# Air Pollution Effects in Allergies and Asthma

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**KEYWORDS**

• Air pollution • Urbanization • Epithelial barriers • Alarmins • Asthma
• Allergic rhinitis • Health effects

**KEY POINTS**

- Outdoor air pollution is associated with exacerbations of allergic diseases, including asthma, allergic rhinitis, and other atopic conditions.
- The main greenhouse gasses generated by human activity that cause health effects are carbon dioxide ($CO_2$), methane ($CH_4$), nitrous oxide ($N_2O$), ambient particulate matter, and gaseous pollutants including nitrogen dioxide ($NO_2$), sulfur dioxide ($SO_2$), and ozone ($O_3$).
- Air pollution and climate changes have led to increased geographic distribution of pollen, prolonged pollination seasons, and these higher pollen counts have contributed to health effects in allergic rhinitis and asthma sufferers; indoor and outdoor air pollutants act synergistically with allergens to magnify allergic responses.
- The epithelium functions as a protective barrier for many organ systems and disruption leads to a permeable epithelium causing dysbiosis, an imbalance in the microflora that can induce tissue inflammation.
- Changes in the microbiome are now recognized as being important for shaping the immune system and tissue homeostasis of the upper and lower respiratory tracts and gastrointestinal tract.

## INTRODUCTION

Outdoor air pollution is associated with exacerbations of allergic diseases, including asthma, allergic rhinitis (AR), and other atopic conditions.[1] Both new onset of these conditions and exacerbation of existing allergic disorders have been shown to occur

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with air pollution.[1] Pollution includes particulate matter (PM), gaseous pollutants (including ozone [$O_3$], nitrogen dioxide, and sulfur dioxide [$SO_2$]), and traffic related air pollution (TRAP).[1] PM (either $PM_{10}$ [diameter: <10 um] or $PM_5$ [diameter: <2 um]) includes metals, such as copper, magnesium, zinc, and iron, which increase free radicals and reduce antioxidants.[2] This leads to a discharge of inflammatory cytokines, oxidative stress, and cellular damage.[2] Urbanization is thought to contribute to air pollution.[1] The increased allergic disease prevalence has been linked to this urbanization, industrialization, and economic growth globally.[3] This causes serious morbidity in allergic diseases.[4] This review provides an overview of the health effects of air pollution on allergic disorders and specifically addresses how it may impact the epithelial barrier in the upper and lower respiratory tracts to facilitate the health effects associated with these exposures.

## AIR POLLUTION EFFECTS ON AEROBIOLOGY

Nearly 100 years ago, F. C. Meier coined the term aerobiology to describe a project evaluating the study of life in the air. Since that time, although there are various definitions, aerobiology is accepted as a branch of science studying the occurrence and effects of airborne microorganisms such as pollutants, viruses, and pollens. Regardless of the specific definition, the importance of aerobiology has become widely accepted to play an integral role in all aspects of human society, including space exploration, biological warfare, industrial as well as agricultural engineering, and human health.

The main greenhouse gasses generated by human activity are carbon dioxide ($CO_2$), methane ($CH_4$), nitrous oxide ($N_2O$). In addition, ambient PM and gaseous pollutants including nitrogen dioxide, sulfur dioxide ($SO_2$), and ozone have caused great health concerns.[5] Since the industrial revolution, the concentration of $CO_2$ in the atmosphere has increased by nearly 50%, from an average of 280 ppm to more than 415 ppm.[6] This increase in greenhouse gasses has led to increased global temperatures and has been a driving factor behind climate change, defined by the United Nations Framework Convention on Climate Change as “a change of climate which is attributed directly or indirectly to human activity that alters the composition of the global atmosphere and which is in addition to natural climate variability observed over comparable period.”[7] Consequently, the increased production of greenhouse gasses has contributed to air pollution and decreased air quality. The World Health Organization reports that greater than 90% of the world’s population live in areas of low air quality, where the concentration of pollutants exceeds recommended guidelines.[8] Air pollution is felt to be one of the leading causes of premature death around the world, with pervasive effects on human health affecting all body systems.[8] Although chronic obstructive pulmonary disease is the leading cause to death attributed to air pollution, air pollution affects non-respiratory organs as well and has a myriad of impacts ranging from mental health to ischemic heart disease.[9] Air pollution has also been linked to increased susceptibility to respiratory viral infections.[10] Potential mechanisms include changes in epithelial cell permeability and impaired local antiviral immunity by the imbalance of mucosal adhesion molecules and T-helper cells.[11] The importance of effects on respiratory viral immunity has never been more important than during the ongoing global coronavirus-19 (COVID-19) pandemic. Studies have suggested exposure to increased air pollution may increase frequency and severity of COVID-19 infection, potentially even contributing to mortality.[12] Finally, aerobiology has an undeniable impact on chronic rhinitis and asthma, reviewed in greater detail in subsequent sections of this review.[13]

