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ORIGINAL ARTICLE

Air pollution exposure is associated with rhinitis in older US adults via specific immune mechanisms

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Abstract

Background: Pathophysiology of rhinitis in older adults is largely unknown. We tested whether air pollution is associated with this condition and how immune mechanisms may play a role in this relationship.

Methods: We analyzed cross-sectional data from the National Social Life, Health, and Aging Project, a nationally representative study of older adults born between 1920 and 1947. Particulate matter ≤2.5 μm ($PM_{2.5}$) air pollution exposure estimates were generated using validated spatiotemporal models. Presence of rhinitis was defined based on medication use (≥1: intranasal medications: steroids, antihistamines, lubricants, and/or decongestants, and/or oral medications: antihistamines and/or decongestants). K-means cluster analysis (Jaccard method) was used to group 13 peripheral blood cytokines into 3 clusters to facilitate functional determination. We fitted multivariate logistic regressions to correlate $PM_{2.5}$ exposure with presence of rhinitis, controlling for confounders, and then determined the role of cytokines in this relationship.

Results: Long- (but not short-) term exposure to $PM_{2.5}$ was associated with presence of rhinitis: 3-year exposure window, odds ratio (OR) = 1.32, 95% confidence interval (CI): 0.98, 1.80, per 1 standard deviation (SD) $PM_{2.5}$ increase. Inclusion of cytokine cluster in the model led to a modestly stronger effect of $PM_{2.5}$ exposure on rhinitis (OR = 1.37; 95% CI: 1.00, 1.87; 3-year exposure window). The particular immune profile responsible for this result was composed of elevated IL-3, IL-12, and IFN-γ (OR = 4.86, 95% CI: 1.10, 21.58, immune profile–$PM_{2.5}$ exposure interaction term).

Conclusion: We show for the first time that IL-3, IL-12, and IFN-γ explain in part the relationship between $PM_{2.5}$ exposure and rhinitis in older US adults. If confirmed, these immune pathways may be used as therapeutic targets.

KEYWORDS
air pollution, innate immunity and rhinosinusitis, particulate matter, rhinitis

1 | INTRODUCTION

Air pollution is associated with increased prevalence of acute rhinitis in urban areas. For example, both short- and long-term exposure to particulate matter ≤10 μm (PM_{10}), particulate matter ≤2.5 μm ($PM_{2.5}$), ozone (O_3), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2) have been linked with increased prevalence of allergic rhinitis.[1,2] Interestingly, children and adolescents are susceptible to these hazardous environmental exposures.[2] In general, these associations tend to be stronger in developing countries compared with developed ones[1] perhaps due to extreme levels of ambient air pollution.[3,4] Little is known about how pollution exposure may affect rhinitis in older adults, where nonallergic forms predominate.

One potential mechanism that may explain this relationship is immune responses generated by the deposition of microparticles on the airway epithelial surface.[5,6] For example, oxidative stress modulates immune response to the T-helper 2 (Th2) and T-helper 17 (Th17) pathways.[7,8] Indeed, diesel exhaust particles are recognized by airway epithelial cells, detoxified by cytochrome P450 family 1-A1, and induce Nrf2 translocation to the nucleus, which increases antioxidant transcription. Failure in this detoxification process leads to production of proinflammatory cytokines (e.g., interleukin [IL]-8, IL-1, IL-6, C-C Motif Chemokine Ligand 20, and tumor necrosis factor [TNF] α).[9,10] This results in chronic inflammation and subsequent airway remodeling in asthmatic individuals.[10] Other mechanisms are possible and those in the upper airway are poorly described, especially in the setting of aging.

How air pollution affects the upper airway of older adults is largely unknown. The immune pathophysiology by which $PM_{2.5}$ causes rhinitis in older adults is largely underexplored. Most of the pathophysiology studies focus on allergic rhinitis in young adults and children, and these mechanisms may differ from the ones responsible for rhinitis (either nonallergic or allergic) in older adults.[10–12] Additionally, large-scale populational studies on the mechanisms by which air pollution results in rhinitis are sparse.

