REVIEW

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Environmental air pollution and chronic rhinosinusitis: A systematic review

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Abstract

Objective: Chronic rhinosinusitis (CRS) is a highly prevalent and burdensome disease. The pathophysiology is not fully elucidated, but environmental pollutants have been suggested to impact the inflammatory component of the disease process. This review aims to summarize the role of environmental pollution in CRS onset and disease severity.

Methods: A systematic review was performed following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. PubMed, EMBASE, Cochrane Library, Web of Science, and Scopus databases were queried in August 2021. Original articles reporting on air pollution exposure in CRS were included. Other forms of sinonasal disease were excluded.

Results: Literature search produced 11,983 articles, of which 10 met inclusion criteria. Outcomes evaluated included incidence/prevalence, disease severity, quality of life, and histopathologic/microbial changes. Air pollutant exposure was associated with higher odds of CRS, particularly with particulate matter (PM) exposure. Increasing air pollution exposure was also associated with worsened disease severity and detectable histopathologic changes. Impact on quality of life was less clear.

Conclusion: Air pollution (particularly PM) is correlated with CRS incidence/prevalence and disease severity, with evidence of histopathologic changes in CRS tissue samples. Further research is warranted to better understand the mechanisms by which air pollution components may cause CRS and type 2 inflammation.

Level of Evidence: 3a

KEYWORDS
air pollutants, environmental pollution, quality of life, sinusitis

1 | INTRODUCTION

Chronic rhinosinusitis (CRS) is a highly prevalent and burdensome disease, with large impacts on both the individual and population scales.[1–7]

Although the pathogenesis of CRS is not well elucidated, multiple factors have been hypothesized to play a role, including chronic mucosal inflammation secondary to mucociliary clearance dysfunction, epithelial barrier abnormalities, or dysregulated immune response.[8–13]

Notably, environmental exposures have been hypothesized to play a key role in disease onset and severity, as nasal mucosa is among the first lines of defense against said exposures. The Environmental Protection Agency (EPA) has defined six criteria air pollutants—ozone (O_3), particulate matter (PM), carbon monoxide (CO), lead (Pb), sulfur dioxide (SO_2), and nitrogen dioxide (NO_2)—for which there are set air quality standards in the United States.[14] PM is often reported as PM_{10} or $PM_{2.5}$, which corresponds to PM 10 μm or less in diameter or 2.5 μm or less in diameter, respectively. Elevated levels of these air pollutants have been repeatedly linked to multiple health conditions (e.g., cardiac disease, asthma, and chronic obstructive pulmonary disease)[15–17] as well as overall morbidity and mortality.[18–21]

Recently, there has been increasing evidence for the role of air pollution in upper airway disease. Many air pollutants (including PM and O_3) have been shown to upregulate reactive oxygen species, leading to DNA damage and increased oxidative stress and inflammation.[22–25] Cellular models and animal studies have supported this link between air pollution and oxidative stress in the pathogenesis, progression, and severity of CRS. One study found that human nasal epithelial cells exposure to PM demonstrated lower cell line viability and increased cytotoxicity.[26] Another group discovered that human sinonasal epithelial cell lines from patients undergoing surgery for CRS that were exposed to PM_{10} displayed disrupted epithelial barrier function.[27] Furthermore, murine models have demonstrated that chronic exposure to $PM_{2.5}$ is associated with increased inflammatory changes[28] and tissue remodeling.[29]

Over the past couple of decades, these hypotheses have been replicated in observational studies in humans. A previous systematic review was performed to evaluate the impact of air quality on CRS in humans,[30] but most of the evaluated studies were related to occupational exposures, and few conclusions could be drawn. Of the studies that considered environmental exposure, none evaluated the impact of the EPA criteria air pollutants. Although occupational exposures undoubtedly have a large impact on upper airway diseases, air pollution encountered in everyday life has the potential to have a significantly broader impact at the population level. Therefore, this systematic review aimed to evaluate the impact of air pollution on CRS pathogenesis, severity, and progression without considering the confounding effects of occupational exposures.

2 | MATERIALS AND METHODS

2.1 | Literature source and search

A literature search was performed following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines utilizing PubMed, Cochrane Library, EMBASE, Web of Science, and SCOPUS.[31] The search was completed on August 5, 2021 by a qualified data informationist. No restrictions were placed on date of publication. Search terms including "environmental pollution," "air pollution," "particulate matter," "ozone," "carbon monoxide," "sulfur dioxide," and "nitrogen dioxide" were combined with "chronic rhinosinusitis," "rhinitis," "sinusitis," "sinonasal disease," and "CRS." Full search summary details can be found online in

Supporting Information S1. No additional records were obtained from outside sources. Studies were managed in Covidence (Veritas Health Innovation, Melbourne, Australia), and articles were reviewed for inclusion based on title/abstract by two independent reviewers (Evelyn M. Leland and Varun Vohra). Any disputes between reviewers were resolved by a third independent reviewer (Murugappan Ramanathan).