Air pollution and changes in climate also have several indirect consequences that impact human health. Warmer temperatures lead not only to increased geographic distribution of pollen but also to prolonged pollination seasons, potentially starting a week earlier and lasting a week longer than previous decades.[14] Plants may also produce higher pollen counts, with increased allergenicity. Ragweed, for example, has been shown to grow faster in urban areas as compared with rural areas.[15] Similarly, birch trees exposed to more ozone produce more pollen as compared with trees in areas of better air quality.[16] Along with increased amounts, pollen adjacent to heavy traffic released more allergenic mediators as well, potentially leading to more significant symptomatology in atopic individuals.[17] Given that pollen not only carries allergen but also highly active lipid mediators (pollen-associated lipid mediators), exposure has immunomodulating effects, including increased local airway inflammation.[18,19] Even local events, like the attacks on the World Trade Centers in 2001, can impact aerobiology by changing local conditions. Following these attacks, there was increased $O_3$ and $SO_2$ in the New York City area, and this correlated with increased asthma-related emergency department visits.[20] Climate change also contributes to extreme weather events, such as increase hurricanes and cyclones, wildfires, droughts, and dust storms. In addition to obvious societal impact, these changes can also impact aerobiology in less obvious ways and can even alter indoor environments. Extreme weather can lead to widespread flooding, as evidenced by Hurricane Katrina in New Orleans and Hurricane Harvey in Houston. Flooding can change indoor conditions, leading to increased microbial and mold growth, and thus impacting sinopulmonary conditions. The indoor environment is also affected by several other factors, including surrounding outdoor pollutants and the quality and ventilation. Indoor activities such as smoking, heating, and cooking also impact indoor aerobiology.[21]

Although everyone is affected by aerobiology and changes due to climate change, there are certain vulnerable populations more impacted by this phenomenon. The impact can start as early as the prenatal stage and may impact children even more than adults. Prenatal exposure to air pollution is consistently linked to the increased risk of asthma and wheezing in children.[22] A meta-analysis looking at 35 studies across 12 countries on the impact of air pollution and AR found children and adolescents to be more susceptible as compared with adult counterparts.[23] At the other end of the spectrum, the growing elderly population may be similarly susceptible to changes in aerobiology. Individuals in urban centers also seem to be at a higher risk of disease as compared with those in more rural environments with increased green space. This distribution may also impact health care disparities and thus warrants special attention.

Given the noteworthy changes in aerobiology and its impact on human health, the question becomes on how to intervene in hopes of changing the current trajectory. Given the recent increasing rates of global warming, climate experts predict continued worsening of annual warming rates unless we implement aggressive mitigation strategies. On a microlevel, individual actions are necessary to affect change. In addition to raising awareness, strategies such as shared transport rather than individual transport can decrease emissions. Decreasing livestock produced by less reliance on meat consumption can impact $CO_2$ production. On a public health level, fossil fuels must be replaced by renewal energy sources. Without these policy changes, there will continue to be an irreversible negative impact on the planet and human health.

## HEALTH EFFECTS OF AIR POLLUTION ON CHRONIC RHINITIS

Air pollutants can be classified as indoor or outdoor, primary (if they are emitted directly into the atmosphere), or secondary (if they react or interact with it, eg, ozone).