To our knowledge, there are no studies demonstrating which specific cytokines are involved in the generation of rhinitis by outdoor pollution in a large-scale population of older adults. To address this gap, we studied how exposure to air pollution is associated with the use of rhinitis medications and whether systemic immune responses could be detected in a nationally representative cohort of older adults.

2 | METHODS

2.1 | Study population

In 2010–2011 and 2015–2016, professional interviewers from the National Opinion Research Center (NORC) at the University of Chicago conducted in-home interviews with 3377 older adults born between 1920 and 1947 and 4777 respondents born between 1920 and 1965, respectively, a nationally representative sample of the US population of community-dwelling older adults. Measures collected included demographic, socioeconomic, and comorbidity data, along with biological measures. Further details on data collection and analyses are provided elsewhere.[13,14] For the present study, we used data obtained in 2010–2011 (National Social Life, Health, and Aging Project [NSHAP] round 2), where cytokine data were collected using peripheral blood samples. Data on use of rhinitis medication was obtained in 2015-2016 (5 year follow-up)[15] (Figure 1).

Demographic data included age (in years), sex, race (standard National Institutes of Health [NIH] categories), and education (less than high school, high school or equivalent, some college, and bachelor's degree or equivalent). Smoking cigarette status was analyzed as dichotomous variable (yes or no). Data on rhinitis-related medication use were collected using a modified version of the Multum Lexicon Plus drug hierarchy; this included nasal steroids, nasal antihistamines, nasal lubricants, and nasal preparations or decongestants. A list of all medications included in these categories is described in Supplementary Table 1. Additional covariates included geographic region (West, Midwest, South, or Northeast; states included in each region are listed in Supplementary Table 2) and rural–urban commuting area (RUCA) codes, as defined by the US Department of Agriculture (a scale from 1 to 10, where 1 corresponds to metropolitan areas' cores and 10 to rural areas).

The detailed process of collection, transportation, and testing for peripheral blood samples is described elsewhere.[13] Briefly, samples were obtained by interviewers using K2EDTA microtainers in the home, stored at 3°C ± 7°C, transported to an interviewer's field base, and shipped cold overnight to the University of Chicago Flow Cytometry Facility. Cytokine levels were measured using Luminex bead array technology (Luminex 100 device; BioRad, München, Germany) at the University of Chicago Flow Cytometry Facility using standard protocols and BioPlex Manager Software (Version 5, BioRad). The measured cytokines included: IL1rα, 1β, 2, 3, 4, 5, 6, 10, 12,

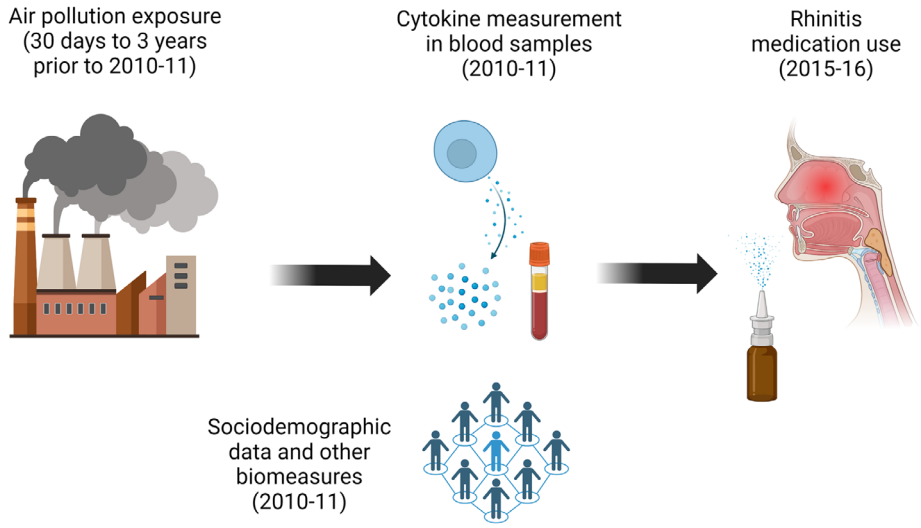

FIGURE 1 Study design.

and 13; vascular endothelial growth factor (VEGF); TNFα; and interferon (IFN) γ.[13]

