has limitations, including a single-center design, its relatively small sample size, and the lack of data on viruses at exacerbation to confirm the mechanism of exacerbation reduction. Our study also has unique strengths in that we could perform symptom and exacerbation assessments in a standardized fashion within a cohort established before the pandemic.

In summary, social distancing measures during the first 12 months of the COVID-19 pandemic were associated with a marked reduction in bronchiectasis exacerbations but no change in individual chronic respiratory symptoms. ■

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Long-Term Exposure to Particulate Matter Air Pollution and Chronic Rhinosinusitis in Nonallergic Patients

To the Editor:

Chronic rhinosinusitis (CRS) is a debilitating condition affecting millions of adults and is associated with depression, anxiety, impaired sleep, and low quality of life (1). Although its pathogenesis remains unclear, recent epidemiological studies have implicated environmental exposures in CRS (2). Indeed, airborne particulate matter $\leq$2.5 μm in aerodynamic diameter ($PM_{2.5}$) exacerbates lower airway conditions causing inflammation (3). Whether $PM_{2.5}$ has similar effects in the upper airway, as might be expected by the "unified airway" concept, has not been demonstrated. In prior mouse studies, we found that $PM_{2.5}$ exposure causes type 2 eosinophilic sinusitis, but human data are limited (4). Thus, the purpose of this study was to determine whether airborne $PM_{2.5}$ exposure is associated with the development of CRS. Data were extracted from the outpatient otolaryngology clinics at an academic medical center and analyzed via a case–control approach. The study was approved by the institutional review board of the Johns Hopkins University School of Medicine.

Cases were defined as new patients aged $\geq$18 years diagnosed with a CRS ICD-10 code by a board-certified otolaryngologist using nasal endoscopy and computed tomography (CT) scans. Patients who gave a history of environmental allergy were excluded. Two control subjects without such diagnosis codes and with clear sinus CT scans were selected for each case using the nearest neighbor strategy to match for age, sex, race, and date of CRS diagnosis. Clinical characteristics were extracted, together with the onset of CRS, defined as diagnosis date. Ambient $PM_{2.5}$ exposure levels were estimated based on validated prediction models (5). Briefly, machine learning approaches that incorporated meteorological measurements, land-use terms, satellite-based measurements, and simulation outputs from a chemical transport model were used to predict daily $PM_{2.5}$ concentrations. We calculated mean $PM_{2.5}$ exposures for each patient based on their residential address postal code at 12, 24, 36, and 60 months before the diagnosis date. A Bayesian space-time downscaler model was used to estimate daily ozone (8-h max) exposure using monitoring data from the National Air Monitoring Stations and Local Air Monitoring Stations.

Conditional logistic regression models were used to determine the association between long-term $PM_{2.5}$ exposure and CRS. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were obtained by adjusting for covariates and potential confounding factors

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Table 1. Demographic and Clinical Characteristics of Participants

Characteristics	Control Subjects (*n = 4,068*)	Patients with CRS (*n = 2,034*)
Age, yr	51.9 ± 17.4	51.1 ± 16.0
Sex, M	1,771 (43.5)	840 (41.3)
Race		
White	2,694 (66.2)	1,333 (65.5)
African American	861 (21.2)	425 (20.9)
Hispanic/Latino ethnicity	177 (4.4)	110 (5.4)
Other	336 (8.3)	166 (8.2)
12-mo $PM_{2.5}$ average, $\mu g/m^3$	9.9 ± 1.9	10.1 ± 1.7
24-mo $PM_{2.5}$ average, $\mu g/m^3$	10.2 ± 2.0	10.4 ± 1.9
36-mo $PM_{2.5}$ average, $\mu g/m^3$	10.4 ± 2.1	10.6 ± 1.9
60-mo $PM_{2.5}$ average, $\mu g/m^3$	10.7 ± 2.1	10.9 ± 1.9
12-mo ozone average, ppb	40.8 ± 2.1	40.7 ± 1.8
24-mo ozone average, ppb	41.0 ± 1.9	41.1 ± 1.6
36-mo ozone average, ppb	41.0 ± 1.9	40.9 ± 1.5
60-mo ozone average, ppb	41.0 ± 2.2	40.9 ± 1.8
BMI, kg/m^2		
Underweight (<18.5)	136 (3.3)	32 (1.6)
Normal weight (≥18.5 to <25)	1,491 (36.7)	623 (30.6)
Overweight (≥25 to <30)	1,265 (31.1)	643 (31.6)
Obese (≥30)	1,176 (28.9)	736 (36.2)
Current smoking status		
Never-smoker	1,245 (30.6)	608 (29.9)
Current smoker	2,353 (57.8)	1,357 (66.7)
Former smoker	478 (11.8)	172 (8.5)
Current alcohol consumption	1,237 (30.4)	505 (24.8)
Hypertension	1,610 (39.6)	974 (47.9)
Diabetes mellitus	435 (10.7)	179 (8.8)
COPD	136 (3.3)	47 (2.3)
Asthma	356 (8.8)	303 (14.9)
Nasal polyps	0 (0.0)	82 (4.0)