2.2 | Inclusion and exclusion criteria

Studies focusing on the relationship between air pollution and CRS in adults (age ≥ 18) were included. The articles had to evaluate at least one of the six EPA criteria air pollutants (O_3, $PM_{2.5}$, PM_{10}, CO, Pb, SO_2, or NO_2).[14] The diagnosis of CRS required documentation of provider diagnosis or use of professionally accepted criteria, such as the European Position Paper on Rhinosinusitis and Nasal Polyps.[32] Studies that included patients based on exclusively subjective symptoms (e.g., "Have you ever had a runny or blocked nose?") were excluded. Additionally, studies without evidence of chronicity (e.g., >3 months) were also excluded. Other exclusion criteria included pediatric population, other rhinitis diagnoses (e.g., allergic rhinitis, vasomotor rhinitis), review articles, or occupational exposures. Although no restriction was placed on language during the initial search, an article was excluded if no English versions of the article were available.

2.3 | Data extraction

Data extraction was performed by two independent reviewers (Evelyn M. Leland and Varun Vohra) with disagreements reviewed by the senior author (Murugappan Ramanathan). Data collected included study period, patient population demographics (diagnosis, diagnostic criteria, age, and sex), pollutant exposure, outcome data, and conclusions. Data and study conclusions were summarized in table format. Meta-analysis was considered but deferred due to small sample sizes and heterogenous nature of available data.

2.4 | Risk of bias assessment

Risk of bias was assessed by two independent reviewers with the methodological index for nonrandomized studies (MINORS), used to assess the quality of nonrandomized surgical studies.[33] Non-comparative studies are scored on either criteria (score 0–16), and comparative studies are scored on 12 criteria (0–24).

3 | RESULTS

3.1 | Study characteristics

The literature search resulted in 11,983 studies (Figure 1). After removal of 228 duplicates, 11,755 studies were screened for inclusion
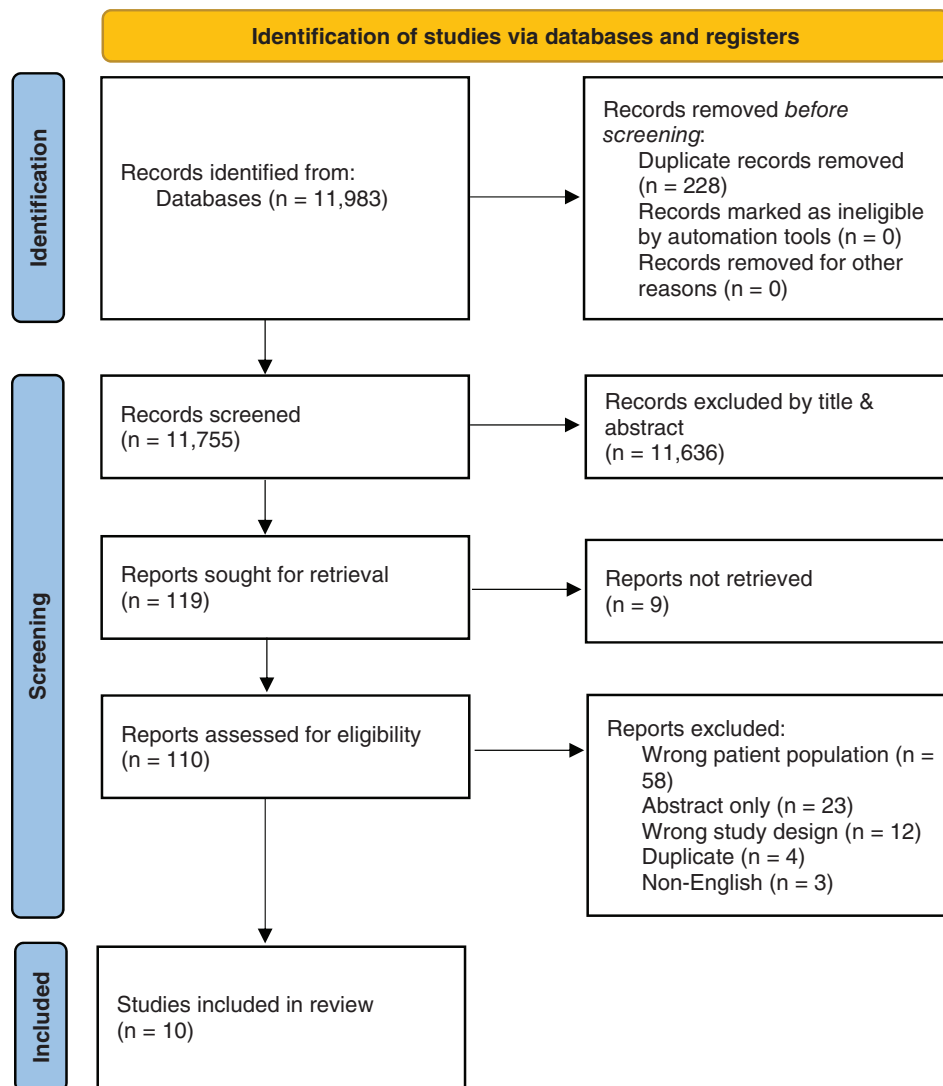
by title and abstract. A total of 115 articles underwent full-text review, resulting in 10 studies meeting criteria for final data extraction and analysis (Table 1). Of the included studies, three were case–control,[34,36,42] and seven were ecological or cross-sectional. Four studies evaluated incidence or prevalence of CRS. Six studies evaluated disease severity or quality of life. Two studies collected tissues for histopathologic or microbiological analysis. MINORS scores were 18 for comparative studies and 10 for noncomparative studies, indicating at least a moderate risk of bias for the included studies.