2.2 | Cluster analyses for cytokine levels

The 12 cytokines were categorized into empiric functional immune profiles. Each cytokine was divided into quintiles based on the actual measured concentration. Values below the detection limit were categorized as the lowest quintile and measurements above the detection limit were included in the highest quintile. We then dichotomized the categorized cytokines in highest quintile (≥80th percentile) versus the remainder of the quintiles. This allowed us to differentiate respondents with elevated levels of cytokines (≥80th percentile) from the ones without elevated cytokines. Lastly, we used the K-means cluster analysis (Jaccard method) to divide the respondents into three functional immune groups.[16,17] The number of clusters was determined by the Calinski–Harabasz (CH) index, a previously validated internal cluster validity method.[18,19] We chose three clusters because it had the largest CH index. A table with CH index values for 2–10 clusters is included in the supplementary materials (Supplementary Table 3). To see whether the selection of the 80th percentile had any influence on the cluster results, we also performed the cluster analysis with continuous values of cytokines, reporting the cytokines' medians in each cluster. The full cluster analysis is shown in Supplementary Table 4.

2.3 | Exposure to air pollution

Ambient exposure to fine particles ($PM_{2.5}$) using the concentration outside each participant's home address averaged for 30, 60, and 90 days and 1, 2, and 3 years prior to each participant's date of NSHAP round 2 data collection (2010–2011). Previously well-validated GIS-based spatio-temporal models were used for this purpose and are described elsewhere.[20] Briefly, $PM_{2.5}$ daily concentrations were estimated for a 6-km grid for the conterminous US. Input variables included $PM_{2.5}$ data from the Environmental Protection Agency (EPA), meteorological and geospatial data, and traffic-related PM point emission (estimated using a Gaussian dispersion model). The model predicted ambient $PM_{2.5}$ concentrations well, with a cross-validation of $R^2 = 0.76$, low bias, and high precision. The mean distance from a model grid point to a participant's residence was 2.23 km.

2.4 | Rhinitis medication variable

Rhinitis medication use was determined from data collected in 2015–2016 and included nasal steroids, nasal antihistamines, nasal lubricants, nasal preparations or decongestants, oral antihistamines, and oral decongestants. The mediations were classified according to a modified version of the Multum Lexicon Plus drug hierarchy. A dichotomized proxy variable for rhinitis was made by older adults that used or did not use these medications. We note that as prevalence of allergic rhinitis decreases with aging, nonallergic rhinitis is much more common in older adults[21,22] although we lack confirmatory testing (negative allergy testing) in this analysis. Thus, we focus here on rhinitis writ large (both allergic and nonallergic forms).

2.5 | Statistical analyses

We restricted our analyses to the older adults in NSHAP with available measured cytokine levels and had

rhinitis medication data available in 2015–2016 ($n = 1839$). We accounted for differential probabilities of nonresponse and selection due to oversampling of African Americans, Latinos, men, and the oldest old using sampling weights and variance estimation by the linearization method. Statistical significance was set at $p < 0.05$, and Stata version 17.0 (StataCorp LLC, College Station, TX) was used to perform statistical analyses.

To explore the relationship of rhinitis and $PM_{2.5}$ exposure, we fitted multivariate logistic regressions, adjusting for potential confounders. We then performed similar regressions with the inclusion of the cytokine cluster group to verify if and how the rhinitis–air pollution relationship changed. We also included an interaction term between $PM_{2.5}$ and cytokine cluster to test whether this immune function variable modified the $PM_{2.5}$–rhinitis relationship. Lastly, the results were reported as odds ratios (OR) and 95% confidence intervals (CI). The OR for $PM_{2.5}$ is in terms of 1 standard deviation (SD) $PM_{2.5}$ increase.

