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The impact of levels of particulate matter with an aerodynamic diameter smaller than 2.5 μm on the nasal microbiota in chronic rhinosinusitis and healthy individuals

Leena V. Padhye, MD[*], **Jennifer L. Kish, MPH**[†], **Pete S. Batra, MD, FACS**[‡], **Gregory E. Miller, PhD**[†], **Mahboobeh Mahdavinia, MD, PhD**[*]

[*]Division of Allergy and Immunology, Department of Internal Medicine, Rush University Medical Center, Chicago, Illinois

[†]Institute for Policy Research and Department of Psychology, Northwestern University, Evanston, Illinois

[‡]Department of Otorhinolaryngology-Head and Neck Surgery, Rush University Medical Center, Chicago, Illinois

Air pollution, which has been linked to many human diseases, has been associated with changes in the sinonasal and respiratory microbiome in both healthy and diseased states. Ambient particu-late 2 matter (PM) is essentially atmospheric aerosols with adverse health effects depending on their size, and are categorized on the basis of aerodynamic diameter—that is, as particles smaller than 10 μm (PM10), 2.5 μm (PM2.5), and 0.1 μm (ultrafine particles). PM2.5 tends to deposit throughout the respiratory tract and is often composed of combustion particles, organic compounds, and metals less than 2.5 μm.[1] Recently, the levels of particular matter (PM2.5 and PM10) have been both inversely associated with nasal microbiota alpha diversity and linked to pharyngeal microbiome changes in healthy individuals, supporting the role of PM in influencing nasal microbiota.[2] Exposure to PM2.5 specifically is linked to airway inflammation, changes in the lower airway microbiome, and poorly controlled asthma.[3] The concentrations of many air pollutants are elevated in low-income neighborhoods, and we have previously reported that living in low-income zip codes is associated with severe respiratory inflammatory conditions.[4,5]

Our study aimed to assess the role of PM2.5 pollution on the sinonasal microbiome while adjusting for socioeconomic factors. The influence of air pollution on nasal microbiota may be relevant in chronic rhinosinusitis (CRS), because there is evidence that the sinonasal inflammation characterizing CRS is associated with changes to the sinonasal microbiome.[6,7] Furthermore, increased PM2.5 has also been linked to an increased need for surgery in patients with CRS without nasal polyposis.[8] In this study, we also aimed to understand whether exposure to PM2.5 is associated with CRS sinus histopathologic biomarkers.

Mahboobeh_mahdavinia@rush.edu.

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A consecutive series of patients with CRS and healthy controls were recruited from a tertiary rhinology clinic between January 2015 and July 2016. The university's institutional review board approved this study, and all participants provided written informed consent. We geocoded each patient's residential address and, using publicly available data sets, characterized particulate matter and socioeconomic conditions. PM2.5 ($\mu g/m^3$) values were obtained from the EJScreen data set from 2011 prepared by the United States Environmental Protection Agency. These values are derived from monitoring stations and Community Multiscale Air Quality modeling using a Bayesian space-time downscaling fusion model approach. PM2.5 was analyzed at the census tract level of resolution, which corresponds to communities of 1000 to 8000 residents. Socioeconomic conditions were obtained from 5-year averages of the American Community Survey. These indices were at the block group level of resolution, which consists of neighborhoods of 600 to 3000 residents.

As previously detailed,[6] nasal swab samples were collected by application of a sterile small cotton swab to the middle nasal meatus under endoscopic guidance. The microbiome samples were collected 2 to 3 weeks before the collection of the tissue during surgery. Total DNA was extracted from swabs and processed by using high-throughput Illumina amplicon sequencing of the V4 variable region of the microbial 16S ribosomal RNA (rRNA) gene. Each nasal sample was rarefied and analyzed (alpha and beta diversity) at a sequence depth of 4400. Data were then clustered into operational taxonomic units at 97% similarity. Differences in the RA of individual taxa from the taxonomic levels of the phylum to species were determined in a tiered fashion for significance using a Kruskal-Wallis nonparametric analysis of variance test and corrected for false discovery at a 5% rate. Linear regression analysis was performed to investigate the association of PM2.5 with different bacterial genera.

A total of 132 individuals, including 111 patients with CRS and 21 controls, were enrolled for the microbiota study, as previously reported.[6] PM2.5 levels in air ($\mu g/m^3$) were significantly higher in the neighborhoods of patients with CRS vs healthy controls (11.28 vs 10.5; $P < .001$). For all patients, higher levels of PM2.5 were negatively correlated with lower RA of Corynebacterium ($r = -0.197$; $P = .02$). PM2.5 correlated with decreased RA of Corynebacterium in both patients with CRS and control groups when the groups were separated ($P = .02$ and $P = .04$ in CRS and controls, respectively). The RA of bacterial phyla, other bacterial genera, or alpha diversity indices were not correlated with PM2.5 levels. Linear regression analysis adjusting for insurance, race, socioeconomic status index (a composite score, which includes the median household income, median home value, the proportion of adults who were unemployed, and the proportion of adults who had higher than a high school education for the individual's block group), asthma, atopy, age, and CRS duration did not affect these results. As reported previously, the RA of Corynebacterium was decreased in patients with CRS compared with controls.[6] The RA of Corynebacterium in this study is similar to the levels in previous reports.