3.2 | Patient population characteristics

There were 4215 patients included in the studies (excluding Lu et al., 2020). Three studies were completed by the same author group, and it was assumed that the patient population was similar between the group.[38,40,41] Therefore, only one of the patient groups was included in the population summary calculations. Average age was 51.0 ± 15.7 ($n = 2669$) for CRS cases and 51.7 ± 17.0 ($n = 4294$) for controls. The CRS group was 43.2% male ($n = 2669$); the control group was 43.8%

male ($n = 4294$). Only two studies reported the distinction between CRSsNP and CRSwNP. In those studies ($n = 517$), there were 48% CRSsNP patients and 52% CRSwNP patients.

3.3 | CRS incidence and prevalence

Four studies investigated whether air pollution was associated with CRS incidence or prevalence, and all noted a significant relationship. Each study was from a different geographical region, and all studies utilized patients' home addresses to estimate air pollutant exposure.

One study performed in Cologne, Germany evaluated the impact of a model-estimated air pollution level (based on the calculated levels of SO_2, total suspended particulate, and NO_x) on rates of CRS patients within predefined city districts.[43] Authors noted that city districts with above average air pollution levels were associated with higher patient rates ($r = .382$, $p < .05$). This was primarily driven by earlier years (1990–1994) versus later years (1995–1999), which authors note may be due to decreasing air pollution over the years.

TABLE 1 Summary of included studies

Author	Data period and location	Patient population — Diagnostic criteria	Sample size	Male % / Age ± SD	Environmental pollution/exposure	Confounders / MINORS score	Conclusions
Padhye et al.[34]	Jan 2015–July 2016 Chicago, Illinois	CRS Nasal swab taken from middle nasal meatus under endoscopic guidance 2–3 weeks before tissue collection during surgery. Patients diagnosed in tertiary rhinology clinic	CRS 111 (71 underwent surgery) Controls 21	NR / NR	$PM_{2.5}$ Exposure based on patient's home address. $PM_{2.5}$ levels from US EPA 2011 Environmental Justice Screen dataset	insurance, race, socioeconomic status, asthma, atopy, age, CRS duration / 18	CRS was associated with higher neighborhood $PM_{2.5}$ levels than controls ($p < .001$). $PM_{2.5}$ was associated with decreased relative abundance of Corynebacterium in CRS ($p = .02$) and controls ($p = .04$). $PM_{2.5}$ levels were associated with eosinophilic aggregation in CRS patients ($p < .01$). Not associated with other evaluated markers
Patel et al.[35]	Jan 2015–May 2019 Chicago, Illinois	Patients with CRS who underwent FESS Age ≥ 18. Diagnosed based on 12 weeks of continuous symptoms supported by positive endoscopy and CT scan, and requirement of ESS after failure of appropriate medical therapy	CRS 291 (CRSsNP 152 CRSwNP 131)	46% / 49.3 ± 16.1	O_3, $PM_{2.5}$ Exposure based on patient's home address. Pollutant levels from US EPA 2018 Environmental Justice Screen Dataset	Race, smoking history, inhalant allergy / 10	CRS: In multivariate models, increasing ozone exposure was associated with more severe inflammation ($p = .031$) and Charcot-Leyden crystals ($p = .039$). No trends were seen based on $PM_{2.5}$ exposure. Subgroups: There was no difference in exposure to O_3 ($p = .306$) or $PM_{2.5}$ ($p = .815$) based in CRSsNP versus CRSwNP subgroups. In CRSwNP, increased O_3 exposure was associated with increased inflammation ($p = .004$), presence of eosinophilic aggregates ($p = .018$), and presence of Charcot-Leyden crystals ($p = .036$). No associations were noted between $PM_{2.5}$ exposure and CRSwNP. No associations were noted with CRSsNP and O_3 or $PM_{2.5}$ exposure. Not associated with other evaluated markers
Zhang et al.[36]	NR Northeast United States	CRS Age ≥ 18	CRS 2034 Controls 4068	CRS: 41.3% Control: 43.5%	$PM_{2.5}$ and O_3 Exposure based on patient's home address at 12, 24, 36, and 60 months before diagnosis date	Age, gender, race, BMI, alcohol consumption status, smoking status, hypertension, diabetes, COPD, asthma	At all time-periods measured before diagnosis, $PM_{2.5}$ exposure was associated with higher odds of CRS diagnosis. This was also noted across all sinusitis locations, most notably in cases of ethmoidal and severe (e.g., four sinus) sinusitis cases

