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CME Review

Effect of air pollution on asthma

Xiaoying Zhou, PhD; Vanitha Sampath, PhD; Kari C. Nadeau, MD, PhD

Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, Massachusetts

Key Messages

- Air pollutants activate both type 2 and non-type 2 inflammatory pathways involved in asthma pathogenesis. This activation includes promoting the release of epithelial cytokines that drive T_H2 responses and inducing oxidative stress and proinflammatory cytokine production.
- Enhanced type 2 inflammation furthered by air pollution-induced airway epithelial barrier dysfunction and disruption of the T_H17/regulatory T cell balance by air pollutants may contribute to asthma exacerbation.
- Prolonged pollution exposure can induce epigenetic alterations. Effects of air pollution exposure on asthma may accumulate over time, potentially having stronger impacts during certain sensitive life periods.
- Further research is needed to characterize the sensitive period in air pollution-induced asthma development and map associated epigenetic biomarkers onto asthma-related genes.

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ABSTRACT

Asthma is a chronic inflammatory airway disease characterized by respiratory symptoms, variable airflow obstruction, bronchial hyperresponsiveness, and airway inflammation. Exposure to air pollution has been linked to an increased risk of asthma development and exacerbation. This review aims to comprehensively summarize recent data on the impact of air pollution on asthma development and exacerbation. Specifically, we reviewed the effects of air pollution on the pathogenic pathways of asthma, including type 2 and non-type 2 inflammatory responses, and airway epithelial barrier dysfunction. Air pollution promotes the release of epithelial cytokines, driving T_H2 responses, and induces oxidative stress and the production of proinflammatory cytokines. The enhanced type 2 inflammation, furthered by air pollution-induced dysfunction of the airway epithelial barrier, may be associated with the exacerbation of asthma. Disruption of the T_H17/regulatory T cell balance by air pollutants is also related to asthma exacerbation. As the effects of air pollution exposure may accumulate over time, with potentially stronger impacts in the development of asthma during certain sensitive life periods, we also reviewed the effects of air pollution on asthma across the lifespan. Future research is needed to better characterize the sensitive period contributing to the development of air pollution-induced asthma and to map air pollution-associated epigenetic biomarkers contributing to the epigenetic ages onto asthma-related genes.

Introduction

Air pollution is a complex mixture containing both particles and gases. The air pollutants for which the Environmental Protection Agency has set National Ambient Air Quality Standards include particulate matter (PM), ground-level or tropospheric ozone (O_3), carbon monoxide (CO), sulfur dioxide (SO_2), and nitrogen dioxide (NO_2).[1,2] Tropospheric ozone is created when nitrogen oxides and volatile organic compounds react in the presence of heat and sunlight. Particulate matter can be divided into the following 3 categories based on the diameter of particles: coarse PM10 (from 2.5 to 10 μm), fine PM2.5 (from 0.1 to 2.5 μm), and ultrafine PM0.1 (<0.1 μm). A total of 99% of the global population resided in areas in which the air quality did not meet the World Health Organization guidelines in 2019.[2] Common sources of air pollution include household combustion devices, emissions from motor vehicles, industrial facilities, and forest fires.[3]

Address correspondence to: Kari C. Nadeau, MD, PhD, Department of Environmental Health and Center for Climate, Health, and the Global Environment, Harvard T.H. Chan School of Public Health and Division of Allergy and Inflammation, Beth Israel Deaconess Medical Center, Harvard Medical Faculty Physicians, 665 Huntington Avenue, Building 1, Boston, MA 02115. E-mail: knadeau@hsph.harvard.edu.

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Participants will be able to demonstrate increased knowledge of the clinical treatment of allergy/asthma/immunology and be able to apply new information to their own practices.

Learning Objectives

At the conclusion of this activity, participants should be able to:

- Specify the link between air pollution on asthma development and exacerbation.
- Summarize the effects of air pollution on the pathogenic pathways of asthma.

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Target Audience

Physicians involved in providing patient care in the field of allergy/asthma/immunology.