Among 111 patients with CRS, 71 had undergone sinus surgery, during which the sinus tissue was collected and subsequently for 12 pathologic markers (Table 1). PM2.5 levels were associated with evidence for eosinophilic aggregation in sinus tis-sue; the mean (±SD) PM2.5 levels were 11.43 (±0.15) in cases with eosinophilic aggregates vs 11.05 (±0.53) in

cases without ($P = .01$). Other pathology data were not associated with PM2.5 levels (Table 1).

We propose that air pollution, specifically PM2.5, may be an important factor that influences changes in the nasal microbiota of all individuals including patients with CRS and healthy individuals.

Both groups—patients with CRS and healthy patients—exhibited a decrease in Corynebacterium RA in association with increased PM2.5. Interestingly, decreased Corynebacterium RA is linked to sinonasal inflammation.[6] Corynebacterium has also been implicated as having a protective role in maintaining the stability in the sinonasal mucosa.[9] Studies in animals and in vitro have reported that PM pollution can result in T_H2 allergic inflammation.[3] This is consistent with our results—finding an association between sinus tissue eosinophilia and increased PM2.5. Perhaps PM2.5 affects the sinonasal microbiome by decreasing Corynebacterium, and thereby plays a role in the disruption of sinonasal homeostasis and induction of T_H2 inflammation. The combination of these factors may play a role in the development of CRS in a susceptible individual. Corynebacterium-dominated nasal microbiota was associated with decreased exacerbation in pediatric asthma in addition to decreased risk in respiratory illness.[10] In CRS, those patients with higher RA of *Corynebacterium tuberculostearicum* had better outcomes after endoscopic sinus surgery.[7] Thus, there may be a loss of a potential protective role of Corynebacterium for some individuals living in higher pollution.

To the best of our knowledge, this is the first study to investigate the association of air pollution markers with nasal microbiota, adjusting for multiple socioeconomic factors at the block group level for each individual. Adjusting for asthma and atopy did not affect these results. The data collected were obtained from reputable governmental sources rather than relying on self-reported data, which is subject to numerous biases. The middle meatus was selected as a representation of the sinonasal cavity because the microbiota of the anterior nares is labile. We used the V4 16S rRNA region for analysis, as mentioned by the Earth Microbiome Project; however, we acknowledge that V2–V3 16S rRNA regions are often used for resolution of low-rank taxa. In addition, we did not have sinus tissue from healthy controls, thus limiting the ability to compare PM2.5-related associations in CRS vs healthy patient tissue.

In conclusion, we found that a decreased relative abundance of Corynebacterium in the nasal cavities of all individuals was associated with a higher PM2.5 exposure. Future studies are needed to evaluate the underlying interplay of pollution on the nasal microbiome and its effects on microbiota changes.

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Table 1

The Association of Histopathologic Markers in Sinus Tissue With Levels of Particulate Matter With an Aerodynamic Diameter Smaller than 2.5 μm in Patients With Chronic Rhinosinusitis

Histopathologic marker	PM2.5 concentration (mean ± SD)	*P* value by ANOVA
Eosinophils aggregates		
Yes	11.43 ± 0.15	.01
No	11.05 ± 0.53	
Eosinophil count		
>10	11.22 ± 0.47	.67
<10	11.01 ± 0.58	
Neutrophilic infiltration		
Yes	11.30 ± 0.33	.44
No	11.10 ± 0.53	
Basement thickening		
Mild	11.11 ± 0.46	.24
Severe	10.95 ± 0.45	
No	11.31 ± 0.49	
Subepithelial edema		
Mild	11.10 ± 0.56	.80
Severe	11.31 ± 0.34	
No	11.22 ± 0.42	
Hyperplastic papillary changes		
Yes	11.31 ± 0.28	.41
No	11.14 ± 0.50	
Mucosal ulceration		
Yes	11.42 ± 0.13	.45
No	11.15 ± 0.48	
Squamous metaplasia		
Yes	11.06 ± 0.52	.63
No	11.18 ± 0.47	
Fibrosis		
Yes	11.03 ± 0.50	.06
No	11.34 ± 0.39	
Charcot-Leyden crystals		
Yes	11.35 ± 0.23	.58
No	11.16 ± 0.48	

Abbreviations: ANOVA, analysis of variance; PM2.5, particulate matter particulate matter with an aerodynamic diameter smaller than 2.5 μm.