study in which there was individual-level data on the degree of viral exposure. Because of the varied implementation of public health nonpharmacological interventions (NPIs) to reduce transmission, alongside the varied availability and uptake of SARS-CoV-2 testing, most current observational studies assessing the acquisition of infection and/or COVID-19 are at high risk of bias. For example, people with asthma have been found to be more likely to test for SARS-CoV-2 and seek healthcare advice on COVID-19 than the general population (34–36). This may relate to the initial global fear of increased risk in asthma or the similarity of COVID-19 symptoms with asthma (37). Physicians also appear to be more likely to incorrectly suspect a diagnosis of COVID-19 in asthma (34). In this review, we, therefore, concentrate on epidemiological studies addressing severe outcomes from COVID-19 (hospitalization and death). Although these studies still carry the usual biases of observational data, and multifarious, unrecorded use of NPIs may influence the findings, there is, however, a low risk of outcome misclassification.

We have focussed in this review only on large nationwide studies; these studies report outcomes of “hospitalization,” “ICU admission,” or “death.” A limitation of this review, therefore, is that these studies treat such outcomes as one phenotype. It may be, however, that people with airway disease present within these outcomes with different pathology.

### COVID-19 and COPD

At the outset of the pandemic, patients with respiratory conditions were considered to be vulnerable to adverse outcomes (37). Yet the initial case series of hospitalized patients from early, major outbreak centers (Wuhan, Lombardy, and New York) had a noticeable underrepresentation of patients with respiratory disease (38–40). This led to the speculation that people with COPD and

**Table 1.** Summary of Effect Estimates for Severe COVID-19 Outcomes from Key Epidemiological Studies Addressing the Susceptibility of COVID-19 in Airways Disease

Airways Condition	Study Population	Categorization	Outcome		
			Hospitalization	ICU Admission	Death
COPD* OpenSAFELY, Williamson, et al. (Nature) <sup>††</sup>	Community population, United Kingdom N = 17,278,392	All patients with COPDs	NA	NA	Adj. HR = 1.63 (1.55–1.71)
	Hospitalized patients with COVID-19, United Kingdom N = 75,463	All COPD with no ICS All COPD with ICS All patients with COPD	NA NA NA	NA NA Adj. OR = 0.66 (0.60–0.72) Adj. HR = 0.89 (0.68–1.17)	Adj. HR = 1.16 (1.12 – 1.22) Adj. HR = 1.10 (1.04 – 1.16) NA
Aveyard et al. (Lancet Respir Med) <sup>†*</sup>	Community population, United Kingdom N = 8,256,161	All patients with COPD	Adj. HR = 1.54 (1.45–1.63)		Adj. HR = 1.54 (1.42–1.67)
Asthma by treatment OpenSAFELY, Williamson, et al. (Nature) <sup>††</sup>	Community population, United Kingdom N = 17,278,392	Asthma with no recent OCS	NA	NA	Adj. HR = 0.99 (0.93–1.05)
	Community asthma, United Kingdom N = 818,490	Asthma with recent OCS ICS (low or medium dose) ICS (high dose)	NA NA NA	NA NA NA	Adj. HR = 1.13 (1.01–1.26) Adj. HR = 1.14 (0.85–1.54) Adj. HR = 1.55 (1.10–2.18)
ISARIC, Bloom et al. (Lancet Respir Med) <sup>†††</sup>	Hospitalized patients with COVID-19, United Kingdom N = 75,463	Age 16–49 yr <sup>§</sup> No asthma therapy	NA	NA	Adj. HR = 1.17 (0.73 – 1.86)
		SABA ICS only LABA plus ICS Most severe asthma	NA NA NA NA	NA NA NA NA	Adj. HR = 0.99 (0.61 – 1.58) Adj. HR = 0.94 (0.62 – 1.43) Adj. HR = 1.02 (0.67 – 1.54) Adj. HR = 1.96 (1.25 – 3.08)
Aveyard, et al. (Lancet Respir Med) <sup>†*</sup>	Community population, United Kingdom N = 8,256,161	Age ≥50 yr <sup>††</sup> SABA	NA	NA	Adj. HR = 1.16 (0.97 – 1.38)
	Community population, United Kingdom N = 8,256,161	ICS only LABA plus ICS Most severe asthma	NA NA NA	NA NA NA	Adj. HR = 0.90 (0.77 – 1.04) Adj. HR = 0.95 (0.82 – 1.11) Adj. HR = 1.24 (1.04 – 1.49) Adj. HR = 0.99 (0.91–1.07)
Bloom, et al. (AJRCCM) <sup>†§§  </sup>	Community population, United Kingdom N = 1,182,675	All asthma	Adj. HR = 1.18 (1.13–1.24)	Adj. HR = 1.08 (0.93–1.25)	Adj. HR = 1.05 (0.96–1.15)
		Active asthma Severe asthma SABA only Intermittent ICS Regular ICS	Adj. HR = 1.26 (1.20–1.33) Adj. HR = 1.29 (1.22–1.37) Adj. HR = 0.94 (0.75–1.17) Adj. HR = 0.90 (0.67–1.21) Adj. HR = 1.27 (1.01–1.61)	Adj. HR = 1.34 (1.14–1.58) Adj. HR = 1.30 (1.08–1.58) NA NA NA	Adj. HR = 1.08 (0.96–1.19) Adj. HR = 1.03 (0.70–1.52) Adj. HR = 0.97 (0.56–1.68) Adj. HR = 1.10 (0.76–1.60)

