



Air Pollution and Allergic Rhinitis: Role in Symptom Exacerbation and Strategies for Management

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Abstract: This article reviews the current understanding of the role of air pollution in both the symptom exacerbation and rising prevalence of allergic rhinitis (AR) for the development of future AR therapeutics and management strategies. We discuss the epidemiological evidence for this relationship through birth cohort studies, the economic impact of AR, and the influence of air pollution through the lens of the exposome framework of allergic disease development. This is followed by a discussion on the influence of diesel exhaust and diesel exhaust particles (DEP) from motor vehicle emissions and their implication in the rising prevalence of allergic disease and allergic sensitization through triggering inflammatory signalling pathways that exacerbate AR symptoms. Finally, a summary is provided of clinical trials assessing the influence of air pollution on AR with a depiction of currently available therapies and management strategies. Future directions in the development of AR modalities given the air pollution-mediated symptom exacerbation are challenged with unfolding the complex gene–environment interaction product of heterogenous AR presentation.

Keywords: diesel exhaust, particulate matter, therapy, vehicle emissions

Introduction

Allergic rhinitis (AR) is a non-communicable, IgE-mediated inflammatory disease caused by type 1 hypersensitivity reactions induced by allergen exposure with common symptomology including rhinorrhea, itching, sneezing, bronchial hyperresponsiveness, or airflow obstruction.^{1,2} Due to the nature of AR symptoms, the condition is often ignored, misdiagnosed, and thought not to be overly detrimental, yet AR amasses substantial socioeconomic burden, adverse effects on sleep length and quality, productivity, and quality of life.³ AR prevalence has been cited to be approximately 10–30% of adult populations, though the true incidence might be indeterminable as data collection necessitates physician diagnosis and does not account for individuals who self-medicate or are undiagnosed.^{4,5} Given the rising prevalence of allergic respiratory disease over the last several decades and increasing air pollution with urbanization, industrialization, and rapid economic growth, there has been longstanding interest in the association between AR development and air pollution. Furthermore, environmental factors influencing AR treatment and management strategies have garnered interest; specifically, the management of allergic rhinitis in urban environments with significant levels of air pollution being a growing focus in the research community. By 2050, it is predicted that 68% of the world's population will be living in urban centres.⁶ Consequently, urban

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outdoor air pollution is responsible for 4.2 million deaths worldwide each year and is observed to increase the risk of developing respiratory conditions including AR, asthma, and chronic obstructive pulmonary disease.⁷

Air pollution refers to substances emitted by processes and sources such as fuel combustion, power generators, industrial facilities, or agricultural waste sites in the ambient air, which may take the form of solid particulate matter (PM), liquid, or gaseous emissions. A substantial environmental contribution to the prevalence of allergic disease has been recognized,⁸ where both symptom exacerbation and allergic disease development may result from exposure to air pollution contents, namely gaseous compounds including NO₂, NO, SO₂, CO, and CO₂, and airborne PM from traffic diesel exhaust particles (DEP). Diesel exhaust particles are a solid agglomeration of carbonaceous material with volatile organic and sulfurous compounds emitted directly by diesel engine fuel combustion with various particle sizes. DEP particle size displays a trimodal distribution, where nanoparticles of <50nm represent the vast majority of particles emitted,⁹ and PM₁₀ of diameter <10mm, fine particles of PM_{2.5} with diameter <2.5mm, and ultrafine particles of PM_{0.1} with diameter <0.1mm being the most common PM sizes in the traffic-related air pollutant (TRAP) group.¹⁰ DEP particle size governs its relative implication in allergic disease exacerbation given the respective particle's diameter where PM₁₀ can reach the lower respiratory tract, PM_{2.5} may penetrate the lungs, and PM of diameter <1.0 mm can penetrate further into the alveoli and thus reach the bloodstream.¹¹ Given the rising burden of air pollution-associated AR, there is currently an ongoing challenge of understanding AR development and the role of air pollution in both symptom exacerbation and the rising prevalence of allergic diseases. Understanding the interaction of environmental exposures like air pollution with the genetic landscape of allergic disease development is critical to the formulation of future therapeutic modalities.