TABLE 1 (Continued)

Author	Data period and location	Patient population — Diagnostic criteria	Sample size	Male % — Age ± SD	Environmental pollution/exposure	Confounders — MINORS score	Conclusions
		CRS ICD9/10 code by board-certified otolaryngologist using nasal endoscopy and CT scans. Excluded those with environmental allergies		CRS: 51.5 ± 16.0 Controls: 51.9 ± 17.4	Machine learning approaches were used to predict daily $PM_{2.5}$ concentrations. Daily O_3 exposure estimated from the National Air Monitoring Stations/State and Local Air Monitoring Stations	18	
Lu et al.[37]	Jan 1, 2015–Dec 31, 2018 Xinxiang, China	Chronic sinusitis. Chronic sinusitis as coded with the ICD-10 J32 code	183,943 cases	49.6% 70.1% between 15–65 years old	NO_2, SO_2, CO, PM_{10}, $PM_{2.5}$, and O_3. Data from China Environmental Monitoring Centre website, gathered from four fixed site monitoring stations	Co-pollutants 12	All pollutants except for O_3 had some impact on hospital outpatient cases of chronic sinusitis. Notably, these trends were seen in patients age < 65 (most significantly in pediatric population), but not significant in a subgroup of adults age ≥ 65. After adjusting for co-pollutants, the relationship between $PM_{2.5}$ and NO_2 and chronic sinusitis cases remained
Velasquez et al.[38]	2013–2015 Pittsburgh, Pennsylvania	CRSsNP CRSwNP ≥18 years old. Same residence and occupation for past 5 years. Imaging studies within 3 years of study protocol. CRS diagnosed based on International Consensus Statement on Allergy and Rhinology. All patients seen by one of the two rhinologists at institution	CRSsNP 96 CRSwNP 113	CRSsNP: 39.6% CRSwNP: 61.1% CRSsNP: 51.2 CRSwNP: 51	$PM_{2.5}$, BC. Utilized home address to estimate exposure based on a spatial model from Pittsburgh air pollution	NR 11.5	Air pollutant exposure did not vary between groups. LMS, FESS, and steroid usage were not associated with air pollutant exposure in CRSsNP or CRSwNP. Authors thought due to small subgroup analyses

(Continues)

TABLE 1 (Continued)