(Continued)

Table 1. (Continued)

Airways Condition	Study Population	Categorization	Outcome		
			Hospitalization	ICU Admission	Death
Asthma by type 2 Zhu, et al. ( <i>J Allergy Clin Immunol</i> ) <sup>†*§</sup>	Community population, United Kingdom N=492,768	Intermittent ICS + add-on	<b>Adj. HR = 2.00 (1.43–2.79)</b>	NA	Adj. HR = 0.87 (0.46–1.66)
		Regular ICS + add-on	<b>Adj. HR = 1.63 (1.37–1.94)</b>	NA	<b>Adj. HR = 1.70 (1.27–2.26)</b>
Bloom, et al. ( <i>Am J Respir Crit Care Med</i> ) <sup>†§   </sup>	Community population, United Kingdom N=1,182,675	1 GP managed exacerbation	Adj. HR = 1.20 (0.90–1.61)	NA	Adj. HR = 0.73 (0.44–1.20)
		>1 GP/hospital exacerbation	<b>Adj. HR = 1.82 (1.34–2.47)</b>	NA	<b>Adj. HR = 1.66 (1.03–2.68)</b>
Yang, et al. ( <i>J Allergy Clin Immunol</i> ) <sup>   ***†††</sup>	Hospitalized patients with COVID-19, South Korea N=4,090	Allergic asthma	Adj. OR = 1.29 (0.96–1.74)	NA	NA
		Atopy	Adj. HR = 0.97 (0.85–1.11)	NA	Adj. HR = 0.89 (0.71–1.11)
		Eosinophil count	NS association (continuous variable)	NA	NS association (continuous variable)
		Allergic asthma	NA	NA	Adj. OR = 1.40 (0.83–2.41)

**Definition of abbreviations:** BMI = body mass index; COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease; GP = general practitioner; HR = hazard ratio; ICS = inhaled corticosteroids; LABA = long-acting β agonists; NA = not applicable; NS = nonsignificant; OCS = oral corticosteroids; OR = odds ratio; SABA = short-acting β agonists. Bold values represent statistically significant effect estimates.

\*In OpenSAFELY and ISARIC, COPD was included in patients with a chronic respiratory condition that was not asthma.

†Reference group is all other community patients within the database.

‡Adjusted for age, sex, ethnicity, socioeconomic status, BMI, smoking, hypertension, chronic heart disease, diabetes, liver disease, cancer, kidney disease, dementia, other chronic neurological disease, rheumatological conditions, organ transplant, and other immunological disease.

§Reference group is patients hospitalized without an underlying chronic respiratory condition.

||Adjusted for age, sex, ethnicity, socioeconomic status, obesity, smoking, chronic cardiac disease, chronic kidney disease, and malignant neoplasm.

¶Adjusted for age, sex, ethnicity, socioeconomic status, region, BMI, smoking, hypertension, diabetes, liver disease, chronic neurological disease, coronary heart disease, stroke, atrial fibrillation, chronic kidney disease, and all other respiratory diseases.

\*\*Reference group is patients with asthma not on ICS.

††Adjusted for age, sex, ethnicity, socioeconomic status, BMI, smoking, hypertension, heart disease, diabetes, cancer, kidney disease, immunosuppressive conditions, and oral steroids.

