

RESEARCH NOTE

Long-term particulate matter exposure is associated with the development of nonallergic rhinitis: A case-control study

Zechariah G. Franks MD¹ | Nyall R. London MD, PhD¹ | Stella E. Lee MD² | Shyam Biswal PhD³ | Murugappan Ramanathan Jr MD¹ | Zhenyu Zhang PhD^{4,5}

¹Department of Otolaryngology-Head and Neck Surgery, Johns Hopkins School of Medicine, Baltimore, MD

²Division of Otolaryngology, Department of Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

³Department of Environmental Health Sciences, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

⁴Department of Global Health, The Peking University School of Public Health, Beijing, China

⁵Institute for Global Health and Development, Peking University, Beijing, China

Correspondence

Murugappan Ramanathan Jr, Johns Hopkins School of Medicine, 601 North Caroline Street, JHOC 6263, Baltimore, MD 21287.

Email: mramana3@jhmi.edu

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1 | INTRODUCTION

Nonallergic rhinitis (NAR) has an estimated prevalence of 200 million worldwide and is a broad classification defined by the presence of rhinitis symptomatology without evidence of chronic rhinosinusitis (CRS) or immunoglobulin E-mediated allergic disease. Several categories of NAR have been described with various documented triggers, such as barometric pressure or temperature changes, but many patients have no identifiable exacerbators. Common treatments include intranasal drugs, such as ipratropium, antihistamines, and corticosteroids, as well as surgical therapies, including inferior turbinate reductions and posterior nasal nerve ablations. Unfortunately, many patients are recalcitrant to these therapies, which makes management of this condition challenging.¹ Increased understanding to what leads to the heterogeneous and highly prevalent condition of NAR would facilitate a bet-

ter understanding of clinical conditions, prevention, and treatment.

Growing evidence suggests environmental air pollution may have a notable impact on the upper and lower airways via increased nonallergic inflammation mechanisms.^{2,3} Recent studies have shown how environmental pollution may contribute to allergic rhinitis, CRS,⁴ and anosmia,⁵ but no studies to date have specifically investigated chronic environmental pollutants and their relationship to NAR. Zhang et al demonstrated use of deep learning neural networks that can accurately estimate the long-term levels of particulate matter with an aerodynamic diameter of $<2.5 \mu\text{m}$ ($\text{PM}_{2.5}$).⁶ Using these models and data extracted from outpatient otolaryngology clinics at an academic medical center, we investigated the long-term exposure of $\text{PM}_{2.5}$ levels and their association with NAR via a case-control study.

2 | METHODS

Under institutional review board approval of the Johns Hopkins University School of Medicine, adult patients

Murugappan Ramanathan Jr and Zhenyu Zhang contributed equally to this work.

TABLE 1 Demographics and clinical characteristics of participants

Characteristics	Controls (n = 764)	Cases (n = 191)	p value
Age in years, mean (SD)	47.1 (16.1)	47.1 (15.7)	0.99
Male sex, n (%)	216 (38.5)	73 (39.0)	0.97
Race/ethnicity, n (%)			0.64
Caucasian	398 (70.9)	130 (69.5)	
African American	122 (21.7)	39 (20.9)	
Hispanic/Latino	14 (2.5)	8 (4.3)	
Other	27 (4.8)	10 (5.3)	
PM _{2.5} exposure, mean (SD), $\mu\text{g}/\text{m}^3$			
12 months	9.95 (1.63)	10.21 (1.65)	0.06
24 months	10.15 (1.66)	10.47 (1.70)	0.02
36 months	10.37 (1.72)	10.72 (1.79)	0.02
60 months	10.68 (1.76)	11.09 (1.77)	0.007
BMI, n (%)			0.38
Underweight, <18.5	18 (3.2)	8 (4.3)	
Normal weight, 18.5 to <25	174 (31.0)	46 (24.6)	
Overweight, 25 to <30	169 (30.1)	59 (31.6)	
Obese, ≥ 30	200 (35.7)	74 (39.6)	
Current smoking status, n (%)			0.22
Never smoked	368 (65.6)	124 (66.3)	
Current smoker	62 (11.1)	13 (7.0)	
Former smoker	131 (23.4)	50 (26.7)	
Current alcohol consumption, n (%)	232 (41.4)	80 (42.8)	0.78
Median household income in US\$, mean (SD)	78,522.07 (31,111.81)	73,815.38 (29,513.44)	0.06
Comorbidity, n (%)			
Hypertension	152 (27.1)	39 (20.9)	0.11
Diabetes	54 (9.6)	12 (6.4)	0.23
COPD	17 (3.0)	1 (0.5)	0.10