In this sense, biological air pollution is caused in part by aeroallergens that may preferentially contribute to atopic diseases indoors or outdoors, such as AR and asthma. AR is an Immunoglobulin E (IgE)-mediated type 1 hypersensitivity disease, triggered by a spectrum of environmental allergens such as outdoor pollen or mold spore allergens and/or indoor allergens such as dust mites, cockroaches, pet allergens, or molds. However, there are other rhinitis phenotypes such as vasomotor rhinitis that are not IgE-mediated but rather induced through neurogenic pathways, which are triggered by a spectrum of chemical irritants, odorants, or weather changes (ie, temperature, barometric pressure).[24]

Presently, the prevalence of AR induced by environmental pollutants in children and adults is poorly elucidated. Reasons for this gap in knowledge may be due to differences in epidemiological study design and exposure assessment methods including exposure duration.[25] However, most studies have found a strong interaction between air pollutants and AR.[26–28] A recent systematic review and meta-analysis found that the effect of air pollutants on AR, except for $PM_{10}$, was significant and higher in developing countries than in developed countries.[23]

### *Outdoor Air Pollution*

The main outdoor air pollutants that affect health, such as particulate matter (PM), $O_3$, TRAP, and DEP, exist in solid or liquid forms and can be anthropogenic or naturally occurring during dust storms, forest fires, or to a lesser extent during volcanic eruptions.[29,30] Likewise, PM can vary in its composition[31] and size[32] and it has been shown in both in vivo and in vitro studies that fine and ultrafine particles are the pollutants most commonly associated with the pathologic changes that occur in the upper and lower respiratory tracts causing symptoms.[33]

In a multicenter study, in five European birth cohorts, it was shown that exposure to PM and nitrogen oxides was associated with a deficit in school-age children's lung function. This same association was also found in a study of five European adult cohorts which demonstrated that greater exposure to nitrogen monoxide (NO), $NO_2$, and $PM_{10}$ from traffic was associated with decreased lung function.[34]

Although studies reporting on the relationship between rhinitis and outdoor air pollution continues to be inconsistent in both adults[35] and children[36]; it has been seen that people living in urban areas are affected more so than those living in rural areas.[37] In addition to the air pollutants already mentioned, there are other particulates related to the deterioration of respiratory health, such as livestock emissions such as organic dust, toxins from microorganisms, and ammonia or methane gases. For example, a Dutch study showed an association between high levels of outdoor air pollution and decreased lung function in rural dwellers including non-farmers.[38]

### *Indoor Air Pollution*

A common source of indoor air pollution is tobacco smoke, which contains at least 4500 toxic chemical compounds, including PM, oxidizing gases, heavy metals, and at least 50 carcinogens. Recently, pyrosynthesis and cigarette combustion related to domestic smoking were identified as key phenomena that increase the levels of PM and toxic chemicals in homes.[39] In addition, other indoor air pollutants include nitrogen dioxide, carbon monoxide (CO), formaldehyde,[40] and chemical volatile organic compounds (cVOCs) such as those generated by construction materials or cleaning products. Generally, indoor pollutants are most frequently generated by gas cooking and heating appliances. Studies have found that the presence of indoor $NO_2$ increases or worsens asthma symptoms in children.[41,42] Similarly, a systematic review reported

the existence of a weak relationship between cVOCs generated by building materials and/or cleaning products with AR, both in children and adults.[43]

An interaction between air pollutants resulting from the consumption of solid fuels, such as coal, and tobacco smoke exposure has been established for asthma in both adults and children.[44] However, until now, there is no conclusive evidence linking the different contaminating agents with AR. Similarly, an interaction between air pollutants and allergens such as mold, dust mites, and furry pets can exacerbate lower respiratory symptoms and reduce lung function,[45] but evidence for this effect on AR is weak and inconsistent.

It is important to emphasize that indoor allergens interact with air pollutants to generate more severe allergy phenotypes in the upper and lower respiratory tract compared with outdoor seasonal allergens.[46] In addition, the presence of humidity in homes or closed spaces can promote colonization of molds or cockroaches, resulting in allergen sensitization of inhabitants.[47,48] In addition, indoor mold infestation can trigger inflammation of the upper and lower respiratory tract through the production of microbial volatile organic compounds (VOCs) and less commonly through by-products such as beta-glucans or mycotoxins.