†††Reference group is patients with asthma without therapy.

§§Adjusted for ethnicity, index of multiple deprivation, obesity, cardiac disease, diabetes, chronic renal disease, cerebrovascular disease, and cancer. Matched on age, sex, and GP practice.

|||The outcome is a composite of death or ICU admission.

\*\*\*Adjusted for age, sex, ethnicity, and BMI.

\*\*\*\*Reference group is propensity score-matched patients hospitalized with COVID-19 without allergic asthma.

††††Adjusted for age, sex, region of residence, history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, COPD, hypertension, chronic kidney disease, Charlson comorbidity index, use of immunosuppressants, use of systemic glucocorticoids, allergic rhinitis, and atopic dermatitis.

asthma were protected and that the commonality between them, ICS, may be the explanation (41). The reason for the initial lack of COPD recording in these populations is unclear but could be because of undiagnosed (common in China [42]) or underreported COPD or owing to effective NPIs in this higher-risk group. Much larger and more robust epidemiological studies then followed, particularly from the United Kingdom, including a prospective cohort of hospitalized patients from multiple centers (ISARIC [International Severe Acute Respiratory and emerging Infection Consortium]), a huge cohort of community patients drawn from national electronic medical records covering 40% of the population (OpenSAFELY) and a third cohort of community patients. All three studies, using different populations and data sources, found COPD to be a significant risk factor for COVID-19 mortality (43–45); furthermore, mortality increased with more severe COPD (46, 47). However, the odds of mechanical ventilation were lower for COPD as compared with hospitalized patients without an underlying respiratory condition (adjusted odds = 0.49; 95% confidence interval [CI], 0.43–0.57;  $P < 0.0001$ ), whereas patients with asthma had no significant difference in their odds of mechanical ventilation (adjusted odds = 1.07; 95% CI, 0.97–1.18;  $P = 0.207$ ), the reason for this is unclear (46). Neither found inhaled corticosteroids to be protective in patients with COPD.

### COVID-19 and Asthma

**Asthma is considered a homogenous condition.** In the preceding respiratory pandemic, the H1N1/influenza A outbreak in 2009, around one-quarter of patients hospitalized had asthma (48). Viruses are a common trigger for asthma exacerbations, and people with asthma are at a much greater risk of severe outcomes from common cold viruses than those without asthma. On the basis of this evidence, it was postulated by the CDC and World Health Organization that people with asthma would be vulnerable to severe COVID-19. Yet, studies defining asthma as a single homogenous condition have found asthma to be neither protective nor detrimental for severe COVID-19 outcomes (49). Even in the 2009 influenza pandemic, although asthma was highly prevalent in patients hospitalized, it was not associated with poor outcomes (48). This lack of association with adverse outcomes may be

because most COVID-19 studies have considered “asthma” as a single disease. Studies that tried to phenotype patients with asthma suggest different findings and are the focus of this review.

**Asthma by disease management.** The first large population study to consider categorizing asthma by treatment, OpenSAFELY, classified adults as either “asthma” or “severe asthma” (43). Severe asthma was defined as a prescription for oral corticosteroids in the past year. This group, although not meeting asthma guideline definitions of severe asthma, was found to have a slightly increased risk of COVID-19–related death. The ISARIC respiratory study of hospitalized patients with COVID-19 applied a broader asthma classification on the basis of inhaled medication use in the two weeks before admission. In this study population, recent use of ICS was found to reduce mortality in adults aged 50 years and older, possibly as use occurred after acquisition of COVID-19, except in those with the most severe asthma (46). Further evidence came from two other large observational studies, an OpenSAFELY study and a study using an alternative smaller database of United Kingdom electronic medical records (45, 47). Although neither study was directly designed to address asthma phenotypes, they both indicated that higher doses of asthma medication were associated with a greater risk of death. The studies were also limited by lack of secondary care data (47) or by a very loose definition of severe asthma (single prescription of a reliever and combination inhaler in the year prior) (45). Recently, more robust phenotyping has been possible, using a different United Kingdom database of electronic medical records (covering 20% of the population) linked to hospital records and Public Health England testing data. This more granular phenotyping found higher use of asthma maintenance medication (either by frequency of use or type of medication), and a history of frequent asthma exacerbations were significantly associated with hospital admission, ICU admission, and death from COVID-19 (34).