3 | RESULTS

Of the 3377 and 4777 NSHAP respondents interviewed in 2010–2011 and 2015–2016, 1839 older adults had rhinitis medication data and had their cytokine levels measured and therefore were included in our primary analysis according to the modular study design. The demographics of the analytic cohort can be found in Table 1. Of note, 225 respondents (12.2%) reported use of at least one rhinitis medication, with oral antihistamines being the most common ($n = 186$), followed by nasal preparations or decongestants ($n = 55$) and nasal steroids ($n = 42$). The rhinitis respondents' distribution within the clusters was 44, 72, and 109 for clusters 1, 2, and 3, respectively. Short-term $PM_{2.5}$ exposures had higher variability (SD 2.65–2.75, 30–90 days intervals) and lower means (8.21–8.78 $\mu g/m^3$) in contrast to long-term exposures which had higher means (8.69–9.17 $\mu g/m^3$, 1–3 years intervals) and lower variability (SD 2.29–2.40) (Supplementary Table 5). We also performed the same analyses using only nasal medications, which showed the same results (data not shown).

3.1 | Cytokine levels and clusters

Cluster 1 contained the largest number of individuals, mostly without elevated cytokine levels (less than 20% of respondents had elevated TNF-α and IL-1β). In contrast, cluster 2 was primarily composed of older adults with high levels of IL-1rα, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-10, IL-13, VEGF, and TNF-α; these are mostly Th2 cytokines.

TABLE 1 Demographic characteristics of the study sample.

	Frequency (%) or mean ± standard deviation (SD)[a]
Rhinitis medication use (yes)	225 (12.2)
Nasal steroids	42 (2.3)
Nasal antihistamines	11 (0.6)
Nasal lubricants	2 (0.1)
Nasal preparations or decongestants	55 (3.0)
Oral antihistamines	186 (10.1)
Oral decongestants	4 (0.2)
Age (years)	70.6 ± 7.5
Gender	
Males	770 (41.9)
Females	1069 (58.1)
Race/ethnicity	
White	1342 (73.2)
Black	248 (13.5)
Hispanic	204 (11.1)
Other	40 (2.2)
Schooling	
<High school	314 (17.1)
High school	448 (24.4)
Some college	595 (32.3)
Bachelors or more	482 (26.2)
Cigarette smoking (yes)	233 (12.7)

[a]These estimates are unweighted.

Cluster 3 contained respondents with elevated levels of IL-3 (87.9%), IL-12 (67.7%), and IFN-γ (62.9%); interestingly, these are mostly Th1 responses (Table 2).

3.2 | Multivariate logistic regressions

We found suggestive evidence that older US adults exposed to higher long-term levels of $PM_{2.5}$ had increased odds of rhinitis (OR = 1.28 per 1 SD increase in $PM_{2.5}$; 95% CI: 0.98, 1.76; $p = 0.07$ [2-year window] and OR = 1.32; 95% CI: 0.98, 1.80; $p = 0.06$ [3-year window]), accounting for age, sex, race/ethnicity, education, cigarette smoking, body mass index (BMI), country region, and urbanicity. When the cytokine cluster variable was included in the regression, the strength of this relationship was increased (OR = 1.33; 95% CI: 0.99, 1.83; $p = 0.06$; [2 years] and OR = 1.37; 95% CI: 1.00, 1.87; $p = 0.05$; [3 years]) (Table 3).

Our analyses suggested that the cytokine cluster modifies the $PM_{2.5}$–rhinitis relationship (overall Wald test for interaction, two degrees of freedom, $p = 0.04$, 2 years; $p = 0.02$, 3 years). In postestimation analyses, respondents in cluster 3 exposed to higher $PM_{2.5}$ had the strongest

TABLE 2 Characteristics of the cytokine cluster groups.[a]

Cytokine	Cluster 1 ($n = 576$[b])	Cluster 2 ($n = 823$)	Cluster 3 ($n = 440$)
IFN-γ	0	245 (29.8)	**277 (62.9)**
TNF-α	95 (16.5[c])	**329 (40.0)**	97 (22.0)
VEGF	0	**392 (47.6)**	131 (29.8)
IL-1β	108 (18.7)	**303 (36.8)**	111 (25.2)
IL-1rα	0	**422 (51.3)**[d]	100 (22.7)
IL-2	0	**501 (60.9)**	22 (5.0)
IL-3	0	135 (16.4)	**387 (87.9)**
IL-4	0	**497 (60.4)**	25 (5.7)
IL-5	0	**406 (49.3)**	118 (26.8)
IL-6	0	**501 (60.9)**	21 (4.8)
IL-10	0	**513 (62.3)**	8 (1.8)
IL-12	0	224 (27.2)	**298 (67.7)**
IL-13	0	**509 (61.5)**	13 (2.9)
n (%) with rhinitis	44 (7.6)	72 (8.7)	109 (24.8)