Author	Data period and location	Patient population Diagnostic criteria	Sample size	Male % Age ± SD	Environmental pollution/exposure	Confounders MINORS score	Conclusions
Park et al.[39]	2009 South Korea	Age ≥ 19 Data from KNHANES CRS diagnosed by trained residents in those with visible nasal polyps endoscopically or with at least two of the following symptoms: anterior/posterior nasal drip, nasal obstruction, facial pain/tenderness, and olfactory dysfunction more than 3 months in duration (either an anterior/posterior nasal drip or nasal obstruction was required as a presenting symptom)	NR	NR NR	PM_{10}, NO_2, O_3, SO_2, CO Data from the Korean National Institute of Environmental Research (2009)	Age, sex, region 10	No correlation between CRS incidence and air pollution levels For each 1 μg/m³ unit increase in PM_{10} level, prevalence of CRS increased significantly, with an OR of 1.22 (95% CI 1.02–1.46; $p = .031$)
Mady et al.[40]	2013–2015 Pittsburgh, Pennsylvania	CRSsNP CRSwNP ≥18 years old Described rhinitis symptoms and had subsequent allergy testing Same residence and occupation for past 5 years Imaging studies within 3 years of study protocol All patients seen by one of the two rhinologists at institution	CRSsNP 58 (22 allergy-negative) CRSwNP 67 (23 allergy-negative)	CRSsNP: 41.4% CRSwNP: 53.7% CRSsNP: 47 ± 15.7 CRSwNP: 49 ± 15.5	$PM_{2.5}$, BC Utilized home address to estimate exposure based on a spatial model from Pittsburgh air pollution	Age, sex 10	Allergy-negative patients had higher exposure levels to both $PM_{2.5}$ ($p = .030$) and BC ($p = .044$) than their allergy-positive counterparts. This trend was carried by CRSwNP patients, in which allergy-negative patients had higher $PM_{2.5}$ ($p = .032$) and BC ($p = .017$) exposure than allergy-positive patients. Allergy-negative CRSwNP patients also had higher $PM_{2.5}$ exposure than allergy-positive CRSsNP patients ($p = .023$) There were no differences in exposure to $PM_{2.5}$/BC noted between allergy-positive and allergy-negative CRSsNP patients. There was no difference in SNOT-22, LMS, or steroid usage between allergy-positive and allergy-negative patients In CRSsNP, BC correlated with SNOT-22 ($r = .55$, $p = .042$, log-transformed $r = .56$, $p = .039$). No correlation with other measured severity metrics In CRSwNP, there was no relationship between $PM_{2.5}$/BC exposure and any evaluated severity metric

TABLE 1 (Continued)

Author	Data period and location	Patient population — Diagnostic criteria	Sample size	Male % / Age ± SD	Environmental pollution/exposure	Confounders — MINORS score	Conclusions
Mady et al.[41]	2013–2015 Pittsburgh, Pennsylvania	CRSsNP CRSwNP ≥18 years old; Same residence and occupation for past 5 years; Imaging studies within 3 years of study protocol; All patients seen by one of the two rhinologists at institution	CRSsNP 96 CRSwNP 138	CRSsNP: 39.6% CRSwNP: 59.4%; CRSsNP: 51.2 ± 16.5 CRSwNP: 51.4 ± 15.4	$PM_{2.5}$, BC; Utilized home address to estimate exposure based on a spatial model from Pittsburgh air pollution	10	Mean $PM_{2.5}$ levels were higher in Pittsburgh (11.28 vs. 10.98 μg/m^3, $p = .002$). CRSwNP patients living in Pittsburgh had higher $PM_{2.5}$ exposure versus patients living elsewhere (11.28 vs. 10.95 μg/m^3, $p = .008$), but this was not seen in CRSsNP patients (11.27 vs. 11.03 μg/m^3, $p = .097$). No significant difference based on BC levels. Air pollutant exposure was not different between CRSsNP and CRSwNP groups for $PM_{2.5}$ or BC. CRSsNP: $PM_{2.5}$ exposure was associated with FESS in CRSsNP patients ($p = .015$), with each unit increased in $PM_{2.5}$ exposure corresponding to a 1.89-fold increased risk in proportion of CRSsNP patients needing more surgery ($p = .015$). BC exposure was associated with SNOT-22 scores in CRSsNP patients ($p = .015$), with each 0.1-unit increase in BC corresponding to a 7.97-unit increase in SNOT-22 scores in CRSsNP patients ($p = .008$). No relationship in other evaluated metrics and $PM_{2.5}$/BC exposure in CRSsNP patients. CRSwNP: No relationship between $PM_{2.5}$/BC exposure and any evaluated metric in CRSwNP patients
Sommar et al.[42]	2008–2010 Swedish cities: Umeå, Uppsala, Stockholm, and Gothenburg	CRS Based on GA^{2}LEN survey from 19 European countries EPOS 2012 criteria	CRS 110 Control 226	CRS: 54% Control: 49%; CRS: 45.4 (95% CI: 42.5–48.3) Control: 47.5 (95% CI: 45.5–49.5)	NO_2, NO_x Exposure based on patient's home address. Pollutant levels estimated based on modeling and local emission data	19	Exposure to nitric oxides did not differ between controls and CRS. European quality of life-5D was not associated with measures of NO_2 and NOx in controls or CRS

(Continues)

TABLE 1 (Continued)