It has also been shown that both external and internal air pollutants act synergistically with allergen to magnify allergic responses. For example, one study showed an increase or amplification of allergic inflammation resulting from the inhalation of DEP before exposure to allergens in the lower respiratory tract of atopic individuals. This phenomenon may be due to the increased recruitment of neutrophils and eosinophils, resulting in the production of interleukin (IL)-8 and IL-5 cytokine production, respectively, as well as other inflammatory biomarkers such as eosinophil cationic protein and monocyte chemotactic protein-1.[25,49] In another study, it was shown that controlled exposure to ozone or VOCs in the upper respiratory tract of healthy individuals generates recruitment of neutrophils, suggesting the establishment of a Th1-type immune response pattern. However, ozone exposure in the lungs of both healthy and allergic patients generated increased recruitment of both eosinophils and neutrophils, suggesting the establishment of a mixed response pattern (T helper lymphocyte 1 [TH 1] and T helper lymphocyte 2 [TH2]) for this air pollutant. Finally, evidence suggests that DEP exposure biases toward a Th2 immune response pattern.[50,51] Collectively, these studies suggest that the establishment of the immune response after exposure to air pollutants varies depending on the subject population studied, their socioeconomic status, the respiratory organ affected, and the specific pollutant studied. It is for these reasons that data establishing a relationship between AR and air pollution are variable and often inconsistent.

## HEALTH EFFECTS OF AIR POLLUTANTS ON ASTHMA

Exposure to air pollution has been associated with increased asthma mortality risk.[52] Outdoor air pollution at higher concentrations has a direct inflammatory and irritant effect on airway epithelium and at lower concentrations causes both airway hyperresponsiveness and inflammation, both characteristics of asthma.[1] The mechanisms include airway remodeling, oxidative damage, airway remodeling, the induction of immune responses, and increasing sensitization to aeroallergens.[1] Certain genotypes can enhance allergic responses to outdoor air pollutants, such as diesel exhaust particles.[53]

Airway pollutants and atmospheric agents involved with asthma include ozone, sulfur dioxide ($SO_2$), and nitrogen oxides.[54] In the United States, pollution sources such as power plants and other nonmobile industries are responsible for about 93% of $SO_2$

emissions, 51% of nitrogen oxide emissions, and about 52% of VOC emissions.[54] Mobile sources of pollution such as automobiles also contribute to these pollutants.[54] Ozone is produced from reactions in the atmosphere involving VOC, nitrogen oxide, and ultraviolet light.[54]

### *Ozone*

Ozone causes neutrophil incursion into the airway, usually a few hours after exposure.[54] There is also eosinophilic inflammation associated with ozone exposure.[54] Other inflammatory mediators include IL-8, IL-6, leukotriene $B_4$, plasminogen activator, and elastase.[54] Epidemiology studies have shown increased emergency department and hospital admissions for asthma after increased atmosphere ozone concentrations, including between 160 and 400 ppb.[55] One large study demonstrated that an increase in ozone by 10 ppb resulted in an elevated risk of death from respiratory causes.[56] There is also a report of an association between fatal asthma and ozone in New York City.[57,58]

### *Sulfur Dioxide*

Sulfur dioxide is associated with coal energy production.[1] In developed countries, levels have been lowered, but this exposure is still elevated in developing nations.[1] One analysis of multiple studies showed that exposure to sulfur dioxide increased risk of asthma exacerbations.[59] Sulfur dioxide has been associated with exercise-induced asthma also, leading to a decrease in Forced expiratory volume ($FEV_1$) by 23%.[58,60]

### *Nitrogen Oxide*

Nitrogen oxides (including $NO_2$) are associated with automobile traffic.[54,60] There is evidence of a bronchoconstrictor response in asthma patients on exposure to $NO_2$ concentrations of 0.1 ppm.[60] In addition, bronchial hyperresponsiveness has been increased with $NO_2$ exposure.[58] Nitric oxide has also been associated with an increased risk of asthma exacerbations.[59]