[a]Count of older adults with elevated levels of each cytokine (80th percentile or more) are presented for each cluster. Respondents can have more than one cytokine increased and thus may be counted more than once or have no elevated cytokines and not be counted at all.
[b]Total number of respondents within the cluster.
[c]Percentage respondents with elevated cytokine within the cluster.
[d]The key distinguishing cytokines for each cluster are shaded (highest percent of older adults between the clusters that have elevated levels [$\geq 80^{th}$ percentile] of the specific cytokine).
Bold signifies the highest percentages of subjects in each cluster with elevation of the specific cytokine.

association with rhinitis (OR = 8.92; 95% CI: 1.90, 41.85; $p = 0.01$ [2-year window] and OR = 7.60; 95% CI: 1.88, 30.75; $p = 0.01$ [3 years]) when compared with other clusters (Table 4 and Figure 2). Full details about the regressions for 1- and 2-year windows of $PM_{2.5}$ exposure can be found in Supplementary Tables 6, 7, 8 and 9.

Interestingly, older adults exposed to short-term $PM_{2.5}$ were not more likely to have rhinitis: 30 days (OR = 1.15; 95% CI: 0.94, 1.41; per 1 SD increase) to 90 days (OR = 1.13, 95% CI: 0.85, 1.49). Full regressions for 30, 60, and 90 days $PM_{2.5}$ exposures can be found in Supplementary Tables 10, 11, and 12, respectively.

4 | DISCUSSION

We demonstrate here that long-term $PM_{2.5}$ exposure appears to be associated with rhinitis as defined by medication use in a nationally representative cohort of older US adults. Additionally, we showed this relationship is strongest among those with elevated IFN-γ, IL-3, and IL-12 levels, which shows that cytokine grouping appears to modify the strength of the relationship between average $PM_{2.5}$ exposure and odds of a rhinitis diagnosis. If confirmed, this could represent a potential immune mechanism by which $PM_{2.5}$ induces rhinitis, providing a clue to the complex pathway between air pollution exposure and upper-airway inflammatory disease.

Analyzing the patterns of cytokines that were elevated in respondents with rhinitis could help to understand how these substances may lead to the development of an inflammatory process in the nose. For instance, INF-γ is released by T lymphocytes and NK cells and induces MHC expression on phagocytes, promotes cell growth and differentiation, and specifically activates macrophages.[23] More specifically, IFN-γ induces the expression of interferon-stimulated genes that act through the Janus kinase (JAK)–signal transducer and activator of transcription (STAT) signaling pathway to promote defense against microbial infections. When dysregulated, this mechanism is involved in autoimmune diseases and chronic inflammation.[24] Regarding respiratory diseases, $CD4^+$ and $CD8^+$ T helper cells exposed to increased $PM_{2.5}$ express higher quantities of IFN-γ mRNA and protein, along with IL-10, IL-17, and IL21. This induces a macrophage-dependent Th1 response, which ultimately leads to changes in the function of respiratory epithelial cells.[25] A similar mechanism involving IFN-γ is also involved in the pathogenesis of a type of chronic rhinosinusitis (CRS), which in some forms involves dysregulation of Th1 responses.[26] Thus, our data are broadly consistent with the concept that airborne PM induces macrophage-dependent cytotoxic T cell response.

IL-3 also exerts a pivotal function in chronic inflammation. This cytokine is part of the β common chain (βc) cytokine family, which also include

TABLE 3 Logistic regressions for 3 years particulate matter ≤2.5 μm ($PM_{2.5}$) exposure–rhinitis relationship, adjusting for potential confounders.