Author	Data period and location	Patient population Diagnostic criteria	Sample size	Male % Age ± SD	Environmental pollution/exposure	Confounders MINORS score	Conclusions
Wolf[43]	1990–1999 Cologne, Germany	Patients with CRS who underwent FESS and	1435 patients, evaluated based on districts	NR	SO₂, TSP, NOx Pollutant levels estimated from modeling programs and simulation study considering meteorological parameters Data then aggregated to level of city "administrative districts." Exposure status determined based on which administrative district the patient lived in.	Demographic and socioeconomic composition of the city districts—social status, family status Social status, residential stability of city district, distance between university hospital and city district 8.5	Evaluated disease prevalence through age-standardized rates of patients per 100,000 inhabitants per year who underwent surgery in the 1990s. Broken into quintiles from low to high rates. In the overall case, there was no relationship between patient rates and air pollution ($r = -.025$). When breaking data down into city districts above and below the average air pollution level and controlling for confounders, city districts with an above average air pollution level were associated with patient rates ($r = .382$, $p < .05$). In districts with air pollution below average, city rates were not associated with air pollution ($r = -.135$, $p > .10$). When broken up by time period, this relationship was maintained in 1990–1994 ($r = .427$, $p < .05$), but not in 1995–1999 ($p = .265$), which authors note was during a period of decreasing air pollution
		Diagnosed at the Otorhinolaryngology Department at the University of Cologne		NR			

Abbreviations: BC, black carbon; BMI, body mass index; CO, carbon monoxide; COPD, chronic obstructive pulmonary disease; CRS, chronic rhinosinusitis; CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps; EPA, Environmental Protection Agency; EPOS, European position paper on rhinosinusitis and nasal polyps; FESS, functional endoscopic sinus surgery; GA²LEN, Global Allergy and Asthma European Network; KNHANES, Korea National Health and Nutrition Examination Survey; LMS, Lund-Mackay Score; MINORS, methodological index for nonrandomized studies; NO₂, nitrogen dioxide; NOₓ, nitrogen oxides; NR, not reported; O₃, ozone; PM₂.₅, particulate matter ≤2.5 μm in aerodynamic diameter; PM₁₀, particulate matter ≤10 μm in aerodynamic diameter; SNOT-22, sinonasal outcomes test-22; SO₂, sulfur dioxide; TSP, total suspended particulate.

Another study based on the Korea National Health and Nutrition Examination Survey evaluated the impact of PM_{10}, NO_2, O_3, SO_2, and CO.[39] There was a significant correlation between PM_{10} exposure and CRS prevalence, with each 1 $\mu g/m^3$ increase in PM_{10} level correlating with a 1.2-fold higher increase in developing CRS (OR: 1.22 [95% CI: 1.02–1.46], $p = .031$). No significant correlation was found between any air pollutant and CRS incidence.

A third study utilized ICD-9/ICD-10 codes from hospitals in Xinxiang, China to identify patients with chronic sinusitis.[37] Authors evaluated the impact of $PM_{2.5}$, PM_{10}, NO_2, O_3, SO_2, and CO on hospital outpatient cases of chronic sinusitis. All pollutants except for O_3 were associated with an increase in hospital outpatient cases. After adjusting for exposure to co-pollutants, only $PM_{2.5}$ and NO_2 relationships remained significant. A 10 $\mu g/m^3$ increase in $PM_{2.5}$ or NO_2 was associated with a 0.48% (95% CI: 0.22–0.74%) and 1.98% (95% CI: 1.31–2.64%) increase in hospital outpatients, respectively. Authors analyzed cases based on patient age, and these relationships were seen in patients age <65, but not in the subgroup of adults ≥65.

Most recently, a large case–control study was performed which evaluated the impact of long-term $PM_{2.5}$ exposure on the development of CRS.[36] The authors determined $PM_{2.5}$ exposure at 12, 24, 36, and 60 months prior to CRS diagnosis, and location of involved sinuses was recorded. At all measured timepoints, a 5 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with higher odds of CRS diagnosis, most significantly in cases of ethmoidal sinusitis (e.g., 60-month OR: 3.27 [95% CI: 2.03–5.25]) and severe (e.g., involving maxillary, ethmoid, sphenoid, and frontal sinuses) sinusitis (e.g., 36-month OR: 7.91 [95% CI: 3.06–20.42]).

3.4 | CRS disease severity and quality of life

Other commonly evaluated outcomes were metrics of disease severity and quality of life. Four studies evaluated these metrics, but notably, three of the studies were performed by the same author group. Common disease severity indicators evaluated included sinonasal outcome test (SNOT-22), Lund-Mackay score (LMS), systemic steroid usage, and functional endoscopic sinus surgery (FESS) requirement.

The first report studied disease severity in CRSsNP and CRSwNP patients through SNOT-22 scores, LMS, steroid usage, and FESS requirement.[41] $PM_{2.5}$ and black carbon (BC, a major component of PM) exposures were calculated. In CRSsNP patients, $PM2_{2.5}$ exposure was associated with FESS requirement ($p = .015$), with each unit increase in $PM_{2.5}$ exposure corresponding to a 1.89-fold increased risk in proportion of CRSsNP patients requiring revision FESS surgery ($p = .015$). Additionally, BC exposure was associated with SNOT-22 scores in CRSsNP patients ($p = .015$), with each 0.1-unit increase in BC corresponding to a 7.97-unit increase in SNOT-22 scores ($p = .008$). There was no relationship with LMS scores or steroid usage in CRSsNP patients, and there was no relationship between air pollution and any disease severity metric in CRSwNP patients. This was not explained by differences in air pollutant exposure, as exposure was similar between CRSsNP and CRSwNP groups.