BMI = body mass index; COPD = chronic obstructive pulmonary disease; PM_{2.5} = particulate matter with aerodynamic diameter <2.5 μm ; SD = standard deviation.

with newly diagnosed NAR by rhinologists across a single health system were identified. Patients diagnosed with NAR were confirmed to have negative allergy testing and to be without comorbid CRS (negative computed tomography findings and rigid endoscopy). Data from 191 patients with NAR were collated and were compared with 764 age- and gender-matched, healthy controls without rhinitis or CRS (1:4 ratio of cases to controls) using the nearest-neighbor propensity score matching strategy for age, sex, and race/ethnicity. Cumulative PM_{2.5} exposure for patients' residential zip code was estimated at 12, 24, 36, and 60 months before the time of diagnosis of NAR by a novel technique incorporating meteorologic measurements, land-use terms, satellite-based measurements, and simulation outputs from a chemical transport model into a deep learning neural networks model. Conditional logistic regression was performed. For detailed Methods, please see the [supporting information](#) online.

3 | RESULTS

Overall, we included 955 patients in our study and identified 191 NAR patients who met the inclusion criteria (Fig. S1) and paired 4 control participants without sinonasal disease per case. We found that patients with NAR were more likely to live in an area with lower household income, and less likely to be diagnosed with hypertension, diabetes, or chronic obstructive pulmonary disease compared with control participants. Mean PM_{2.5} exposure levels were higher in patients with NAR before the time of diagnosis compared with control participants at all measured estimates with a 12-, 24-, 36-, and 60-month mean concentrations (Table 1).

Concentration-response curves with conditional logistic regression model suggested that long-term exposure to PM_{2.5} was associated with an increased risk of