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Authors:

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Asthma is a chronic inflammatory airway disease characterized by respiratory symptoms (such as wheezing, shortness of breath, and chest tightness), variable airflow obstruction, bronchial hyperresponsiveness, and airway inflammation.[4] There are several factors that can influence the development of asthma. The asthma-associated loci across the genome are identified using genome-wide association studies of asthma,[5-8] suggesting genetic predisposition is one of the risk factors for developing asthma (Fig 1). Furthermore, epigenetic changes, including DNA methylation, chromatin remodeling, histone modifications, and noncoding RNAs, are considered important additional mechanisms in the development of asthma and are highly influenced by environmental exposures (Fig 1).[9-11] Moreover, exposure to air pollution has been clearly found as a high-risk factor for the development and exacerbation of inflammatory disease of the lower airways, such as asthma (Fig 1).[12] Moreover, PM2.5 is one of the main components of air pollution, and it can deposit deep in the bronchioles and alveoli of the lungs, sites proximal to asthma, in which it induces the inflammatory responses.[13-16] Outdoor PM originates from sources such as mineral dust, pollen, vehicle exhaust, and heating combustion. Indoor PM sources encompass smoking and incense burning, vacuum cleaning, sanitary and hygienic sprays, clothing residues and fiber breakage, friction, domestic animals, and cooking.[17] In addition to PM2.5, other major air pollutants related to asthma contain a significant portion of noxious gases, including SO_2, NO_2, and O_3.[12]

It has been found that climate change could worsen air quality, and the reduced air quality can have direct adverse impacts on human health.[18] Climate change events have led to increased frequency, duration, severity of pollen exposures, and the formation and spread of air pollutants such as ground-level ozone, dust storms, infections, wildfires, and thunderstorms; all of which can exacerbate allergies and asthma.[18-20] Furthermore, wildfire smoke is a potent natural source of numerous air pollutants, including PM, CO, methane, NO_2, formaldehyde, acrolein, polycyclic aromatic hydrocarbons, trace minerals, and various other compounds.[21,22] Wildfire smoke has been found to have a positive impact on respiratory hospitalization, such as asthma.[23]

The aim of this review is to summarize recent data on the effects of air pollution on the development and exacerbation of asthma, specifically the effects of air pollution on the pathogenic pathways of asthma, including type 2 and non-type 2 inflammatory responses, and airway epithelial barrier dysfunction. Given air pollution exposure effects may accumulate over the life course, with stronger impacts potentially during sensitive periods, we also review the effects of air pollution on asthma across the lifespan.

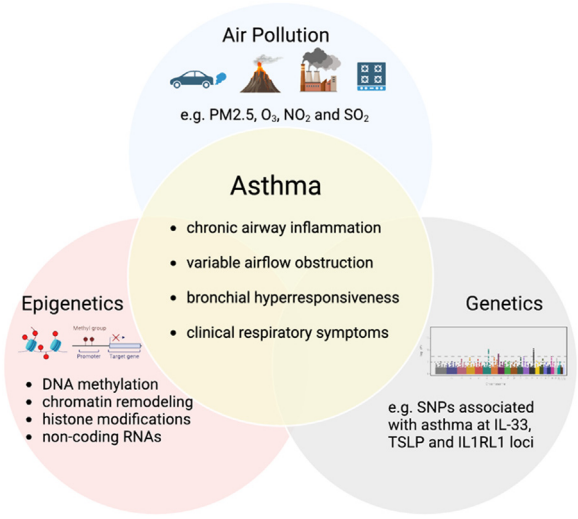

Figure 1. Risk factors contributing to the development of asthma. IL, interleukin; IL1RL1, interleukin 1 receptor-like 1; NO_2, nitrogen dioxide; O_3, ozone; PM2.5, particulate matter that has a diameter of 2.5 μm or smaller; SNP, single-nucleotide polymorphism; SO_2, sulfur dioxide; TSLP, thymic stromal lymphopoietin.