### *Particulate matter*

PM consists of multiple substances, including black carbon, metals, biologic contaminants, and organic residues.[54] They can include roadway dust, automobile tire wear particles, and automobile brake wear particles, and diesel exhaust particles (also known as TRAP).[1] Common molecules in diesel exhaust particles are polyaromatic hydrocarbons, including phenanthrenes, fluorenes, naphthalenes, fluoranthrenes, and pyrenes.[61] They can be very difficult to measure, given their heterogeneity but are associated with IgE and cytokine production, with potential effects on T cells, mast cells, epithelial cells, and macrophages.[54,61] Sulfuric acid is a form of PM and controlled studies using it have shown a decreased $FEV_1$ during exercise in asthma patients.[58] Increases of over 10 $\mu g/m^3$ in $PM_{10}$ have been associated with increased emergency department asthma visits.[58] Even PM concentrations of less than 10 $\mu g/m^3$ annual mean are associated with increased asthma incidence.[62] Diesel exhaust particulate exposure has been linked to an increase in methacholine responsiveness within 24 hours of exposure.[63]

### *Lipopolysaccharides*

Lipopolysaccharide (LPS) or endotoxin has been found in PM, and this has been shown to cause airway inflammation (predominantly neutrophils) in bronchial challenges.[54] Patients with allergic asthma can thus be more affected by exposure to LPS.[54]

### *Clinical effects of air pollution*

Older asthma patients may be more susceptible to a reduction in lung function and increased hospital admissions due to $PM_{2.5}$, ozone, and nitrogen dioxide.[64] One study in the greater Cincinnati area showed mean daily residential exposure to traffic exhaust was linked to worse asthma symptom control of older adults.[64]

Children with asthma are thought to be at risk from air pollution adverse effects due to developing lungs, increased ventilation rates, and developing metabolism.[1] Increased symptoms and medication use have been associated with PM air pollution in children in southern California.[58] Another study from California demonstrated that hospital visits for asthma are associated with local air pollution, especially with girls and infants.[65] One study in the Seattle, WA, area found increases in $PM_{2.5}$ and $PM_{10}$ accompanied greater risks of asthma medication use and asthma exacerbations.[66] International studies have shown similar associations.[67,68] However, there is no certain evidence that air pollution is implicated in the actual development of asthma.[58]

### *Prevention*

Asthma patients should live at a distance of at least 300 m from major traffic roadways.[1] Local communities and governments should issue pollution alerts on days when PM or ozone levels are elevated.[1] On days of high pollution, asthma patients should ideally stay indoors and avoid prolonged outdoor air exposure.[1] Finding alternative commuting routes away from major roadways can also be beneficial.[63] Policy issues worldwide should work to reduce the production of air pollutants.[1]

## THE IMPACT OF AIR POLLUTANTS ON EPITHELIAL BARRIERS IN ALLERGIC DISEASE STRUCTURE

The epithelium functions as a protective barrier for many organ systems including the skin, nose, lungs, and gastrointestinal tract.[69] Epithelial barriers are very complex structures composed of tight junctions (TJs) that form an apical junctional complex (AJC) surrounding the apicolateral region, apical junctions located underneath the TJs that regulate the apical-basolateral membrane structure and desmosomes, located on the lateral surface of the epithelial cells, which connect the epithelial cells (**Fig. 1**).[69] Epithelial cells are polarized consisting of membrane-bound lipids and proteins and their polarity partly depends on the formation of cell–cell junctions that comprise the AJC.[69] Adherens junctions and TJs are continuously undergoing

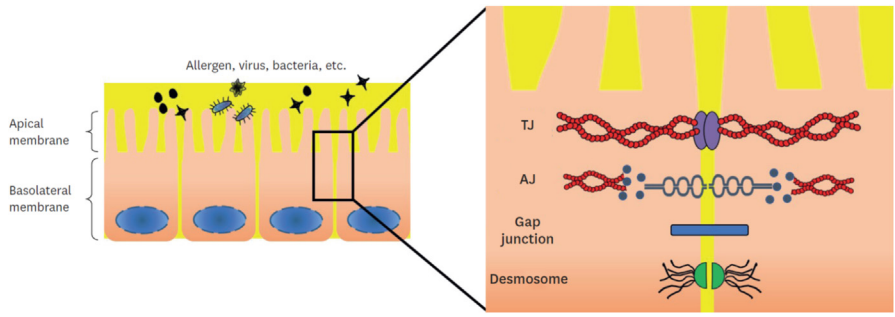


**Fig. 1.** Structure of the epithelial barrier. (*From* Leland EM, Zhang Z, Kelly KM, Ramanathan M Jr. Role of Environmental Air Pollution in Chronic Rhinosinusitis. *Curr Allergy Asthma Rep*. 2021;21(8):42. Published 2021 Sep 9.)