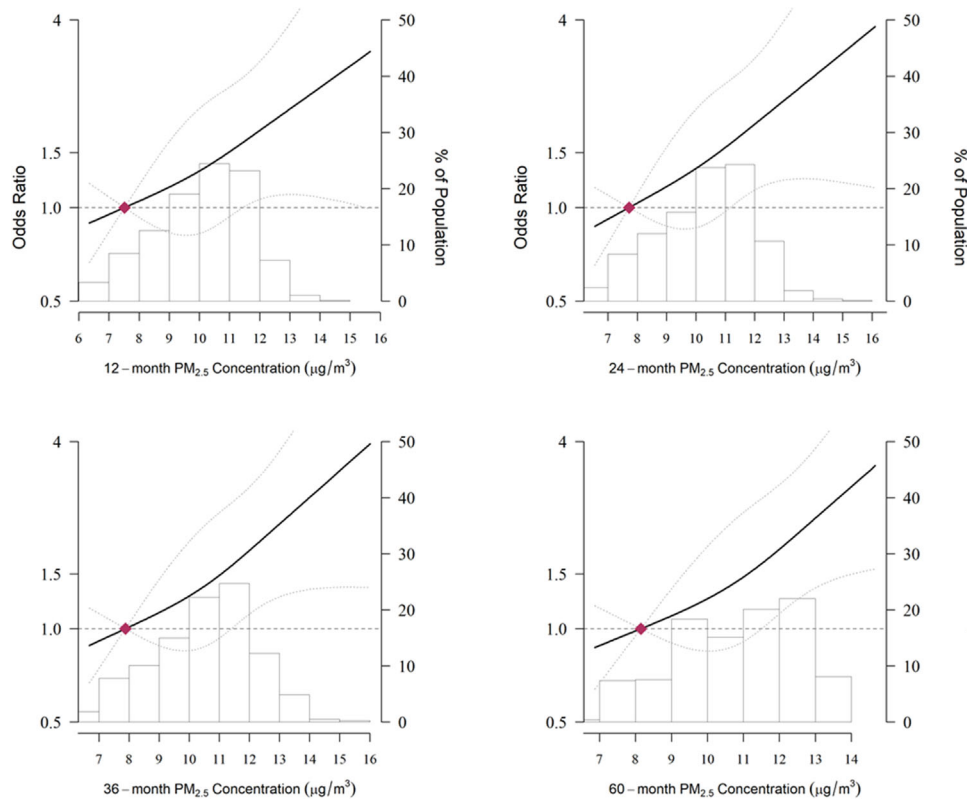


FIGURE 1 Odds ratio for risk of nonallergic rhinitis by the level of exposure to particulate matter with an aerodynamic diameter of $<2.5 \mu\text{m}$ ($\text{PM}_{2.5}$) concentration. Concentration-response curve with conditional logistic regression model suggests that long-term exposure to $\text{PM}_{2.5}$ is associated with an increased development of nonallergic rhinitis. A dose-response curve was calculated using restricted cubic splines with knots at the 10th, 50th, and 90th percentiles of the distribution of 12-month $\text{PM}_{2.5}$ concentrations. The reference exposure level was set at 10th percentile of the distribution of 12-, 24-, 36-, and 60-month $\text{PM}_{2.5}$ concentrations and were 7.52, 7.72, 7.88, and 8.15 $\mu\text{g}/\text{m}^3$, respectively.

developing NAR (Fig. 1). Odds ratios (ORs) were adjusted for age, sex, race/ethnicity, body mass index (BMI), current alcohol consumption status, current smoking status, median household income of zip code of individual's residence, and medical history of hypertension, diabetes, and chronic obstructive pulmonary disease. In the fully adjusted models the ORs for development of nonallergic rhinitis associated with a $5\text{-}\mu\text{g}/\text{m}^3$ increase in 12-, 24-, 36-, and 60-month $\text{PM}_{2.5}$ exposure were 1.99 (95% confidence interval [CI], 1.12-3.54), 2.16 (95% CI, 1.23-3.80), 2.18 (95% CI, 1.27-3.76), and 2.47 (95% CI, 1.42-4.29), respectively (Table S1).

Furthermore, the NAR risks associated with $\text{PM}_{2.5}$ exposure did not differ significantly across various subgroups. No significant interactions were observed with regard to BMI, smoking status, and presence of cardiovascular risk factors, but patients who formerly smoked and patients with hypertension and diabetes tend to have a higher risk of developing NAR compared with control patients (Table S2).

4 | DISCUSSION

Environmental pollutants are a known cause of sinonasal inflammation,² upper airway disease,⁷ and lower airway disease,⁸ and these data are the first of their kind to specifically demonstrate a robust association between long-term $\text{PM}_{2.5}$ exposure and the development of NAR in a large, well-defined patient population with objective testing and otolaryngologist diagnosis. Although several studies have demonstrated an association between $\text{PM}_{2.5}$ and sinonasal inflammation and upper respiratory disease, the pathophysiology linking NAR and $\text{PM}_{2.5}$ remains unclear. Several mechanisms have been proposed to explain the inflammation caused by PM, which include upregulation of gene expression, cytokine upregulation, macrophage alteration, and reactive oxygen species elicitation.^{9,10} Although these studies link sinonasal inflammation and PM, further studies are needed to better understand how $\text{PM}_{2.5}$ mechanistically contributes to the pathogenesis of NAR.

In conclusion, this is the first study to report that long-term exposure to fine particulate matter air pollution increases the odds of developing NAR. Cumulative PM_{2.5} exposure was estimated by novel techniques incorporating patients' residential zip codes into a deep learning neural networks model. PM_{2.5} levels were significantly higher in patients with NAR as compared with healthy controls at 1, 2, 3, and 5 years preceding diagnosis. An increased odds of developing NAR was associated with a 5-μg/m³ increase of PM_{2.5} concentrations over all measured time-points before diagnosis. 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 or air purifiers to reduce the enormous burden of this condition. Given the increasing global burden of air pollution and increasing population density in global urban centers further prospective studies are warranted to define this air pollution and its connection to NAR.

AUTHOR CONTRIBUTIONS

All authors listed made substantial contributions to this manuscript. Z.F., N.R.L., S.E.L., S.B., Z.Z., and M.R. contributed to data analysis, reporting, and drafting the work. Z.Z., M.R., and Z.F. contributed to revising and final approval of the work.

COMPETING FINANCIAL INTERESTS

All authors declare they have no actual or potential competing financial interests.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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