	Model 1[a]			Model 2[b]		
Variable	**OR**	***p*-Value**	**95% CI**	**OR**	***p*-Value**	**95% CI**
3 years $PM_{2.5}$ (per 1 SD increase)	**1.32**	**0.06**	**0.98-1.80**	**1.37**	**0.05**	**1.00-1.87**
Cluster of cytokines (vs. cluster 1)						
2				1.68	0.27	0.66-4.27
3				1.56	0.08	0.98-3.69
Age (per year)	0.99	0.51	0.95-1.04	0.98	0.46	0.94-1.03
Sex (vs. male)	1.07	0.82	0.60-1.90	1.09	0.77	0.62-1.91
Race/ethnicity (vs. Caucasian)						
African American	0.57	0.27	0.21-1.58	0.58	0.28	0.21-1.58
Hispanic	0.91	0.87	0.27-3.08	0.91	0.88	0.28-3.00
Education (vs. < High school)						
High school	0.86	0.81	0.25-2.98	0.86	0.80	0.26-2.86
Some college	1.61	0.40	0.52-4.93	1.60	0.39	0.54-4.76
Bachelors or more	1.25	0.69	0.41-3.81	1.24	0.69	0.42-3.70
Smoke cigarettes (vs. no)	0.80	0.78	0.15-4.11	0.82	0.81	0.16-4.18
BMI	1.07	0.01	1.02-1.12	1.07	0.01	1.02-1.12
Urbanicity (RUCA codes)[c]	1.08	0.26	0.94-1.24	1.09	0.23	0.94-1.25
Country region (vs. West)						
Midwest	0.98	0.98	0.22-4.26	0.94	0.93	0.22-4.08
South	1.62	0.45	0.46-5.74	1.56	0.49	0.43-5.67
Northeast	1.98	0.22	0.66-5.97	2.05	0.19	0.69-6.10

Note: Model 1 without cytokine cluster group, Model 2 with cytokine cluster group.

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio; RUCA, rural–urban commuting area; SD, standard deviation.

[a]Model 1 Pseudo R^2 0.42.

[b]Model 2 Pseudo R^2 0.57.

[c]RUCA codes were treated as continuous variables on a 1–10 scale, in which 1 was the most urbanized areas (metropolitan cores) and 10 was the least urbanized ones (rural areas).

We highlight the key main results from each analysis.

granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-5.[27] IL-3 binds to IL-3 receptor α (IL-3Rα/CD123) and associates with βc subunit, which signals through JAK2-STAT5A/B. Through this signaling pathway, IL-3 promotes basophil growth and differentiation, which are involved in allergic rhinitis.[27,28] Additionally, IL-3 has strong hematopoietic effects, promoting the production of granulocytes, monocytes, mast cells, basophils, and macrophages, which could also promote airway inflammation[29] in response to air pollution.

Finally, IL-12 is part of a family of cytokines (IL-23, IL-27, and IL-35) which mediate many complex immune functions. IL-12 is produced by dendritic cells, macrophages, and B cells and drives a positive feedback loop with IFN-γ (produced by T cells and also elevated in our analyses) to promote inflammation.[30] Interestingly, IL-12 is produced by dendritic cells localized close to mast cells at the mucosal interface, showing a potential role of IL-12 in atopic airway processes. To this end, increased levels of IL-12 have been already associated with allergic rhinitis in children.[31] Segboear et al. have also pointed out that IL-12 could also be associated with nonallergic rhinitis to a lesser degree.[32]

We also need to highlight that our rhinitis immune mechanisms' outcomes were dissimilar to previous studies on air pollution-induced CRS, showing the complexity of nasal diseases. It is suggested that in vitro immune mechanisms induced by PM in CRS with nasal polyps is mainly due to Th2-related responses, with IL-4, IL-6, and IL-33 driving this association.[33] One animal study also found that $PM_{2.5}$-exposed mice were more likely to express IL-13, eotaxin-1, and eosinophil accumulation in the sinonasal mucosa.[34] Our results were consistent with systemically elevated IL-3, IL-12, and INF-γ in older adults, which fits better with Th1 responses. To make this comparison though, we need to consider that the cited studies are in vitro and animal studies, while our study analyzed humans. Moreover, the cited studies focus on CRS and our study on rhinitis, which demonstrates the mechanistic complexity of nasal diseases.

