

What is the Role of Air Pollution in Chronic Rhinosinusitis?



Hannah L. Schwarzbach, BA^{a,1}, Leila J. Mady, MD, PhD, MPH^{b,2},
Stella E. Lee, MD^{a,b,*}

KEYWORDS

• Air pollutants • Environmental exposure • Occupational exposure
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KEY POINTS

- The negative health effects of air pollution have been recognized in the lower airway, for example, chronic obstructive pulmonary disease, and asthma, but more recent studies demonstrate interactions between pollutant exposure and chronic rhinosinusitis (CRS) as well as nonallergic rhinitis.
- Pollutant exposure may be associated with CRS pathophysiology, and, among CRS patients without nasal polyps, exposure is associated with disease severity and decreased quality of life.
- Mechanisms of pollutant exposure in disease may be due to several factors, including disruption in the integrity of the sinonasal barrier, induction of chronic inflammation, and alteration of the nasal microbiome, among other causes not yet investigated.

GLOBAL AND LOCAL HEALTH EFFECTS OF ENVIRONMENTAL POLLUTANTS

Air pollution poses significant and pressing risks to the environment and human health worldwide. Although generally agreed that both environmental and host factors play a role in chronic rhinosinusitis (CRS), the effects of exposures encountered daily, such as pollutants in the air and occupational exposures, is unclear.¹ The US Environmental Protection Agency has identified 6 criteria pollutants that are common in the United States and pose a threat to the environment and human health. These pollutants include

^a University of Pittsburgh School of Medicine, Pittsburgh, PA, USA; ^b Department of Otolaryngology–Head and Neck Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

¹ Present address: University of Pittsburgh School of Medicine, 3550 Terrace Street - S594, Scaife Hall, Pittsburgh, PA 15261.

² Present address: University of Pittsburgh Department of Otolaryngology, 203 Lothrop Street - Suite 500, Pittsburgh, Pennsylvania 15213.

* Corresponding author. UPMC Mercy, 1400 Locust Street – Suite 2100, Pittsburgh, PA 15219.

E-mail address: lee6@upmc.edu

lead, carbon monoxide, sulfur dioxide, ozone, nitrogen dioxide, and particulate matter (PM) 2.5 (PM_{2.5}) and PM 10 (PM₁₀), and although National Ambient Air Quality Standards attempt to regulate ambient pollutant levels, many parts of the United States are in nonattainment.² In regard to PM_{2.5}, 3 Pennsylvania counties, 1 county in Idaho, and 14 in California are in nonattainment as of August 2019. There are nonattainment regions for ozone in Arizona, California, Colorado, Connecticut, District of Columbia, Georgia, Illinois, Kentucky, Maryland, Michigan, Nevada, New Jersey, New Mexico, New York, Ohio, Pennsylvania, Texas, Utah, Virginia, and Wisconsin.³ Studies have shown significant associations of poor air quality with chronic obstructive pulmonary disease (COPD) and asthma as well as other conditions, such as rheumatoid arthritis, anxiety and depression, cognitive impairment, and cardiovascular disease.^{4–8} In COPD, pollutant exposure is associated with increased rescue inhaler use, more frequent emergency room visits, hospitalizations, and decreased pulmonary function.^{9,10} Among a unique tobacco-naïve population of COPD patients, the most important risk factor was exposure to biomass smoke, which is a major source of airborne particulates and gaseous pollutants that originate from burning organic matter.¹¹ Comparable findings have been described in asthma, and a study on the effectiveness of air pollutant emission reduction policies found that hospital visits decreased by up to 16% in the first 10 years after these environmental policies were enforced.¹²