Definition of abbreviations: BMI = body mass index; COPD = chronic obstructive pulmonary disease; CRS = chronic rhinosinusitis; $PM_{2.5}$ = particulate matter ≤2.5 μm in aerodynamic diameter.
Data are shown as mean ± SD or *n* (%).
The *P* values for differences of means of proportions comparing the CRS and control groups were calculated using one-way ANOVA for continuous variables and chi-square test for categorical variables.

including age, sex, race, body mass index, alcohol consumption status, smoking status, hypertension, diabetes, chronic obstructive pulmonary disease, and asthma. We used 5 $\mu g/m^3$ as the scale to facilitate comparison with previous studies. To determine if any associations were specific to anatomy, we examined CRS subtypes based on anatomy involved as secondary outcomes, including chronic maxillary, frontal, ethmoidal, and sphenoidal sinusitis, based on sinus CT scans. We also examined severe disease (presence in all four sinuses). Statistical analyses were conducted using STATA (version 16.0; Stata Corp.) and R (version 4.1; R Development Core Team).

A total of 6,102 subjects met inclusion criteria: 2,034 cases and 4,068 controls, 90% residing in the Northeast. Age, sex, and race were similar between groups (Table 1). The mean (SD) $PM_{2.5}$ exposures during the 12-, 24-, 36-, and 60-month periods before diagnosis were 10.1 (1.7), 10.4 (1.9), 10.6 (1.9), and 10.9 (1.9) $\mu g/m^3$, respectively. Cases had a higher prevalence of obesity (36.2% vs. 28.9%) and current smoking (66.7% vs. 57.8%).

CRS was more likely to be diagnosed in patients exposed to higher concentrations of $PM_{2.5}$ across all windows of exposure (e.g., 12 months; OR, 1.29; 95% CI, 1.07–1.55 per 5-$\mu g/m^3$ $PM_{2.5}$ increase; Table 2). This association was present across all anatomic locations, particularly for ethmoid sinusitis (OR, 2.90; 95% CI, 2.00–4.21 for each 5-$\mu g/m^3$ 12-month $PM_{2.5}$ increase). When evaluating severe sinusitis involving all four sinuses, there was a progressive increase in the odds of developing CRS peaking at 36-month exposure (OR, 4.65; 95% CI, 1.37–15.73 for each 5-$\mu g/m^3$ 60-month $PM_{2.5}$ increase).

In this study, we demonstrate that long-term $PM_{2.5}$ exposure is significantly associated with CRS diagnosis, especially in the ethmoid sinus, which anatomically has the most airflow, and in the most severe cases. Our study provides the strongest evidence to date that $PM_{2.5}$ exposure is associated with CRS in a well-characterized cohort, consistent with mouse models, supporting a role for long-term $PM_{2.5}$ exposure in causing eosinophilic rhinosinusitis. In addition, these associations were robust after adjusting for ozone. These data are consistent with prior studies that used less strict inclusion criteria (self-reported CRS), had unclear timing of disease onset, or examined other settings (established disease). For example, Bhattacharyya used the National Health Interview Survey to identify an association between air quality improvements and the declining prevalence of self-reported sinusitis (acute or chronic) (6). Mady and colleagues correlated $PM_{2.5}$ levels to an increased need for sinus surgery and medication use in patients with established CRS (7). Others have demonstrated that patients with CRS exposed to higher $PM_{2.5}$ levels had sinonasal biopsies with increased eosinophilic inflammation (8). Soldiers exposed to dust and air pollution in combat zones show increased sinonasal disease rates (9).

Strengths of this study include a large, well-defined patient population (objective testing, otolaryngologist diagnosis); matching strategy for controls, who had clear sinus imaging; adjustment for confounding variables; and assessment of exposure with high spatial and temporal resolution.