Air Pollution and the Development and Exacerbation of Asthma

Numerous published studies provide epidemiologic evidence supporting the association between air pollutant exposure and the onset and progression of asthma. A study revealed that prolonged exposure to PM2.5 was associated with a higher risk of asthma in Chinese preschool children; those residing in suburban or rural areas in this survey were considerably more susceptible to PM2.5 exposure.[24] Carlsten et al[25] evaluated the associations between exposure to traffic-related air pollutants (NO, NO_2, black carbon, and PM2.5) at birth year and new-onset asthma assessed asthma at age 7 years and found that an IQR of PM2.5 concentration at birth year of 4.1 $\mu g/m^3$ was associated with a significantly increased risk of developing asthma in children (odds ratio: 3.1, 95% CI: 1.3-7.4). Lavigne et al[26] conducted a population-based cohort study, including 1,130,855 singleton live births between 2006 and 2014 in the province of Ontario, Canada, and identified 167,080 children who developed asthma before the age of 6 years. In their adjusted models, outdoor PM2.5 mass concentrations during childhood were associated with an increased incidence of childhood asthma (hazard ratio for each 1 $\mu g/m^3$ increase = 1.026, 95% CI: 1.021-1.031). A recent study involving 30,325 preschool children aged 3 to 6 years in the People's Republic of China during 2019 to 2020 suggested that early life exposure to PM2.5 was significantly associated with an increased risk of asthma and wheezing.[27]

Air pollution exposure, such as PM2.5, O_3, NO_2, and SO_2, has been also implicated in the exacerbation of asthma, as evidenced by increased hospitalization rates in patients with asthma because of air pollution exposure.[12,28-30] A previous study revealed that short-term exposure of PM2.5 had an adverse impact on asthma-related emergency department visits, especially in children who were a high-risk population, particularly during periods of elevated PM2.5 concentrations.[31] A study investigating the impact of O_3 on asthma hospital admissions also revealed a significant association between O_3 levels and asthma-related hospital admissions, and the susceptibility to O_3 was found to be age-dependent, with children being at the highest risk.[28] These results suggest that children are at high-risk population for asthma exacerbation induced by air pollution exposure. This may be due to the unique anatomy and physiology of children. They breathe more quickly and inhale more air relative to their body weight than adults, which renders them more susceptible to the impacts of poor air quality.[32]

Air Pollution and Asthma Over Life Course

The health impact of air pollution can accumulate over time or have a stronger effect during certain sensitive periods throughout the life course. In an epidemiologic study involving a cohort of 6501 children in Jinan, People's Republic of China, high-level of O_3 exposure after birth was associated with asthma and wheezing in young children (hazard ratio: 2.10, 95% CI: 1.31-3.37).[33] Specifically, this study revealed the existence of 2 sensitive windows in early life, identified correlated insults between high levels of O_3 and other pollutants, and opened windows contributing to the asthma-inducing effect.[33] Although this report described the associations between air pollution exposure and the onset of asthma in early life and identified the sensitive period related to the onset of asthma, future studies should further explore how exposure at different epochs throughout life course are related to the development or exacerbation of asthma in young, adult, and older ages and identify the sensitive period contributing to the development of asthma.

Previous studies revealed that both long- and short-term exposure to air pollution can affect telomere length (TL), but in different directions. Long-term exposure to PM is associated with a reduction in TL,[34,35] whereas short-term exposure is linked to a rapid increase in blood TL.[36,37] Miri et al[38] conducted a meta-analysis, revealing a positive significant association between short-term exposure to PM2.5 and TL, whereas for long-term exposure to PM2.5, a negative association was observed. TL is a common biomarker of biologic aging.[39,40] Telomeres progressively shorten with each cell cycle division and lead to cellular senescence because of the "end replication problem" which is incomplete replication at chromosomal ends by DNA polymerase.[41,42] A study of the Coronary Artery Risk Development in Young Adults cohort in the United States over 25 years revealed that the incidence of adult-onset asthma increased with age and the prevalence trend over time for adult-onset asthma was greater among individuals with nonallergic asthma compared with those with allergic asthma.[43] Another study based on physician-diagnosed asthma data from questionnaires completed by 4173 participants in Finland in 2016 also revealed that the incidence rate of nonallergic asthma increased after middle age, being highest in older age groups compared with children and young adults.[44] In addition, a study of patients enrolled in the Severe Asthma Research Program revealed that the probability of severe asthma increased with each year of life until 45 years, after which the age-related risk of severe asthma continued to rise in men but not in women.[45] Although there is currently no conclusive evidence regarding the association between air pollution-induced changes in TL and age-related adult-onset asthma or severe asthma, further research to explore this relationship could provide insights into whether accelerated biologic aging due to prolonged air pollution exposure-induced shortened telomeres during early life influences susceptibility to asthma phenotypes that typically emerge in adult groups.