Interestingly, patients using biologics for severe asthma do not appear to be at greater risk of severe COVID-19 outcomes (50, 51). A large study from Israel found biologics were not associated with severe COVID-19 outcomes (50). In contrast, the use of oral corticosteroids was associated with poor outcomes (50). Putting together

the lack of association with biologics but significant association with frequent use of maintenance medication and exacerbations may suggest that achieving asthma control is critical to reducing severe COVID-19 outcomes, although the impact of NPIs was not quantified in these studies.

### Asthma by type 2 inflammation.

Studies have also phenotyped patients with asthma by the presence or absence of markers of type 2 inflammation. Two large studies using alternative sources of United Kingdom data, biobank data (self-reported atopy), and electronic medical records (including doctor-reported atopy and blood eosinophil counts in asthma and allergic rhinitis without asthma), found no association with severe COVID-19 outcomes and markers of raised type 2 inflammation (34, 52). A third study, using South Korean administrative healthcare data, also found no significant risk with allergic asthma (53). Neither the biobank study nor the South Korean study accounted for asthma severity.

### Comparing COVID-19 with Pneumonia and Seasonal Influenza

Three large studies from the United States, France, and Germany conducted before COVID-19 vaccination programs found an overall excess mortality from COVID-19 compared with that from seasonal influenza (54–56). This disparity in case fatality rate may be influenced by differences in the pathogenicity of the viruses, healthcare provision, or the host response, owing to the age and underlying comorbidities of those infected and the availability of an influenza vaccine. Yet, in patients with underlying respiratory conditions, there is a higher prevalence of COPD and asthma in those hospitalized with influenza than those with COVID-19 (48, 55, 56). A large French study specifically addressing people with chronic respiratory disease found COPD and asthma contributed to a much higher proportion of patients hospitalized with influenza but a lower proportion of in-hospital deaths compared with COVID-19 (57). Of those admitted to the ICU, asthma contributed to a higher proportion of COVID-19 than influenza, whereas COPD contributed to a much lower proportion of ICU admissions for COVID-19 than influenza. The finding of reduced COPD ICU admissions in France parallels COVID-19 data from the United Kingdom (46). However, the French study only reported unadjusted estimates even though there were significant differences

(by age, sex, and comorbidities) in the COVID-19 study population compared with the influenza study population. The United Kingdom asthma phenotyping study used the same study population to compare COVID-19 hospitalization rates to influenza and pneumonia hospitalization rates in the year prior. They found the same high-risk patient groups (those with higher medication use or frequent exacerbations), after adjusting for known risk factors, to be at similar degrees of relative risk of hospitalization for COVID-19 as for influenza and pneumonia, although there were much higher total numbers of COVID-19 hospitalizations (34). This finding suggested that although COVID-19 was a relatively more prevalent disease in the time periods assessed, the same phenotype of asthma patient has a significantly elevated risk for all three acute respiratory infections.

Host and viral factors determine patterns and severity of infection and disease. It, therefore, follows that the host response to

SARS-CoV-2 differs compared with its response to other respiratory viruses. At the point of infecting the host cell, as discussed above, SARS-CoV-2 uses different receptors and cleaving proteins (ACE2) to other viruses, such as rhinovirus, which uses ICAM-1, and influenza, which uses sialic acid. Influenza tends to target the pulmonary epithelial cells, from the trachea to the bronchioles and alveoli. Epithelial cells with high ACE2 expression, the target of SARS-CoV-2, appear to be more prevalent in the nasal epithelium of the upper respiratory tract than in the more distal airways (58). Inflammatory pathways and repair responses appear to differ between the different viruses, which is particularly relevant in patients with airway disease who already have impaired and altered defense mechanisms such as mucociliary clearance or a predisposition to a type 1 or type 2 inflammatory response, as discussed above.

Healthcare behavior and government strategies such as shielding may also play a

role. The approach has been different to SARS-CoV-2 compared with seasonal influenza. This is, however, beyond the scope of this review.

## Conclusions

With the rollout of vaccination programs, many people have a reduced risk of developing severe COVID-19. Nonetheless, with vaccine hesitancy, limited vaccine access, and variant breakthroughs, there remains a continuing need for therapeutic options. Ongoing studies to identify the vulnerability of those with airway disease and further research into the mechanisms of susceptibility will enable us to better identify and manage those most at risk. ■

**Author disclosures** are available with the text of this article at [www.atsjournals.org](http://www.atsjournals.org).

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