AIR POLLUTION AND EFFECTS ON CLINICAL OUTCOMES IN CHRONIC RHINOSINUSITIS AND ALLERGIC RHINITIS

Earlier studies investigating the role of air pollution in sinonasal disease examined the effects of exposure to sulfur dioxide, nitrogen dioxide, ozone, carbon monoxide, and PM. There was a significant association between PM₁₀ exposure and the risk of CRS, with risk increasing by 1.22% with each 1 µg/m³ increase in PM₁₀, but there was no association between ear, nose, and throat pathology and the other 4 pollutants.¹³ This same study found no association between pollutant exposure and the prevalence of allergic rhinitis (AR). A similar study on traffic-related air pollution (TRAP) measured near patients' homes and schools reported no association between exposure and AR or asthma.¹⁴ These findings conflict with 2 studies that did report an association between pollutant exposure and AR, but it is important to note that most of these studies were specifically measuring TRAP exposure.^{15,16} TRAP typically consists of carbon monoxide, carbon dioxide, nitrogen oxides, hydrocarbons, and PM, but the amount and relative concentrations of each component vary significantly based on factors, including vehicle type, age, condition, and fuel. Study participants also likely encountered a heterogeneous mixture of TRAP components, depending on distance from the road, meteorologic conditions, and pollutant characteristics, so it is difficult to classify exposure specifics in each study.¹⁷

The authors' group studied the relationship between PM_{2.5} and black carbon exposure and disease severity in CRS using spatial modeling data from regional pollutant monitoring sites. The authors analyzed CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSSNP) and found that among CRSSNP patients, increased PM_{2.5} exposure was associated with increased risk of proceeding to functional endoscopic sinus surgery (FESS). When specifically looking at 6 patients who were exposed to PM_{2.5} levels greater than 12.0 µg/m³, which is the exposure limit proposed by the Environmental Protection Agency to protect public health, 4 patients (66.7%) required FESS compared with 38 patients (42.2%) with significantly less PM_{2.5} exposure. Levels of exposure seem directly related because ordinal logistic regression found a 1.89-fold increase in the proportion of CRSSNP patients requiring surgery for each unit increase in PM_{2.5} exposure ($P = .015$). Black carbon exposure had a

significant impact on subjective symptom severity among CRSsNP patients, with higher levels associated with increased Sino-Nasal Outcome Test (SNOT)-22 scores. There were no significant associations between PM_{2.5} or black carbon exposure and CRSwNP outcomes in the authors' cohort.¹⁸

The authors also investigated how air pollutant exposure relates to AR in CRS patients. Reports of AR prevalence among CRS patients range from 50% to 80% compared with 10% to 20% of the general population.^{19,20} The authors' study showed that both PM_{2.5} and black carbon exposure were significantly higher, however, among CRS patients with negative allergy testing compared with atopic CRS patients. These findings show that pollutant exposure may contribute to nonallergic rhinitis (NAR) in the CRS population.¹ The role of NAR in CRS is poorly understood and has not been studied extensively, but the authors' findings align with another study that examined AR and NAR in CRS. In a study of 115 patients, NAR patients had higher average global symptom scores than their allergic counterparts.²¹ In the authors' study, among patients who tested negative for allergies, CRSsNP patients had significantly higher SNOT-22 scores than CRSwNP patients, suggesting that air pollutants could be driving the increased symptomatology seen in CRS patients without atopy.¹