Importantly, prolonged air pollution exposure can lead to epigenetic alteration.[46] Epigenetic modifications are associated with aging, and DNA methylation-based aging biomarkers are used to evaluate epigenetic age across various cells, tissues, and populations.[47] PM2.5 exposure has been found to be associated with Horvath DNAmAge,[48,49] which is an epigenetic age estimated using the Horvath multitissue age-prediction model, based on the DNA methylation levels at the 353 CpG sites.[50] In addition, air pollution around a sensitive period in young-to-middle adulthood is linked to accelerated epigenetic aging, as revealed in a study encompassing a cohort of 525 older Scottish adults with life course residential addresses linked to historic air pollution concentrations.[51] However, currently little is known about the life course during which air pollution might have a stronger impact on asthma-related epigenetic modifications or whether the effect of air pollution on asthma accumulates over time. Further studies may investigate whether the air pollution-associated CpGs contributing to the epigenetic ages are mapping to genes involved in the development of asthma.

Air Pollution and Type 2 Inflammation in Asthma

Extensive research has been conducted to evaluate the biologic mechanisms underlying the effects of air pollution on asthma.[13,52] The immune responses in both the adaptive and innate immune systems induced by exposure to air pollution associated with the pathogenesis of asthma have been investigated. Asthma can be mediated by type 2 and non-type 2 airway inflammations.[53,54] Type 2 inflammation is driven by $CD4^+$ T_H2 cells, which secrete T_H2 cytokines, such as interleukin (IL)-4, IL-5, and IL-13, and are involved in the activation and migration of eosinophils (Fig 2). These produced T_H2 cytokines can promote the synthesis of IgE (Fig 2). In human in vitro studies, the air pollutants, such as PM2.5, diesel exhaust particles, and black carbon, have been found to promote the production of epithelial

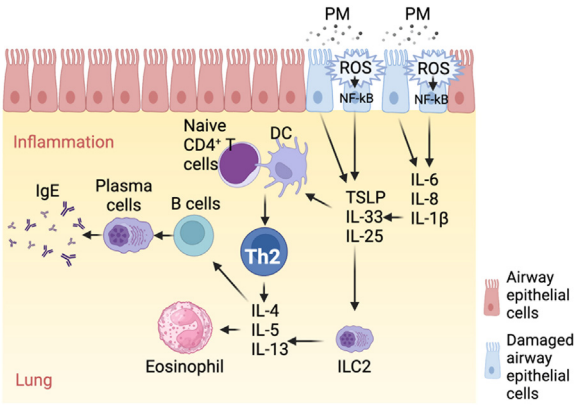

Figure 2. Cellular pathways of type 2 inflammatory effects caused by PM exposure. DC, dendritic cell; IL, interleukin; ILC2, type 2 innate lymphoid cell; PM, particulate matter; ROS, reactive oxygen species; TSLP, thymic stromal lymphopoietin.

cytokines (IL-33 and thymic stromal lymphopoietin [TSLP]) in human bronchial epithelial cells (HBECs), and these epithelial cytokines can induce T_H2-type cytokine synthesis[55-58] (Fig 2). Furthermore, the genetic variations in the IL-33 and TSLP genes have reproducibly been found to be associated with asthma in genome-wide association studies, suggesting that the effect of air pollution on asthma can be directly mediated by type 2 immune response.[11,59-62] In addition, the proinflammatory cytokines, such as IL-6, IL-8, and IL-1β, in HBECs have been found to be induced by PM2.5[63-65] (Fig 2). In HBEC air-liquid interface culture, IL-1 has been found to trigger the production of type 2 inflammation cytokines, such as IL-33, TSLP, and granulocyte-macrophage colony-stimulating factor,[66-68] suggesting IL-1 signal pathway may contribute to type 2 inflammation in asthma (Fig 2). In addition, the air pollutants, such as PM2.5 and O_3, are potent oxidants and can induce oxidative stress initiated by reactive oxygen species (ROS)[69] (Fig 2). The increased production of ROS can lead to direct oxidative damage and enhance intracellular calcium concentrations that precede IL-33 release in HBECs[70] (Fig 2). ROS can also induce the production of inflammatory cytokines, such as IL-6, IL-8, and IL-1β, by activating the redox-sensitive transcription factor NF-κB[71,72] (Fig 2). These results suggest that air pollution-induced ROS is associated with the development of type 2 inflammation in asthma.