There are several limitations. Our retrospective design has inherent weaknesses related to coding accuracy, inability to assess causality, and potential sampling bias. Our $PM_{2.5}$ exposure model relied on mapping to the patient's residential address but did not account for other exposures (commuting, work) or indoor exposures. In addition, data on occupational or environmental exposure to allergens or the use of medications were not available. Lastly, subgroup analysis for severe disease was limited by a small sample size, reducing precision in our associations, and may suffer from inadequate matching.

To our knowledge, this is the first study to report that long-term exposure to fine particulate matter air pollution increases the odds of developing CRS, particularly the most severe form of the disease. Ultimately, identification of environmental determinants of inflammatory disease in the upper airway may provide new strategies to mitigate resultant effects and justify public health interventions, such as the use of $PM_{2.5}$ filtered facemasks, to reduce the enormous burden of this condition. Potential therapies directed at the antioxidant transcription factor, Nrf2, may warrant further investigation based on the previous human *in vitro* studies demonstrating restoration of ambient PM-induced sinonasal epithelial cell barrier disruption by Nrf2 activation (10). ■

Table 2. Conditional Logistic Regression Analyses for the Association between Long-Term $PM_{2.5}$ Exposure and Diagnosis of CRS

Pollution	Model 1*	Model 2†	Model 3‡
CRS ($N = 6,102$)			
$PM_{2.5}$ 12-mo	1.18 (0.99–1.41)	1.26 (1.05–1.52)	1.29 (1.07–1.55)
$PM_{2.5}$ 24-mo	1.43 (1.18–1.73)	1.54 (1.26–1.88)	1.56 (1.28–1.91)
$PM_{2.5}$ 36-mo	1.25 (1.03–1.53)	1.33 (1.08–1.63)	1.35 (1.10–1.66)
$PM_{2.5}$ 60-mo	1.34 (1.08–1.67)	1.42 (1.13–1.77)	1.44 (1.15–1.81)
Maxillary sinusitis ($n = 4,092$)			
$PM_{2.5}$ 12-mo	1.35 (1.09–1.68)	1.39 (1.11–1.74)	1.41 (1.12–1.77)
$PM_{2.5}$ 24-mo	1.69 (1.33–2.14)	1.76 (1.37–2.25)	1.77 (1.38–2.28)
$PM_{2.5}$ 36-mo	1.50 (1.17–1.91)	1.54 (1.20–2.00)	1.55 (1.20–2.01)
$PM_{2.5}$ 60-mo	1.58 (1.21–2.06)	1.60 (1.21–2.12)	1.61 (1.22–2.14)
Frontal sinusitis ($n = 1,644$)			
$PM_{2.5}$ 12-mo	1.18 (0.83–1.69)	1.30 (0.90–1.88)	1.28 (0.88–1.87)
$PM_{2.5}$ 24-mo	1.41 (0.96–2.09)	1.57 (1.05–2.35)	1.59 (1.06–2.40)
$PM_{2.5}$ 36-mo	1.45 (0.97–2.18)	1.62 (1.07–2.46)	1.64 (1.07–2.51)
$PM_{2.5}$ 60-mo	1.26 (0.81–1.97)	1.40 (0.89–2.22)	1.43 (0.90–2.28)
Ethmoidal sinusitis ($n = 1,851$)			
$PM_{2.5}$ 12-mo	2.49 (1.77–3.51)	2.74 (1.91–3.94)	2.90 (2.00–4.21)
$PM_{2.5}$ 24-mo	2.81 (1.91–4.13)	3.09 (2.06–4.63)	3.39 (2.23–5.15)
$PM_{2.5}$ 36-mo	2.85 (1.92–4.24)	3.05 (2.01–4.62)	3.31 (2.15–5.08)
$PM_{2.5}$ 60-mo	2.87 (1.85–4.43)	3.04 (1.92–4.81)	3.27 (2.03–5.25)
Sphenoidal sinusitis ($n = 948$)			
$PM_{2.5}$ 12-mo	1.23 (0.80–1.89)	1.37 (0.87–2.16)	1.43 (0.90–2.28)
$PM_{2.5}$ 24-mo	1.33 (0.80–2.20)	1.50 (0.88–2.56)	1.61 (0.93–2.77)
$PM_{2.5}$ 36-mo	2.16 (1.26–3.70)	2.46 (1.40–4.33)	2.64 (1.48–4.69)
$PM_{2.5}$ 60-mo	1.41 (0.78–2.57)	1.57 (0.84–2.94)	1.68 (0.89–3.17)
Severe sinusitis§ ($n = 369$)			
$PM_{2.5}$ 12-mo	4.00 (1.71–9.34)	3.49 (1.41–8.67)	4.07 (1.53–10.82)
$PM_{2.5}$ 24-mo	3.72 (1.39–9.99)	3.67 (1.24–10.8)	4.30 (1.36–13.61)
$PM_{2.5}$ 36-mo	6.69 (2.98–15.06)	6.80 (2.80–16.55)	7.91 (3.06–20.42)
$PM_{2.5}$ 60-mo	4.06 (1.44–11.48)	3.98 (1.26–12.55)	4.65 (1.37–15.73)