turnover and recycling (see Fig. 1).[69] The cytosolic side of the AJC is made-up of structural proteins and their assembly and disassembly regulate epithelial cell shape and differentiation.[69] TJs act as boundaries between apical and basolateral domains of the AJC and act as semipermeable barriers important for transport of ions, solutes, and water.[69] Thus, TJs are critical for formation of epithelial and endothelial cell sheets that form the structural walls and barriers of skin, blood vessels, and body organs that are important for protecting the host from external threats such as allergens, air pollutants, and infectious agents and for maintaining homeostasis.[69] The structural components of transmembrane junctional components are discussed in greater detail elsewhere.[69,70]

### *Immunopathogenesis of the Epithelial Barrier*

There is a complex interaction between the epithelium, environmental determinants, and the immune system. Epithelial cells secrete the cytokines, IL-25, IL-33, and thymic stromal lymphopoietin (TSLP), called alarmins in response to several allergic and nonallergic triggers. These cytokines activate dendritic cells and Group 2 innate lymphoid cells (ILC2s), which produce IL-4, IL-5, IL-9, and IL-13 and other effector molecules that lead to a Th2 immune response (Fig. 2).[71,72] It has also been reported that ILC2s may disrupt the epithelial barrier through IL-13.[73]

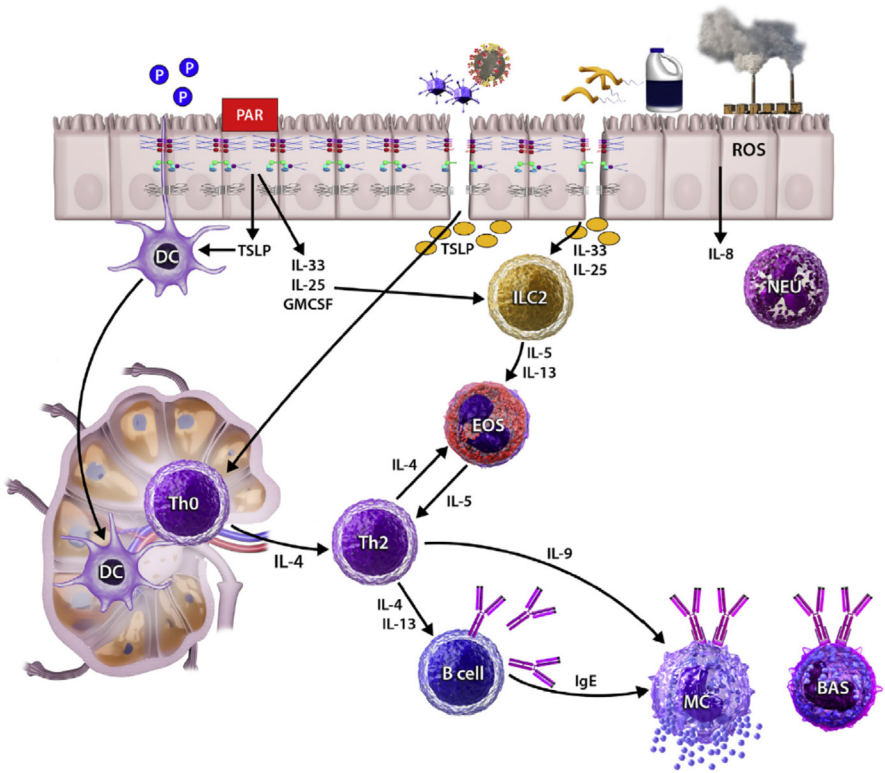


**Fig. 2.** Epithelial cell activation leading to type 2 inflammation. (*From* Celebi Sözener Z, Cevhertas L, Nadeau K, Akdis M, Akdis CA. Environmental factors in epithelial barrier dysfunction. *J Allergy Clin Immunol*. 2020;145(6):1517-1528.)