A second paper by the same author group was performed similarly but considered allergy status of patients.[40] In this report, similar to above data, in CRSsNP patients, BC exposure was associated with higher SNOT-22 scores. $PM_{2.5}$ exposure was not correlated with disease severity metrics in CRSsNP patients, and neither air pollutant was associated with outcomes in CRSwNP patients. Allergy status was not associated with severity metrics in either CRSsNP or CRSwNP patients. Interestingly, allergy-negative patients were associated with higher exposure levels to both $PM_{2.5}$ ($p = .030$) and BC ($p = .044$) than allergy-positive counterparts. This trend was carried by CRSwNP patients—in which allergy-negative patients had higher $PM_{2.5}$ ($p = .032$) and BC ($p = .017$) exposure than allergy-positive patients—but not seen in CRSsNP patients.

Finally, the third paper from the group evaluated the impact of both air pollutants and occupational exposures on CRSsNP and CRSwNP disease severity.[38] This review will focus solely on the air pollutant exposure. In this study, air pollutant exposure did not vary between subgroups, and disease severity metrics were not correlated with air pollutant exposure in either CRSsNP or CRSwNP groups. Although this is presumably the same study population as the previous papers,[40,41] a subgroup analysis on aspirin-exacerbated respiratory disease was also performed by Velasquez et al. Authors hypothesized the loss of significance was due to small subgroup analyses.[38]

The last paper evaluated the quality of life in CRSsNP and CRSwNP patients based on NO_2 and NO_x exposure.[42] Authors utilized the Swedish Global Allergy and Asthma European Network to collect data on patients with CRS and/or asthma. There was no difference in air pollutant exposure between CRSsNP and CRSwNP patients. The Euro Quality of Life questionnaire was utilized, and air pollution was not associated with the quality of life in CRS patients.

3.5 | CRS histopathology and microbiology

Two studies evaluated the impact of air pollution exposure on histopathologic features of CRS tissue samples. Notably, as tissue samples were obtained from patients undergoing FESS, this suggests cases of severe disease that have failed conservative/medical management.[44]

One study assessed O_3 and $PM_{2.5}$ exposure in patients with CRSsNP and CRSwNP.[35] In the overall CRS population, O_3 exposure was associated with increased inflammatory changes ($p = .031$) and Charcot–Leyden crystals ($p = .039$), but no associations were seen based on $PM_{2.5}$ exposure. Subgroup analysis revealed that this trend was carried by CRSwNP. In patients with CRSwNP, increased O_3 exposure was associated with increased inflammation ($p = .004$), presence of eosinophilic aggregates ($p = .018$), and presence of Charcot–Leyden crystals ($p = .036$). Again, no associations were seen between $PM_{2.5}$ exposure and CRSwNP, and there were no significant associations between CRSsNP and either evaluated pollutant. Notably, these changes were not due to varying exposure levels, as exposure to O_3 and $PM_{2.5}$ did not vary between CRSsNP and CRSwNP patients.

On the other hand, another study looked at the impact of only $PM_{2.5}$ in both cases and controls.[34] Cases of CRS were associated with higher neighborhood $PM_{2.5}$ levels than controls (p <.001). $PM_{2.5}$ levels were also associated with eosinophilic markers in CRS patients (p <.01), but no other relationship was noted with other histopathologic markers evaluated. Additionally, Padhye et al. (2021) assessed for microbial changes associated with air pollution. Interestingly, higher $PM_{2.5}$ exposure was associated with relatively lower amounts of Corynebacterium in both CRS and control cases ($r = -.197$, $p = .02$). Authors note that decreased Corynebacterium has previously been associated with sinonasal inflammation, supporting a link between air pollution exposure and CRS.[45]

4 | DISCUSSION

The pathophysiology of CRS is complex and multifactorial, with chronic inflammation likely playing a large role. Given nasal and sinus mucosa are among our first lines of defense against air pollution, previous studies have investigated and demonstrated that air pollution may be involved in CRS pathogenesis or progression. This systematic review identified and analyzed 10 human studies investigating the impact of EPA criteria air pollutants on CRS disease onset and severity. Overall, most studies indicated evidence of a correlation between air pollution and CRS. All studies investigating the impact of air pollution on CRS incidence/prevalence found a correlation, notably with PM ($PM_{2.5}$ and PM_{10}) and NO_x pollutants. Additionally, disease severity was worse in CRS patients with higher PM or BC exposure, but only in CRSsNP patients. The biological plausibility of a relationship between environmental exposures and CRS was supported by evidence of objective histopathologic and microbial changes with air pollutant exposure.