OCCUPATIONAL EXPOSURES, TOBACCO, AND CHRONIC RHINOSINUSITIS PATHOPHYSIOLOGY

Although the relationship between air pollution and CRS has not been studied as extensively as its role in lower respiratory conditions, there is a growing body of literature on the relationship between other environmental exposures and sinonasal disease. A 2015 systematic review on occupational and environmental risk factors for CRS identified 41 studies on occupational risk and environmental risk but determined that no strong conclusions could be drawn, because the definition of CRS used in these studies did not fit accepted diagnostic guidelines, and many exposure assessments relied on patient-reported exposures.²² A more recent study that used participant interviews to study occupational and environmental CRS risk factors found that occupational exposure to dust and occupational exposure to poisonous gas were significantly associated with self-reported CRS, but these imprecise exposure data are challenging to interpret. For example, the survey referenced "poisonous gas" exposure without explaining what constitutes a poisonous gas, so study participants responded based on their own interpretations of this variable.²³ The relationship between occupational exposures and CRS subtypes (CRSwNP, CRSsNP, and aspirin-exacerbated respiratory disease [AERD]) was recently analyzed by the authors' group to evaluate this knowledge gap. Exposures included vapors, gases, dusts, fumes, fibers, and mists (VGDFFiM) and diesel fumes. Instead of using spatial modeling based on patients' addresses, occupational exposures were estimated based on patients' reported occupations and the occupational airborne chemical exposure matrix described by Sadhra and colleagues.²⁴ Exposure to VGDFFiM was significantly higher among CRSsNP patients compared with CRSwNP and AERD patients, but there was no significant difference in diesel fume exposure between these groups. VGDFFiM and diesel fume exposure both were associated with higher steroid doses, and VGDFFiM was associated with an increased risk of proceeding to FESS. A subgroup analysis of exposure outcomes between CRSwNP, CRSsNP, and AERD was not significant.²⁵ Subgroup analysis based on CRS phenotypes, however, is likely an oversimplification, with a growing number of studies using cluster analysis to identify unique CRS endotypes demonstrating a spectrum of unique inflammatory and clinical behaviors.^{26–29} Mechanisms of VGDFFiM exposure may be related to disruptions in the epithelial

barrier and ciliary dysfunction. Ciliary dyskinesia has been described after occupational exposures, and a recent cross-sectional study of gas station employees found a positive correlation between length of work and nasal mucociliary transport time.³⁰

Tobacco smoke exposure also may modify CRS disease severity, with a recent meta-analysis showing that 11 of 13 studies described a significant association between exposure and CRS prevalence.³¹ Another study found that current and former smokers had higher odds of CRS than never smokers, but this study relied on self-reported symptoms without support from objective examination.³² CRS severity also has been associated with both amount and duration of smoke exposure.³³ Secondhand smoke exposure is relevant as well, and a review of 112 studies found an association between CRS and both passive and active smoking, attributing this relationship to decreased ciliary beat frequency and increased sinonasal epithelial inflammation on smoke exposure.³⁴ A recent prospective cross-sectional study compared CRS severity among tobacco cigarette smokers and tobacco smokers who also habitually use cannabis and found that health-related quality of life burden and Lund-Kennedy endoscopic scores were significantly higher among patients who use a combination of tobacco and cannabis.³⁵ This data are particularly interesting in light of the increasing number of states that are legalizing cannabis for recreational and medical use.³⁶

MECHANISMS OF POLLUTANT EXPOSURE IN CHRONIC RHINOSINUSITIS

Several studies have linked air pollution exposure to both systemic inflammation and local epithelial dysfunction. Epithelial cells release proinflammatory cytokines on PM exposure, and these circulating inflammatory markers sustain a systemic inflammatory state.^{37–40} One study examined the biomarkers of systemic inflammation after PM exposure in young, healthy patients. A significant association was found between PM exposure and inflammatory cytokines, including tumor necrosis factor (TNF)- α , interleukin (IL)-8, and IL-6.⁴¹ Another study found similar results when looking at the association between chronic residential PM exposure and C-reactive protein, an acute-phase protein and inflammatory marker that increases after IL-6 secretion.⁴² In addition to these systemic effects, similar inflammatory profiles were seen in upper airway epithelium after exposure. With regard to diesel exhaust particles (DEPs), a traffic-related pollutant, 1 study found increased IL-6 and IL-8 expression in human inferior turbinate fibroblasts after DEP exposure, and DEP exposure has been shown to decrease sinonasal epithelial integrity in mice, providing another mechanistic explanation for DEPs' proinflammatory properties.^{43,44} A study using RPMI 2650 cells from human nasal septum tissue found increased expression of TNF- α , IL-13, IL-6, and IL-8 after PM exposure, and another reported that PM_{2.5} was associated with tight junction protein degradation and epithelial barrier disruption.^{45,46}