Epidemiology

AR prevalence is estimated at 10–30% of adults in the United States and Europe, reported as the most frequent atopic disease in developed countries with up to 40% incidence in children.¹² These values exhibit discordance between epidemiological studies of varying sizes,¹³ possibly due to methodological disparities between positive allergy testing and self-reported allergy. Larger studies including the Swiss Study on Air Pollution and Lung Disease in Adults (SAPALDIA) and The National Health

and Nutrition Examination Surveys (NHANES) found that self-reported allergy tends to overpredict AR incidence,^{13,14} that epidemiological analysis is markedly varied amongst different populations of individuals and the geographic location studied. AR further complicates study results by numerous phenotypic and endotypic presentations with categorization into seasonal AR, perennial AR, and mixed rhinitis. Additional complexity is conferred due to the nature of the allergic disease being a product of the interaction between genetic predisposition, epigenetics, and environmental exposure contributing to the heterogeneity of AR presentation.

AR incidence has been increasing in most industrialized countries of the world with rapid urbanization, linked to increasing air pollution in both symptom exacerbation and the rising prevalence of atopy. Given AR commonality in developed countries, there is substantial socioeconomic burden and associated co-morbidities impacting quality of life with facilitation of both presenteeism and absenteeism, representing 76% to 93% of total AR costs in a 2005 to 2015 study assessing AR and work productivity.¹⁵ Further, that AR symptoms impact sleep quality with increased sleep disturbances given moderate and severe AR, perpetuating daytime sleepiness and ability to work along with depression, anxiety, and impaired cognitive function.¹⁶ 80% of AR patients develop symptoms before the age of 20,¹⁷ where AR is estimated to generate \$2 to \$5 billion annually in direct health-related cost expenditures including \$2 to \$4 billion in lost annual productivity in the United States alone.¹⁸

Recently, various experimental and epidemiologic studies have well demonstrated this association between air pollution, particularly PM, and the rising prevalence of allergic diseases.^{19,20} Air pollution can be classified as part of the exposome, a measure of all the exposures of a subject in their lifetime, and how they influence health. AR, as a complex gene–environment interaction product, has been described through a framework called the exposome, with three separate domains: internal, specific external, and general external.²¹ The internal domain consists of innate host-related factors including metabolism, microbiome, epigenetics, and age, whereas the general external exposures include the larger socioeconomic, geographic, and psychological factors.²¹ Most relevantly, the last domain encompasses individual-level specific external exposures, including cigarette smoke and air pollution. The exposome thus represents a point of analysis, where exposome examination through birth cohort studies

represents an avenue to better appreciate the environmental contribution to allergic disease development.

Current ongoing studies investigating the exposome include the Canadian Healthy Infant Longitudinal Development (CHILD) birth cohort study, which aims to address the developmental origins of allergy, in which environmental exposures in both pre-natal and postnatal life influence susceptibility to allergy development through epigenetic mechanisms.⁸ The study recruited over 3500 pregnant women, who gave birth between 2009 and 2012 and examines early-life, human, genetic, epigenetic, and microbiome data through biological samples, questionnaires, and home and clinical assessments.⁸ Comparably, the Kingston Allergy Birth Cohort (KABC) compliments the CHILD study, which found a significant correlation among both pre-natal and postnatal factors, including socioeconomic status, housing type, urban residence, and garage type.²⁶ The study recruited mothers in their 2nd and 3rd trimesters of pregnancy and used assessments of psychosocial characteristics, household exposures, birth characteristics, nutrition, and biological samples of blood, urine, nasal swabs, stool, and breast milk. Overall, the study found that the general external domain acted as a critical modifier of the specific external domain with a significant association between caesarean section, gestational age, and older siblings with decreased respiratory reports.²⁶ Further, the cohort found a negative association between gestational age and respiratory symptom risk, consistent with pre-term children studies on lung function, where allergic disease incidence was associated with pre-natal smoke exposure, mold, and air freshener usage.²⁶