**Table 1**
**Environmental factors and mechanisms for disruption of the epithelium**[69]

| Environmental Factor | Mechanism |
|---|---|
| Protease allergens | • Elicit non-IgE-mediated reactions via proteinase-activated receptors<br>• Degrade barrier proteins<br>• Increase epithelial permeability |
| Detergents | • Impair lipid–lipid, lipid–protein interactions of stratum corneum<br>• Disrupt TJs by cleaving occludin and ZO-1<br>• Increase paracellular permeability<br>• Induce Th2 response by increasing IL-33 and TSLP |
| Cigarettes and E-cigarettes | • Increase alveolar epithelial permeability<br>• Decrease the level of TJ and AJ proteins<br>• Impact the adhesive intercellular junctions<br>• Disrupt monolayer integrity<br>• Destabilize cell adhesion<br>• Cause worse alveolar fluid clearance |
| Ozone | • Cause cell stress, desquamation, and death through ROS<br>• Increase protein leakage, and neutrophil and macrophage influx<br>• Induce IL-1$\alpha$ and IL-33 production from epithelial and myeloid cells<br>• Alter cell junction proteins<br>• Increase peribronchial collagen deposition<br>• Chronic exposure cause remodeling, fibrosis, and emphysema |
| $PM_{2.5}$, $PM_{10}$, diesel exhaust | • Damage TJ proteins such as occludin, claudin-1, and ZO-1<br>• Downregulate claudin-1 expression in human airway cells<br>• $PM_{2.5}$ suppresses the levels of E-cadherin (in a mouse model)<br>• $PM_{10}$ and diesel exhaust particles cause reduction and dissociation in occludin from ZO-1<br>• Increase ROS in the epithelium<br>• Loss of cytokeratin, filaggrin, and E-cadherin |
| NPs | • Have strong affinity to lipids<br>• Wrap themselves within epithelial membranes<br>• Disrupt cell membrane integrity<br>• Increase paracellular permeability<br>• Induce ROS<br>• Induce cell death (apoptosis, pyroptosis, necrosis) |
| Microplastic | • Aid in lipid movement in the lipid bilayer<br>• Changes the structure of cell membranes<br>• Because of their 3-dimensional structure they are internalized by cells<br>• Induce proapoptotic protein expression<br>• Alter metabolic profile of bronchial epithelial cells<br>• Cause oxidative stress |

*Abbreviation*: ZO-1, zonula occludens -1.
$PM_{10}$, PM with diameter <2.5 $\mu$m.
*Adapted from* Celebi Sözener Z, Cevhertas L, Nadeau K, Akdis M, Akdis CA. Environmental factors in epithelial barrier dysfunction. *J Allergy Clin Immunol*. 2020;145(6):1517-1528.

### *Health Effects of Air Pollutants on a Disrupted Epithelium*

Disruption of the epithelium leads to a permeable epithelium causing dysbiosis which is an imbalance in the microflora that can induce tissue inflammation.[74] Changes in the microbiome are now recognized as being important for shaping the immune system and tissue homeostasis of different organ systems including the upper and lower respiratory tracts and gastrointestinal tract (see **Fig. 2**).[70,74] In general, when the host is exposed to chemical irritants, pollutants or protease allergens, non-IgE-mediated reactions occur through activation of protease-activated receptors (ie, protease-activated receptor 2) causing epithelial cells to release alarmins such as TSLP, which induces an innate immune response leading airway inflammation (see **Fig. 2**).[69] This response can also facilitate allergen presentation to the immune system, thereby increasing allergic sensitization leading to secondary inflammatory reactions.