Air Pollution and Non-Type 2 Inflammation in Asthma

In addition to the common type 2 asthma, non-type 2 inflammation is primarily associated with abnormal immune responses and neutrophilic inflammation, leading to severe asthma.[73] T_H1 pathway and T_H17 pathway have been implicated in non-type 2 asthma. Previous study revealed a distinct immune response in severe asthma characterized by a dysregulated T_H1 cytokine interferon gamma/secretory leukocyte protease inhibitor axis that affects lung function.[74] The T_H17 cytokine IL-17 plays a crucial role in neutrophilic inflammation.[73] Levels of this cytokine in bronchial biopsies correlate with airway neutrophil infiltration and are elevated in patients with severe asthma compared with those with milder disease.[73] In mice, the air pollutant O_3 has been found to induce neutrophilic airway inflammation and production of IL-1β, IL-18, IL-17A, granulocyte colony-stimulating factor, and interferon gamma-inducible protein 10.[75] A study in a rodent model revealed that the introduction of the IL-17 antagonist after PM2.5 exposure led to a significant decrease in inflammatory factor levels in bronchoalveolar lavage fluid and pathologic scores of lung tissues.[76] A recent study in a mouse model suggests that PM2.5 could inhibit autophagy of BECs and promote pulmonary inflammation and fibrosis by inducing the secretion of IL-17A in γδT and T_H17 cells and regulating the PI3K/Akt/mTOR

signaling pathway.[77] Piao et al[78] revealed that in an ovalbumin (OVA)-induced mouse model of combined allergic rhinitis and asthma syndrome, exposure to PM2.5 can active the NF-κB signaling pathway and increase the production of cytokines, such as GATA3, RORγ, IL-4, IL-5, IL-13, and IL-17 in bronchoalveolar lavage fluid. Although there is currently no convincing evidence to reveal the production of IL-17 in human airway epithelial cells in response to exposure to air pollutants, the results in mice and rodent models suggest that air pollution-induced IL-17 mediates non-type 2 inflammation in asthma.

Our published study revealed that asthma was associated with higher differentially methylated regions of Foxp3, and both short-term and long-term exposures to high levels of CO, NO_2, and PM2.5 were associated with alterations in differentially methylated regions of Foxp3, suggesting the role of epigenetic modifications of regulatory T (Treg) cells in the effects of air pollution on asthma.[79] Sun et al[80] revealed that in a mouse model, PM2.5 disrupted the balance of $CD4^+$ T_H17 cells/Treg cells through aryl hydrocarbon receptor (AhR)-hypoxia-inducible factor 1α and AhR-glutamate oxaloacetate transaminase 1 molecular pathways. PM2.5 impaired the differentiation of Treg cells, promoted the differentiation of T_H17 cells, and exacerbated asthma in an AhR-dependent manner.[80] This study also observed similar regulatory effects on T_H17/Treg cell imbalance in human T cells after exposure to PM2.5 or polycyclic aromatic hydrocarbons, and in a case-control design, polycyclic aromatic hydrocarbon exposure seemed to be a potential risk factor for asthma.[80] The imbalance of T_H17/Treg cells induced by PM2.5 was further observed in a study using an OVA-sensitized rat model.[81] This study revealed that the STAT3/RORγt-STAT5/Foxp3 signaling pathway was involved in PM2.5-induced imbalance of T_H17/Treg cells in asthma exacerbation.[81] In addition, the alteration of DNA methylation in *STAT3*, *STAT5*, and *RORγt* genes may be involved in asthma exacerbation as well.[81] A recent study investigated the differential chromatin accessibilities in human lung epithelial cell line BEAS-2B cells before and after exposure to PM2.5 using assay for transposase-accessible chromatin with sequencing and RNA sequencing, and PM2.5 induced up-regulated genes in the ferroptosis signaling pathway were identified.[82] In addition, in an asthma mice model exposed to PM2.5, the airway inflammation was alleviated by inhibition of ferroptosis.[82] Ferroptosis has been found to facilitate T_H17 responses,[83] suggesting that its role in PM2.5-induced asthma exacerbation may be mediated by T_H17 response.