In conjunction with some of the findings in the KABC study, exposure to airborne PM and other air pollutants has been implicated in several pre-natal and childhood exposure studies suggest that the timing of exposure or cumulative exposure to specific pollutants may uniquely influence allergic disease development. A 2016 study by Deng et al surveyed exposure to air pollutants during pregnancies to assess the risk of childhood atopic diseases. The study, which surveyed 2598 preschool children, found that maternal exposure to NO₂ during the third semester was associated with children's lifetime incidence of allergic rhinitis.²² AR prevalence was found to be significantly positively correlated with age-related accumulative PM₁₀, SO₂, and NO₂ exposure in preschool children, but not associated with site-specific background concentrations of pollutants.²³ Furthermore, Norbäck et al (2019) found that postnatal exposure to NO₂ and PM₁₀ is associated

with an increased prevalence and lower remission of childhood allergic rhinitis.²⁴ Notably, a similar epidemiological study which collected data on PM sources, antibiotics use, ambient temperature and ambient air pollution found that PM₁₀ exposure can synergistically enhance risk factors, such as antibiotics and environmental tobacco smoke, for childhood allergic rhinitis.²⁵

Mechanisms of Diesel Exhaust Particles and Allergic Rhinitis

Diesel exhaust particles (DEPs) act as adjuvants, augmenting the immune response to aeroallergens associated with allergic rhinitis (AR) through numerous mechanisms. DEP enhances IgE production when co-administered intranasally with ovalbumin in mice,^{27,28} and when immunized with pollen grains and DEP in a rat pollen model.²⁹ The polycyclic aromatic hydrocarbon (PAH) components of DEP enhance basophil activation in individuals with birch pollen allergy with IL-4, a Th2 developmental cytokine, and IL-8 secretion,³⁰ a granulocyte chemoattractant with a role in human lung IgE-mediated lung inflammation.³¹ In a sequence of articles, Diaz-Sanchez et al demonstrated that DEP can augment mast cell degranulation of histamine alone or subsequent to antigen-FCεRI engagement, and can promote de novo mucosal IgE response to an allergen in individuals without previous sensitization, suggesting an adjuvant role in enhancing IgE response to neoantigens.³² This has led to a more comprehensive understanding of DEP's role in driving allergic sensitization. DEP enhances antigen presentation through the upregulation of HLA-DR and CD86 expression in cultured nasal epithelial cells,³³ cell-surface molecules typically restricted to antigen-presenting cells, contributing to the enhancement of allergic reactions through upregulation of these co-stimulatory signals involved in T-cell activation and survival. Further, nasal fibroblasts increase expression of IL-6 and IL-8 through activation of p38, Akt, and NF-κB signalling pathways, aggravating allergic rhinitis through promoting local nasal inflammation.³⁴ Epithelial cells play a key role in allergic inflammation with upregulated expression of intercellular adhesion molecules ICAM-1 and VCAM-1, critical in cell-cell attachment for T cell activation, consequently increased with the presence of DEP in bronchiolar epithelium.³⁵ The nasal epithelial barrier acts as the primary physiological barrier against paracellular allergen invasion, maintained by apical tight junctions (TJ) between epithelial

cells which are disrupted in individuals with nasal allergy. DEP disrupts tight junctions to increase the paracellular permeability of allergens in vivo through downregulation of zonula occludens-1 and claudin-1 transmembrane TJ protein expression, independent of the transcriptional regulation of TJ constituents.³⁶ DEP accomplishes TJ disruption through a reactive oxygen species (ROS)-mediated pathway, where ROS production by nasal epithelial cells mediates DEP-induced TJ disruption lasting for several days with a single DEP treatment.³⁶ In bronchiolar epithelium, ROS was generated by DEP component metabolism including PAH and quinones, resulting in MAPK signal transduction pathway and NF- κ B transactivation-induced release of proinflammatory cytokines with nuclear translocation of the Nrf2 transcription factor for antioxidant protein-encoding genes.³⁷ DEPs thus trigger numerous signalling pathways that lead to an enhanced inflammatory response through ROS generation that exacerbates allergic rhinitis.