TABLE 4 Logistic regressions for 3 years particulate matter ≤2.5 μm ($PM_{2.5}$) exposure–rhinitis relationship, adjusting for potential confounders.

	Model 3[a]		
Variable	**OR**	***p*-Value**	**95% CI**
3 years $PM_{2.5}$ (per 1 SD increase)	1.56	0.41	0.54-4.55
Cluster of cytokines (vs. cluster 1)			
2	1.57	0.32	0.63-3.95
3	1.36	0.47	0.58-3.22
Cluster of cytokines and 3-year $PM_{2.5}$ interaction term			
2	0.49	0.44	0.08-3.02
3	**4.86**	**0.03**	**1.10-21.58**
Age (per year)	0.99	0.49	0.95-1.02
Sex (vs. male)	1.14	0.66	0.63-2.05
Race/ethnicity (vs. Caucasian)			
African American	0.53	0.19	0.20-1.39
Hispanic	0.90	0.85	0.27-2.94
Education (vs. < High school)			
High school	0.86	0.79	0.26-2.76
Some college	1.65	0.34	0.58-4.72
Bachelors or more	1.26	0.65	0.46-3.42
Smoke cigarettes (vs no)	0.80	0.78	0.16-3.98
BMI	1.07	0.01	1.02-1.12
Urbanicity (RUCA codes)[b]	1.08	0.25	0.94-1.24
Country region (vs West)			
Midwest	0.93	0.92	0.21-4.07
South	1.77	0.38	0.48-6.58
Northeast	2.08	0.18	0.70-6.23

Note: Model 3 with cytokine cluster and inclusion of an interaction term between cytokine cluster and $PM_{2.5}$.

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio; RUCA, rural–urban commuting area; SD, standard deviation.

[a]Model 3 Pseudo R^2 0.68.

[b]RUCA codes were treated as continuous variables on a 1–10 scale, in which 1 was the most urbanized areas (metropolitan cores) and 10 was the least urbanized ones (rural areas).

We highlight the key main results from each analysis.

Our results are consistent across long-term windows of $PM_{2.5}$ exposure. However, short-term exposures were not significantly associated with rhinitis. Our interpretation of this finding is that pollution exposure may have a cumulative effect on rhinitis development in older adults (as is the case with many other diseases such as chronic obstructive pulmonary disease, asthma, and lung cancer).[35–38] Reducing exposure to air pollution, therefore, may decrease other rhinitis-related burdens faced by older adults, which include decreased productivity, diminished good-quality sleep, increased rates of depression, and decreased quality of life.[39–41] Additionally, decreasing the rates of rhinitis in the geriatric population could potentially mitigate polypharmacy, which is independently associated with adverse events, morbidity, and even mortality in the elderly.[42,43]

Our outcomes were robust to the addition of age, sex, race/ethnicity, education, cigarette smoking, and BMI. We did not find any association of rhinitis with any of these variables, except for BMI, which was associated with rhinitis (older adults with increased BMI were more likely to have rhinitis). Obesity may produce a proinflammatory state and has been associated with asthma and atopy in children, although this is a topic of debate in the literature.[44–47] Perhaps by a similar mechanism, obese adults are more likely to have an increased prevalence of nonallergic rhinitis.[48] Nevertheless, our findings of increased BMI and rhinitis in older adults add to the complex body of evidence on this topic.

There were several limitations of our study. Our design is cross-sectional, so we cannot identify causal relationships. Longitudinal studies to define causal pathways are