The pathophysiology of CRS is further complicated by the different disease classifications—CRSsNP (80%) and CRSwNP (20%). Although these phenotypes may present with significant overlap clinically, there are differences in histopathologic findings, inflammatory markers, and associated comorbidities.[7,46–48] Importantly, it has been suggested that there are distinct pathophysiologic mechanisms for CRSsNP and CRSwNP. Only three studies demonstrated a difference in outcomes based on polyp status of patients, while others did not classify patients as CRSsNP or CRSwNP. In two such papers (with the same patient population), worsened air pollution was associated with worsened disease severity in CRSsNP patients.[40,41] On the other hand, CRSwNP patients demonstrated histopathologic changes associated with air pollution that were not seen in CRSsNP patients, suggesting that the two subtypes may respond differently to air pollution.[35] Thus, studies that do not account for this distinction in subtypes may arrive at alternate conclusions.

Another confounding factor in the diagnosis and management of rhinosinusitis is the role of allergens. The one study considering the impact of allergens noted that pollutant exposure ($PM_{2.5}$ and BC) was higher in allergy-negative CRS patients than allergy-positive patients.[40] Notably, this trend was driven by CRSwNP but not seen in CRSsNP patients. Additionally, allergy status played no role in disease severity outcomes. This study further highlighted the complex relationship between air pollution, CRS subtypes, and allergens but suggests that environmental pollutants may have more of an impact on nonallergic disease than allergic disease.

Multiple evaluated pollutants were associated with CRS, including PM, BC (a major component of PM), NO_x, and O_3. Of the evaluated pollutants, PM is the most well studied. Most studies (8/10) investigated the impact of PM (either $PM_{2.5}$ or PM_{10}), and even when controlling for additional air pollutant exposure, the independent impact of PM alone was apparent. PM is formed from chemical reactions between other pollutants produced from various sources, including industrial plants and cars.[14] Since 1990, $PM_{2.5}$ and PM_{10} emissions have dropped 38% and 31%, respectively, and emissions of the other criteria air pollutants have fallen even more dramatically over the same time period.[49] Despite these improvements, almost 100 million Americans are living in a county with at least one air pollutant over the National Ambient Air Quality Standards.[49] Additionally, data from other parts of the world demonstrate challenges in controlling air pollutant exposure.[50,51] Given the demonstrated large impacts that air pollution has on the health of individuals, increased effort on regulation and control of this pollution has the potential to impact millions of lives.

This review benefits from many strengths, including being the first systematic review focused on EPA air pollutants and CRS disease markers. By including only studies utilizing objective diagnostic criteria, this review limits the ambiguity in diagnosis for CRS, although it is challenging to limit completely. Additionally, by including only papers that evaluated at least one EPA criteria air pollutant, this review studies the impact of large-scale pollutants that affect populations worldwide. Therefore, this review provides evidence for the utility of a large-scale population study evaluating the effects of criteria air pollutants on CRS, with emphasis on the distinction between CRSsNP and CRSwNP.

Despite the strengths of the review, there are inherent limitations in the studies included. Studies utilized home addresses to determine pollutant exposure criteria. Although this is a commonly employed technique that allows for estimated exposure levels to be calculated, it is imprecise and does not account for time spent away from the home or other encountered sources of exposure. Although the use of personal air pollution monitors worn by study participants would allow for better approximations of air pollutant exposure, this would be a challenging, costly study design, which may limit its application. Additionally, in the available studies, there is significant heterogeneity in the data, especially with regard to the type of environmental pollutants evaluated, the methodology for determining exposure, and the outcomes of interest. Therefore, this limits the ability to make definitive conclusions. Finally, most studies were retrospective in nature without defined healthy control groups. Future studies would benefit from the addition of control populations to determine the impact of air pollution on those without diagnosed upper airway disease.

5 | CONCLUSION

Recent evidence suggests a role for air pollution in the onset and severity of CRS, most notably with relation to $PM_{2.5}$ exposure. This

supports previous in vitro and in vivo models of pollution in CRS. This further adds to the existing body of literature demonstrating the many negative health impacts of exposure to air pollution, including impacts on upper airway disease, lower airway disease, cardiac disease, and overall morbidity and mortality. Given this evidence, consideration should be given to further investigation and implications for air pollution exposure and supports the need for increased regulation toward measures to improve air quality.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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