Recent Studies and Current Treatments

AR management and therapies aim to prevent or reduce symptoms associated with allergic inflammation. With the increasing levels of air pollution and epidemiological studies displaying a relationship between air pollutants and exacerbation of allergic/respiratory symptoms, it may be increasingly appropriate for AR treatments to be assessed under environmental conditions mimicking outdoor air pollution.^{20,38} Several studies investigate the mechanisms that contribute to exacerbated AR symptoms and the efficacy of medications (Table 1). In these studies, AR or nonatopic subjects are commonly exposed to DE or DEP via a controlled allergen exposure facility, pollution chamber, intranasal challenge, or breathing apparatus. Combined DEP and allergen exposure was found to exacerbate AR symptoms relative to sole allergen exposure.³⁹ Currently, fexofenadine hydrochloride is the only medication that has been tested in a controlled allergen exposure facility to alleviate AR symptoms during DEP and allergen co-exposure.³⁹ DE and allergen co-exposure negatively impacts lung function, increases CD4, IL-4, CD138, and nasal elastase in the respiratory submucosa of AR subjects; increases in blood neutrophils (24 hours) and eosinophils (24 and 48 hours) post-exposure were also found.^{39,40} Additionally, co-exposure to allergen and DE alters the expression of allergen-

induced secreted proteins linked to the protein phosphatase 2A pathway and the MAPK1-ERK1/3 axis, which regulates the response to oxidative stress and inflammation, respectively.⁴¹ Other forms of air pollutant exposure include oil fly ash, a particulate produced from coal combustion. Hauser et al (2003) found increased nasal lavage leukocytes, neutrophils, and IL-4 in AR subjects co-exposed to an allergen and residual oil fly ash.⁴² Co-exposure with allergen and atmospheric levels of ozone resulted in elevated nasal lavage neutrophils, eosinophils, and mononuclear cells.⁴³ Extended co-exposure with nitrogen dioxide (NO₂) elevated levels of eosinophilic cationic protein in nasal lavage fluid.⁴⁴

Surveying the results of these trials, a number of considerations should be noted. An investigative study suggests that the order and timing of exposure may be an important differentiation when comparing results. Clifford et al (2016) found that allergen and DE co-exposure was not associated with significant changes in DNA methylation in bronchial epithelial cells. However, exposure to allergen and DE separated by four weeks resulted in methylation changes in over 500 CpG sites, which differed depending on the order of exposure.⁴⁵ Besides alterations in DNA methylation, there may be other lingering effects in subjects due to DE or allergen exposure prior to a study or between study visits.

Exposure to DEP versus DE and the gas composition of DE is another differentiator. The toxicity and depth of deposition of DEP in the lungs is dependent on its size, which may be affected if the study methods involve the collection and re-aerosolization of DEP.^{46–48} The most numerous and most toxic particles fall into the fine (PM_{2.5}) and ultrafine (PM_{0.1}) range.⁴⁸ DEP forms aggregates when stored in a bulk source, which may make their atmosphere particle size distribution difficult to replicate during aerosolization.⁴⁸ Lastly, the use of DE treatments or high-efficiency particulate absorbing (HEPA) filters, which are commonly installed in automobiles and some breathing apparatuses, may be relevant to study design. In Wooding et al (2019), HEPA filters reduced PM_{2.5} 94% and VOCs 9.5%, while increasing NO₂ content 350% in DE. Electrostatic precipitation in HEPA filters oxidizes nitrous oxide (NO), thereby increasing the levels of NO₂ in DE. Instead of alleviating the exacerbated AR symptoms expected from co-exposure studies, lung function was further impaired compared to DE and allergen co-exposure. The impairment in lung function is partially attributed to elevated NO₂, which is consistent with other

Table I Summary of Interventional and Investigative Studies Assessing Air Pollution and Allergen Exposure in Subjects with Allergic Rhinitis