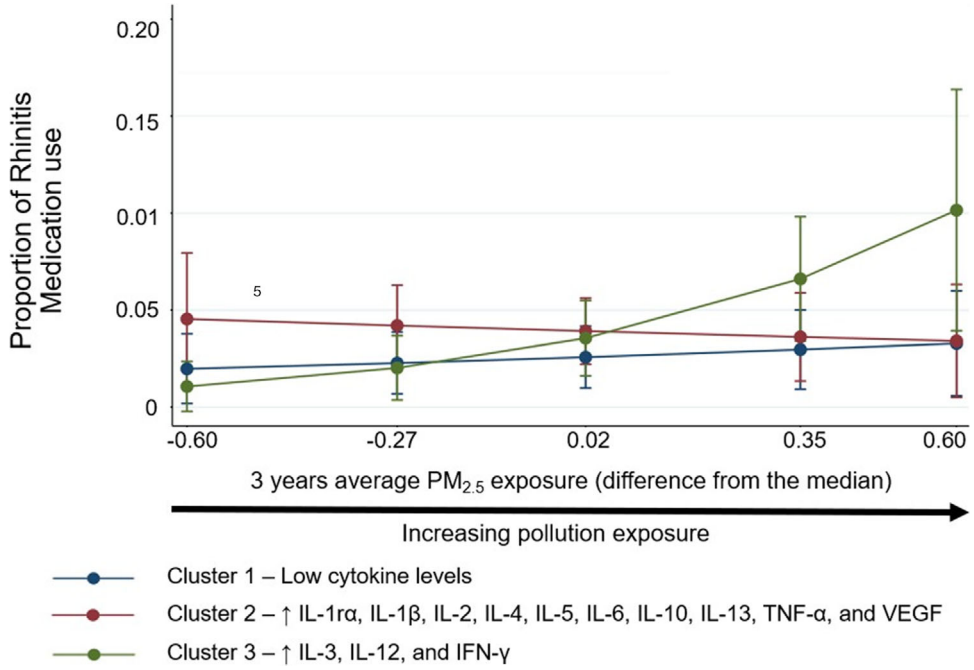

FIGURE 2 Adjusted predictions of rhinitis medication use among the three cytokine clusters with 95% confidence interval (CI) when exposed to increasing particulate matter ≤2.5 μm ($PM_{2.5}$) (3 years average minus median).

needed. Secondly, we lack the ability to determine actual rhinitis symptoms and atopy status, as these data were not included in NSHAP. Direct information on symptoms and allergy testing to distinguish allergic and nonallergic rhinitis are needed to determine specific relationships with air pollution by these forms of the disease. Our study involved in-home interviews of older adults, but we had no access to electronic medical records for clinical information nor to diagnostic testing (e.g., allergy testing, rhinoscopy, nasal endoscopy). Thus, we cannot distinguish other indications for these medications (CRS, nasal polyposis, etc.). However, we note that rhinitis diagnosis is made mainly based on clinical information on symptoms (nasal congestion, sneezing, nasal pruritus, excessive mucus production), and the medications commonly used for those symptoms were present in our analyses.[49,50] Moreover, allergic rhinitis prevalence decreases with age, which makes the diagnosis of nonallergic rhinitis in older adults more likely.[21,22] The k-means clustering method was used to describe the immune function by identifying cytokine patterns by standard methods. Such immune profiles are crude, but more complex immunophenotyping (B and T cell function, etc.) was not possible in the omnibus study performed in homes across the country. More sophisticated methods to measure immunologic metrics are possible in smaller-scale clinical studies to follow up these findings. Moreover, we lack information on nasal physiology; nasal sampling would be useful in subsequent studies to examine the differences between local effects in the airway versus systemic effects in the peripheral blood. Finally, we note that the measures of short-term $PM_{2.5}$ exposure have a bigger variance than long-term exposures, meaning that data from short-term exposures are noisier and sometimes less precise than long-term. This could alternatively explain why we did not find any associations for short-term $PM_{2.5}$ exposures and rhinitis.

5 | CONCLUSION

To our knowledge, we are one of the first studies to propose that specific immune functions (through IL-3, IL-12, and IFN-γ) connect ambient $PM_{2.5}$ exposure to rhinitis in a nationally representative sample of older US adults. Further work is necessary to precisely characterize the immunologic processes that connect air pollution to rhinitis and delineate causal mechanisms. Identifying the underlying molecular processes that are involved will allow to develop new precision therapies to reduce the burden of environmentally mediated rhinitis in older adults.

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CONFLICT OF INTEREST STATEMENT

JMP: Speaker's bureau for Regeneron/Sanofi; site investor clinical trials for Regeneron/Sanofi; advisory boards for Optinose and Connect BioPharma. All the other authors have no financial disclosures. All authors have read the manuscript, agree with submission, and accept responsibility for the manuscript's contents.

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