

**Reply to Chen et al.***From the Authors:*

We appreciate comments and questions raised by Chen and colleagues for our paper about associations between air pollution exposure and coronavirus disease (COVID-19)-related severity and mortality (1). For the first question regarding residual confounding, we went back and extracted information from our electronic medical records on whether the patients had each of the following diseases by International Classification of Diseases codes before the COVID-19 diagnosis: diabetes, hypertension, cancer or metastatic carcinoma, renal disease, asthma, chronic obstructive pulmonary disease, myocardial infarction, and congestive heart disease. We replaced Charlson Comorbidity Index by these diseases' indicators (yes vs. no for each) in the model as covariates. This alternative analysis resulted in similar estimates of the associations between air pollution and COVID-19 severity and mortality and did not change our study conclusions. The corresponding multipollutant adjusted odds ratios (95% confidence intervals [CIs]) associated with a 1-SD increase in 1-year particulate matter ≤ 2.5 μm in aerodynamic diameter ($\text{PM}_{2.5}$) (SD, 1.5 $\mu\text{g}/\text{m}^3$) were 1.24 (1.16–1.32) for COVID-19-related hospitalization, 1.32 (1.19–1.47) for intensive respiratory support (IRS), and 1.31 (1.15–1.50) for ICU admission; the odds ratios (95% CIs) associated with 1-month NO_2 (SD, 3.3 ppb) were 1.12 (1.06–1.17) for hospitalization, 1.18 (1.10–1.27) for IRS, and 1.21 (1.11–1.33) for ICU. The hazard ratios (95% CIs) for mortality were 1.14 (1.02–1.27) for 1-year $\text{PM}_{2.5}$ and 1.08 (0.99–1.17) for 1-month NO_2 .

For the second question regarding interaction with patients' age, we have already tested the interactions and presented stratified results by age groups, sex, and race/ethnicity in our published paper in supplementary Tables E5–E7 (1). We did not find statistically significant interactions between age and 1-month NO_2 and 1-year $\text{PM}_{2.5}$ exposures. However, the effect sizes of the associations were generally larger for hospitalization, IRS, and ICU for age ≥ 65 years (supplemental Table E5 in Reference 1).

For the third question regarding mortality, we restricted the time window within 60 days after COVID-19 diagnosis to minimize the potential misclassification of the death due to other health issues or

life-threatening accidents. Causes of death were generally not recorded in electronic medical records and claim-based records; thus, we would not be able to specifically restrict the mortality due to COVID-19. Determining whether a patient died of or with COVID-19 requires in-depth medical record review and adjudication of cause of death. Adjudication review was outside the scope of this study. However, all these patients had COVID-19 diagnosis within 60 days before death, and we have adjusted for major preexisting comorbidities as mentioned above. ■

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Reference

- Chen Z, Sidell MA, Huang BZ, Chow T, Eckel SP, Martinez MP, et al. Ambient air pollutant exposures and COVID-19 severity and mortality in a cohort of COVID-19 patients in Southern California. *Am J Respir Crit Care Med* 2022;206:440–448.

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**Susceptibility of Patients with Asthma to a Poor Outcome of COVID-19***To the Editor:*

In their lucid review, Conway and colleagues (1) imply inconsistent cell mechanisms, virus receptors, and T2 inflammation as regards coronavirus disease (COVID-19) occurrence in asthma, including effects of corticosteroids. Observations with rhinovirus,

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coronavirus229E, and influenza are also included (1). An early innate antiviral airway response, unrevealed by cell studies, is not mentioned.

Asymmetry of Airway Epithelial Barrier

Conway and colleagues iterate that epithelial barrier breaks in asthma facilitate viral infections (1). However, it needs underscoring that “bedside” data, by contrast, reveal normal absorption rates of inhaled molecules (2). Paradoxically, bronchial exudation of plasma macromolecules simultaneously characterizes asthma (2, 3). Such dual, direction-dependent epithelial barrier properties are also observed in infected and in experimentally challenged human airways (3). Importantly, elevated plasma protein concentrations on airway mucosal surfaces of human airways require no barrier breaks but reflect noninjurious physiological microvascular–epithelial cooperation (3). The question arises, what does this dramatic epithelial barrier asymmetry mean for innate defense opportunities?