Studies have investigated the health effects of PM, ozone, diesel exhaust, cVOCs emitted from cleaning products, nanoparticles, and microplastics (**Table 1**).[69] PM has been the best characterized, and there are many potential mechanisms for the effect of these pollutants on the epithelium leading to inflammatory changes such as gene transcription, cytokine production, and macrophage polarization.[69] In a model using human nasal epithelial cells, PM has been previously demonstrated to disrupt the TJ leading to increased cytotoxicity due to the release of cytokines (ie, Tumor necrosis factor [TNF]-$\alpha$, IL-1$\beta$, and IL-6) and several micro-RNAs (miRNAs) (ie, MiR-19a and MiR-614) that target the 3′-untranslated region (UTR) of retinoic acid-related orphan receptor alpha (ROR$\alpha$) important for inhibiting inflammation.[75] Air pollutants (ie, PM, $O_3$, and diesel exhaust particulate) also result in increased production of reactive oxygen species (ROS) that can damage deoxyribonucleic acid (DNA), lipids, and proteins resulting in the production of increased inflammatory cytokines that can increase recruitment of inflammatory cells such as neutrophils, macrophages, monocytes to different organ systems including the nasal cavity and lung, leading to chronic rhinitis and asthma, respectively.[69,70,75]

## SUMMARY

Air pollutants are well-known to disrupt the epithelium leading to specific diseases in any organ system that has epithelial linings. The nose and lung are direct targets of respirable air pollutants. Over the last two decades, the discovery of alarmins released by epithelial cells has resulted in a better understanding of the pathogenesis of inflammatory responses associated with allergic and non-AR and asthma. This has led to the recent development of novel biologics that block TSLP, IL-25, and IL-33, culminating with the recent Food Drug Administration (FDA) approval of an anti-TSLP monoclonal antibody for the treatment of asthma.[76–78] Based on our current understanding of the health effects of air pollutants, the charge of the allergist/immunologist should be to advise their patients on avoiding irritant exposures that could damage the epithelial layer in the upper and lower respiratory tracts. On a broader scale, it is our responsibility to advocate for realistic environmental legislation that can achieve necessary standards for improving outdoor and indoor air quality that will favorably impact societal health and prevent disease.

## CLINICS CARE POINTS

- Studies suggest that the establishment of the immune response after exposure to air pollutants vary depending on the subject population studied, their socioeconomic status,

the respiratory organ affected, and the specific pollutant studied. It is for these reasons that data establishing a relationship between AR and air pollution are variable and often inconsistent.

- The prevalence of allergic rhinitis induced by environmental pollutants in children and adults is poorly elucidated likely due to methodologic differences in epidemiological study design and exposure assessment methods including exposure duration. However, a recent systematic review and meta-analysis found that the effect of air pollutants on allergic rhinitis (AR), except for particulate matter ($PM_{10}$), was significant and higher in developing countries than in developed countries.
- Asthma patients should live at a distance of at least 300 m from major traffic roadways. Local communities and governments should issue pollution alerts on days when PM or ozone levels are elevated. On days of high pollution, asthma patients should ideally stay indoors and avoid prolonged outdoor air exposure. Finding alternative commuting routes away from major roadways can also be beneficial. Policy issues worldwide should work to reduce the production of air pollutants.
- Air pollutants disrupt the epithelium leading to specific diseases involving the nose and lung. The discovery of alarmins, TSLP, IL-25, and IL-33, released by epithelial cells has resulted in a better understanding of the pathogenesis of inflammatory responses associated with allergic and nonallergic rhinitis and asthma culminating with the recent FDA approval of an anti-TSLP monoclonal antibody for the treatment of asthma.

## CONFLICTS OF INTEREST

A. Nanda: None.

S.S. Mustafa: Genentech, Regeneron/Sanofi, GSK, AstraZeneca, CSL Behring, Aimmune.

M. Castillo: None.

J.A. Bernstein: INEOS; Speaking: Sanofi-Regeneron, AZ, GSK, Novartis, Genentech, Takeda/Shire, CSL Behring, Biocryst, Pharming, Optinose; Research and consultant: Sanofi-Regeneron, AZ, GSK, Novartis, Genentech, Takeda/Shire, CSL Behring, Biocryst, Pharming, Kalvista, IONIS, Celldex, TLL, ONO, Escient, Cycle, Blueprint Medicine, Biomarin, Merck, Amgen.

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