Identifier	Study Type	Patients	Exposure	Results
Air Pollution Particulate and Diesel Exhaust Particle Exposure				
Ellis et al 2019 ³⁹	Phase 3, single-center, sequential and parallel-group, double-blind, randomized study	257 adults with allergic rhinitis	DEP ($600 \pm 100 \text{ ng.m}^{-3}$), Ragweed pollen ($3500 \pm 500 \text{ grains.m}^{-3}$), Allegra [®] /Telfast [®] (Fexofenadine Hydrochloride) 180 mg	Allegra [®] /Telfast [®] 180 mg significantly decreased pollution-exacerbated AR symptoms by 21% ($p = 0.0148$) in adult allergic rhinitis patients. Exposure to combined ragweed and DEP significantly increased TNSS ($p < 0.0001$).
Hauser et al 2003 ⁴²	Randomized, crossover, exposure study	5 adults with allergic rhinitis 3 adults nonatopic subjects	Residual fly ash particulate* (1.00 mg.m^{-3}), Ragweed pollen, Birch pollen, Oak pollen	A 143% and 130% enhancement of nasal lavage leukocytes and neutrophils, respectively, were found in atopic but not in nonatopic subjects exposed to particulate and allergen. No significant enhancement in IL-3, TNF- α , or total IgE in group of subjects during exposures.
Diesel Exhaust Exposure				
Clifford et al 2017 ⁴⁵	Randomized, crossover, exposure study	17 adults with allergic rhinitis	DE ($300 \text{ }\mu\text{g.m}^{-3}$), House dust mite, Timothy/Pacific grass pollen, Birch pollen	Exposure to an allergen and DE separated by 4 weeks resulted in significant changes in more than 500 CpG sites 48 hours post-exposure. Sites of differential methylation differed depending on the order of exposure. Analysis of differentially methylated CpG sites identified genes for transcriptional factor activity, protein metabolism, cell adhesion, and vascular development.
Hosseini et al 2016 ⁵²	Blinded, crossover, exposure study	12 adults with allergic rhinitis	DE ($300 \text{ }\mu\text{g.m}^{-3}$), House dust mite, Pacific grass pollen, Birch pollen	Allergen-DE co-exposure resulted in significantly elevated CD4, IL-4, CD138, and neutrophil elastase in the respiratory submucosa of atopic subjects compared to filtered air and saline exposure.
Mookherjee et al 2018 ⁴¹	Randomised, blinded, crossover, exposure study	14 adults with allergic rhinitis	DE ($300 \text{ }\mu\text{g.m}^{-3}$), House dust mite, Pacific grass pollen, Birch pollen	Protein changes in the lungs unique to allergen-DE co-exposure include the significantly enhanced (≥ 16 -fold) production of cystatin-SA, complement C4B, lipocalin-I, mucin-I6, and transcobalamin-I compared to allergen-filtered-air exposure.
Wooding et al 2019 ⁴⁰	Randomized, double-blind, crossover, exposure study	14 adults with allergic rhinitis	DE ($300 \text{ }\mu\text{g.m}^{-3}$), Particle depleted diesel exhaust, House dust mite, Pacific grass pollen, Birch pollen	Allergen-particle depleted diesel exhaust exposure impaired lung function (decrease in FEV ₁ at 30 min) 7.5% greater than allergen-DE exposure. Significantly greater impairment was observed in participants with genetic risk score exposed to allergen-particle depleted diesel exhaust ($p = 0.008$ for condition-by-genetic risk score interaction).

(Continued)

Table 1 (Continued).