Features of Plasma Exudation as First-Line Airways Defense Response

Ubiquitous, superficial microcirculations supply oxygenized blood to the mucosa of the human nose, trachea, and bronchi. Extravasation of plasma from these vessels is controlled by autacid-mediated, reversible formation of gaps between endothelial cells. Clinical challenge data indicate that epithelial passage of bulk plasma proteins promptly follows. The epithelial transmission of macromolecules reflects direction-specific yielding of elastic cell junctions of pseudostratified epithelium. Neither mucosal edema nor increased lymphatic protein transport is observed (3).

Although plasma exudation offers specificity by location and duration, its molecular content does not. Lack of size selectivity of plasma exudation (3) means that potent cascade systems (complement, kinin/kallikrein, coagulation), natural antibodies (IgG, IgM), pentraxins, and more would emerge and get activated locally on engaged airway epithelial surface sites. Cathelicidine, representing antimicrobial peptides, may exclusively be a component of exuded plasma in asthma (3).

Plasma exudation is a baseline asthma feature (2, 3). Reflecting its nonsieved nature, large plasma proteins, including fibrinogen, alpha2-macroglobulin and IgM, exude along with albumin (3, 4). Hence, plasma exudation may contribute baseline antimicrobial defense in asthma. The caveat is that inhaled microbes then need to deposit on the same discrete mucosal sites where plasma exudation occurs.

Plasma Exudation at Viral Infection

Common cold (coronavirus229E and rhinovirus)–induced nasal plasma exudation agrees with bronchial plasma exudation in influenza A and B (3, 5). Without causing epithelial injury or reduced barrier function, nonsieved plasma protein exudation lasts until infection resolves (3, 5).

Epithelial Loss, a Feature of Asthma Potentially Worsened by COVID-19

Experimental, nonsanguineous, asthma-like patchy denudation *in vivo* evokes local plasma exudation. Thus, exuded plasma

promptly covers the naked membrane with a fibrin/fibronectin gel and creates a biological milieu suited for defense and speedy epithelial regeneration. All types of epithelial cells bordering a denuded patch dedifferentiate into fast-migrating regeneration cells. As soon as a first cellular barrier is established, exudation stops, and the gel is shed (*see* references in References 2 and 3). At denudation, local plasma exudation would contribute both barrier and defense/repair milieu consistent with bedside observations of unreduced epithelial barrier in this desquamatory disease (2, 3).

Effects of Treatment

Inhaled corticosteroids have not reduced inflammatory challenge–induced airway plasma exudation (3), suggesting unimpeded humoral innate defense. Inhaled corticosteroids also do not affect susceptibility to COVID-19 (1).

Gustafson and colleagues demonstrated that oral corticosteroids inhibited rhinovirus-induced nasal plasma exudation. Simultaneously, viral titers were increased (6). Inasmuch as plasma exudation in conducting airways impedes the march of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to the lung (2, 3), these data agree with nationwide epidemiology studies singling out treatment with oral corticosteroids as a risk factor for severe COVID-19 in asthma (1, 3). Furthermore, the inhibition of plasma exudation did not reduce runny nose indices (6), consistent with plasma exudation being a low-volume response strictly restricted to infected spots. ■

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References

- Conway FM, Bloom CI, Shah PL. Susceptibility of patients with airways disease to SARS-CoV-2 infection. *Am J Respir Crit Care Med* 2022; 206:696–703.
- Persson C. ‘Bedside’ observations challenge aspects of the ‘epithelial barrier hypothesis’. *Nat Rev Immunol* 2021;21:829.
- Persson C. Early humoral defense under the radar: microvascular-epithelial cooperation at airways infection in asthma and health. *Am J Physiol Lung Cell Mol Physiol* 2022; 322:L503–L506.
- Van Vyve T, Chanez P, Bernard A, Bousquet J, Godard P, Lauwerijs R, *et al*. Protein content in bronchoalveolar lavage fluid of patients with asthma and control subjects. *J Allergy Clin Immunol* 1995;95:60–68.
- Winther B, Gwaltney JM Jr, Humphries JE, Hendley JO. Cross-linked fibrin in the nasal fluid of patients with the common cold. *Clin Infect Dis* 2002; 34:708–710.
- Gustafson LM, Proud D, Hendley JO, Hayden FG, Gwaltney JM Jr. Oral prednisone therapy in experimental rhinovirus infections. *J Allergy Clin Immunol* 1996;97:1009–1014.

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