The aforementioned effects of pollutant exposure on inflammation and epithelial dysfunction were demonstrated in vivo in a murine model of PM_{2.5} exposure by Ramanathan and colleagues.⁴⁷ Mice were subjected to PM_{2.5} inhalation over the course of 16 weeks with mean airborne PM concentrations approximating the values found in many global cities. Examination of the epithelial integrity after PM exposure showed that claudin-1 and E-cadherin, 2 proteins that contribute to intercellular tight junctions, were significantly lower in PM-treated mice. Eosinophils, neutrophils, macrophages, and lymphocytes also were higher in nasal airway lavage fluid from exposed mice compared with controls, and nasal mucosa PCR demonstrated higher expression of several inflammatory cytokines including IL-1 β and IL-13.⁴⁷ Although several studies describe increased IL-6 and IL-8 in epithelial tissues after pollutant exposure^{41–43,45,46}, Ramanathan and colleagues describe an eosinophilic inflammatory profile.⁴⁷ Nonallergic eosinophilic inflammation also was described, which recapitulates a unique

clinical entity found in patients who suffer from NAR with eosinophilia syndrome.⁴⁷ These findings may explain the relationship between PM exposure and disease severity among nonallergic CRSsNP patients, which is consistent with the findings from the authors' group's earlier studies.^{1,18}

In addition to its impact on inflammation and epithelial dysfunction, air pollutants may have an impact on the nasal microbiome, contributing to the dysbiosis seen in CRS. Black carbon has been shown to affect bacterial colonization, and both *Streptococcus pneumoniae* and *Staphylococcus aureus* biofilms develop more thick and complex structures when exposed to black carbon. *S pneumoniae* and *Staphylococcus aureus* also are more resistant to antibiotics after black carbon exposure.⁴⁸ Given the proposed role of bacterial infection, colonization, and *S aureus* superantigens in the pathophysiology of CRS, this information provides additional data that can provide further insight into the links between chronic inflammation, microbiome disturbances, and environmental exposures.⁴⁹

FUTURE CONSIDERATIONS AND SUMMARY

CRS is a complex disorder with several factors contributing to disease expression and progression, but recent studies on the relationship between environmental exposures and CRS suggest that pollution has an impact on disease prevalence and severity. In addition to clinical studies that describe an association between pollutants and CRS, molecular studies about effects on epithelial integrity, chronic inflammation, and nasal dysbiosis provide further mechanistic influences on CRS pathophysiology.

The studies currently described in the literature, including the studies conducted by the authors' group, are limited by the currently available means of quantifying exposure in an individual patient. Spatial modeling based on patients' home addresses and surrogate measures based on occupation or job title likely relate to exposure but fail to address several important variables (eg, real-time exposures, time spent outdoors, and mixed-environment jobs). It may be helpful to compare the exposure data collected from local pollutant modeling sites with data collected from personalized, wearable monitors from patients in that region. A study that utilizes wearable pollutant monitors would be helpful to collect more high-fidelity data. Most studies on this topic also have been cross-sectional, and prospective analyses are needed. By longitudinally following diseased populations and healthy populations over time, the associations between exposure and disease progression and new CRS incidence in previously healthy people could be examined. Tissue samples from patients also could be collected and analyzed to examine the relationship between molecular indications of exposure and clinical outcomes.

From an advocacy and public health standpoint, it would be useful to longitudinally evaluate CRS severity following the enforcement of new environmental exposure legislation. These studies could evaluate macroscopic exposure at the state or national level in addition to examining smaller populations after regional policies or workplace policies are implemented. If these studies demonstrated a significant decrease in disease burden, this information would be valuable to support future clean air legislation. Even without these future studies, the currently available literature on the relationship between air pollution and CRS suggests that exposure is associated with both disease prevalence and severity, and public health initiatives to further decrease ambient pollutant levels are warranted.

DISCLOSURE

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