Air Pollution and Airway Epithelial Barrier

The disruption of airway epithelial function, along with the activation of type 2 immune responses, is considered to contribute to allergic airway inflammation.[84] Karki et al[85] revealed that treatment with PM causes dose-dependent disruption of the endothelial cell barrier in human pulmonary endothelial cells. They also revealed a mechanism for the sustained dysfunction of the pulmonary endothelial cell barrier, driven by PM-induced generation of truncated products of phospholipid oxidation causing destabilization of cell junctions. The increase of airway epithelial barrier permeability may lower the threshold of epithelial damage, activation of type 2 immune responses, and production of inflammatory cytokines, which itself may disrupt the barrier function, thus generating a positive feedback loop of increased epithelial permeability. In addition, a group of genes associated with asthma has been reported to be related to epithelial function, such as ORMDL3,[86-89] PCDH1,[90] and CDHR3.[91-93] Previous studies have reported on the regulatory role of these 3 genes in airway epithelial barrier dysfunction. ORMDL3 gene encodes a transmembrane protein localized in the endoplasmic reticulum.[94] A study in a mouse chronic asthma model induced by OVA−respiratory syncytial virus revealed up-regulation of ORMDL3 and down-regulation of the junction proteins claudin−18 and E-cadherin.[95] In addition, overexpression of ORMDL3 in HBECs was found to decrease transepithelial electric resistance, further down-regulating claudin-18 and E-cadherin and inducing epithelial permeability.[95] The PCDH1 gene encodes an adhesion molecule that localizes to cell-cell junctions.[96] The knockdown of PCDH1 gene in BECs has been found to disrupt both tight and adhesion junctions, resulting in increased epithelial permeability.[97] This suggests an important role for PCDH1 in maintaining airway epithelial barrier function. CDHR3 is a member of the cadherin family of transmembrane proteins,[98] and knockout of CDHR3 using CRISPR-Cas9 in human airway epithelial cells led to decreased transepithelial resistance and compromised epithelial integrity.[99] Further research on the association between the expression of these genes in human pulmonary cells and air pollutants is needed.

Conclusion

In conclusion, epidemiologic studies provide evidence that exposure to air pollutants is associated with the development and exacerbation of asthma. Children may be more susceptible to the impact of air pollution because of their developing respiratory systems.

The effects of air pollution exposure may accumulate over time, and the air pollution may have stronger impacts in the development of asthma during certain sensitive life periods. Prolonged pollution exposure can induce epigenetic alterations. However, future research is needed to better characterize the sensitive period contributing to the development of air pollution-induced asthma and to map air pollution-associated epigenetic biomarkers contributing to the epigenetic ages onto asthma-related genes.

Air pollutants can activate both type 2 and non-type 2 inflammatory pathways involved in asthma pathogenesis. They promote the release of epithelial cytokines that drive T_H2 responses and induce oxidative stress and production of proinflammatory cytokines. The enhanced type 2 inflammation furthered by air pollution-induced dysfunction of the airway epithelial barrier may be associated with the exacerbation of asthma. The T_H17/Treg balance can be disrupted by air pollutants, and this imbalance is related to asthma exacerbation.

Overall, this review highlights the impacts of air pollution exposure on the development and exacerbation of asthma, particularly, the effects of air pollution on the pathogenic pathways of asthma, including type 2 and non-type 2 inflammatory responses and airway epithelial barrier dysfunction.

Disclosures

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