Identifier	Study Type	Patients	Exposure	Results
Gaseous Air Pollutant Exposure				
Bascom et al 1990 ⁴³	Randomized, crossover, exposure study	12 adults with allergic rhinitis	Ozone (0.5 ppm), Ragweed pollen, Grass pollen	Exposure to ozone and allergen caused a significant increase in upper and lower respiratory symptoms, a 7-fold increase in nasal lavage neutrophils, a 20-fold increase in eosinophils, a 10-fold increase in mononuclear cells, and a significant increase in nasal albumin concentration compared to clean air and allergen exposure.
Wang et al 1995 ⁴⁴	Randomized, single-blind, crossover study	16 adults with allergic rhinitis	Nitrogen dioxide (400 ppb), Grass pollen (mixed)	Allergen challenge after exposure to Nitrogen dioxide but not air, significantly increased levels of only eosinophil cationic protein in nasal lavage fluid ($p < 0.05$).

Note: *Coal combustion product.

Abbreviations: DE, diesel exhaust; DEP, diesel exhaust particles; TNSS, Total Nasal Symptom Score.

studies demonstrating that NO₂ can enhance airway response to an allergen, but a definite cause is unclear.^{40,49}

Management of Allergic Rhinitis Exacerbated by Air Pollution

The first-line treatment of AR includes oral or nasal corticosteroids and avoidance of allergens and irritants such as tobacco smoke, moulds, and DE. Pollen exposure can be reduced by closing windows, window screens, and avoidance of parks during peak pollen seasons. Air pollution exposure can be reduced by avoiding rush hours and avoiding time outdoors during the afternoon of summer months when ground-level ozone levels are highest.⁵⁰ Outdoor air pollution and allergen exposure in the workplace may be mitigated by shift rotations, personal protective equipment, and adjusted working hours. Following avoidance and corticosteroids, second-line therapies include decongestants, cromolyn, H₁ antihistamines, leukotriene receptor antagonists, and allergen immunotherapy.⁵¹ Fexofenadine hydrochloride (Allegra[®]) is an oral non-sedating antihistamine; the 180 mg dose has been verified to alleviate AR symptoms aggravated by diesel exhaust particulates.³⁹ Since there are no specific indicators that differentiate AR aggravated by air pollution, and few targeted AR medications for combined exposure, education to improve awareness of air pollution may be advisable. Avoidance of peak commuting hours in combination with peak pollen season may be recommended to individuals living in areas with high levels of air pollution.

Further clinical trials and studies are needed to determine more effective methods of mitigating pollution-exacerbated AR symptoms. While designing future studies, there are a variety of air pollutant constituents, allergens, and exposure methods. For example, DE produced by different engines have variable levels of PM and gas composition. Re-aerosolization during exposure to PM may replicate outdoor particulate distributions with relative success.⁴⁸ A simultaneous pollutant and allergen exposure may be possible if a pollution chamber or controlled allergen challenge facility is available but may otherwise be delivered via a breathing apparatus. The availability of exposure facilities may also dictate whether a subject with AR is exposed to an allergen and pollutants simultaneously, or after one another. Future studies may be designed to improve understanding of the priming effect exposure to DE, DEP, or allergen has on subsequent exposure to air pollutants and allergens. Interventional studies may also investigate whether medications are effective at alleviating exacerbated AR symptoms during co-exposure to O₃, NO₂, or DE with elevated DEP levels.

Conclusion

Allergen and air pollutant co-exposure have been shown to exacerbate AR symptoms and induce changes in the allergic immune response relative to sole allergen or air pollution exposure. Epidemiological and investigative studies demonstrate the immunological effects from allergen and air pollutant co-exposure, which include exacerbated AR symptoms and enhanced inflammatory response with the

recruitment of inflammatory cells, cytokines, and interleukins. Despite advances in understanding the priming or adjuvant effect of air pollutants, such as DEP, there is a lack of research in potential methods of managing AR exacerbated by air pollution. A survey of clinical trials reveals fexofenadine hydrochloride as the only therapy that has been shown to alleviate exacerbated AR symptoms during pollen and DEP co-exposure. Other investigative clinical trials support the continued evaluation of potential AR therapies during co-exposure and air pollution avoidance in AR symptom management. However, in many instances, complete avoidance of allergens and air pollution is not feasible. Education of subjects with AR and further assessment of current and future AR therapies are needed to establish a complete program to manage AR exacerbated by air pollution exposure.

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