Definition of abbreviations: CRS = chronic rhinosinusitis; $PM_{2.5}$ = particulate matter ≤ 2.5 μm in aerodynamic diameter.
Data are shown as odds ratio (95% confidence interval).
*Adjusted for age, sex, and race.
†Further adjusted for body mass index, current alcohol consumption status, and current smoking status.
‡Further adjusted for comorbidity (history of hypertension, diabetes, chronic obstructive pulmonary disease, and asthma).
§Indicates concomitant chronic maxillary, ethmoid, sphenoid, and frontal sinusitis.

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Interalveolar Pores Increase in Aging and Severe Airway Obstruction

To the Editor:

Interalveolar pores are believed to equalize pressure between adjacent alveoli through collateral ventilation, but their extent, in both aging and lung disease, remains unclear. We recently demonstrated an association between aging and small airway loss (1), but changes in collateral ventilation might form another hallmark of aging. This may especially be true in pathological conditions with severe airway obstruction to prevent retro-obstructive alveolar collapse. Bronchiolitis obliterans syndrome (BOS) after lung transplantation represents a typical airway-centered disease with irreversible obstructive pulmonary function deficit due to obliterative bronchiolitis (2). We therefore provide a detailed assessment of interalveolar communications in a cohort of aging lungs, correlate these findings with terminal bronchiole counts and other physiological and structural parameters related to aging, and assess interalveolar communications in BOS-explant lungs. We hypothesize that aging and BOS are associated with increased interalveolar communications.

Methods

We included 20 unused donor lungs from never-smoking donors, previously used to demonstrate decreased small airway counts in aging (1), and 10 BOS-explant lungs (Table 1). One explant lung was processed as previously described (1), and two initially extracted tissue cores from matched locations from each lung (upper–lower lobe, total $n = 60$) were included and processed for scanning electron microscopy (Philips XL30). Twenty representative images (350× magnification) were obtained per location ($n = 40$/lung); pores were analyzed using open-source FIJI software. Terminal bronchiole counts, Global Lung Function Initiative–predicted FEV_1/FVC ratio, computed tomography–calculated lung volume, mean linear intercept, and surface density results were obtained from the

Table 1. Patient Characteristics

	Aging Cohort	BOS
Patients, *n*	20	10
Donor characteristics		
Age, yr	52.7 ± 20.2	36.9 ± 16.0
Sex, M	15 (75)	4 (40)
Weight, kg	75 ± 12	68 ± 12
Height, cm	173 ± 8	171 ± 9
Cause of death in donor		
Cerebral ischemia	11 (55)	4 (40)
Cardiac arrest	3 (15)	—
Craniocerebral trauma	2 (10)	5 (50)
Suicide	2 (10)	1 (10)
Extrapulmonary tumor	1 (5)	—
Hemodynamic collapse	1 (5)	—
Recipient characteristics		
Age, yr	—	50.4 ± 13.5
Sex, M	—	5 (50)
Weight, kg	—	61.3 ± 18.8
Height, cm	—	168 ± 12
Time to BOS, yr	—	3.11 ± 2.23
Time from LTx to graft loss, yr	—	5.15 ± 2.75
Time from BOS onset to graft loss, yr	—	2.12 ± 1.78
Total graft age, yr	—	42.1 ± 14.8
Pulmonary function*		
FEV_1, L	3.44 ± 0.83	0.61 ± 0.21
FEV_1%	—	19.5 ± 4.9
FVC, L	4.32 ± 0.95	1.79 ± 0.62
FVC%	—	48.7 ± 12.8
FEV_1/FVC	0.79 ± 0.036	0.34 ± 0.056

Definition of abbreviations: BOS = bronchiolitis obliterans syndrome; LTx = lung transplantation.
Data are presented as *n* (%) or mean ± SD.
*For the aging cohort, FEV_1 and FVC values are Global Lung Function Initiative–predicted values; for patients with BOS, the last available pulmonary function test before graft loss was included.

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