

Ozone in the Development of Pediatric Asthma and Atopic Disease



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KEYWORDS

• Asthma • Ozone • Children • Lung function • Allergic rhinitis • Atopic dermatitis

KEY POINTS

- Preclinical models show that O₃ exposure during lung development causes morphologic and structural changes.
- Ozone (O₃) exposures over the short term are associated with reduced lung function in both children and adults, independent of asthma status.
- The effects of O₃ exposure during the prenatal and infancy periods on long-term lung growth need to be further evaluated.
- Ozone exposure during early life increases the risk of developing asthma, allergic rhinitis, and atopic dermatitis; effects on food allergy and eosinophilic esophagitis are unknown.

INTRODUCTION

Air pollution is an umbrella term used to describe the presence of substances in the atmosphere that are harmful to humans and other living organisms. These pollutants are also influenced by weather patterns. The most common air pollutants are ground-level ozone (O₃) and particulate matter (PM). Anthropogenic activities such as burning of fossil fuels, deforestation, land use, livestock production, fertilization, and industrial processes have increased greenhouse gas (GHG) emissions and ground-level O₃ production.¹ The increase in air pollution not only has had an impact on climate change but also on public and individual health.²

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It is estimated that roughly 40% of Americans—more than 135 million people—are living in areas that have unhealthy levels of O₃ or particle pollution.³ While O₃ present in the stratosphere is protective, it is harmful when present in high concentrations at ground level.⁴ When inhaled, O₃ has deleterious effects on the respiratory and cardiovascular systems.⁵ Individuals with underlying lung pathology such as asthma are at a higher risk for symptom severity and exacerbations.² The pediatric population is also at higher risk for lung pathologies due to several factors, most notably the anatomic differences of the airway and lungs during early development.

Asthma is one of the most common causes of morbidity and hospitalizations in childhood.⁶ Studies have shown evidence that asthma is a complex and dynamic disease influenced by many environmental and genetic factors.⁷ Asthma exacerbations are a major cause of disease morbidity and are responsible for significantly higher health care costs.⁸ Patients that require emergency department (ED) visits/hospitalizations for an exacerbation are at a significantly higher risk for future exacerbations and hospitalizations.⁹ Although the exact mechanism(s) for the development of early childhood asthma have yet to be elucidated, evidence has shown that air pollution plays a significant role in both the development and exacerbation of asthma.

It is well established that O₃ exposure increases the risk of asthma exacerbations among children [recently reviewed by¹⁰]. As children are typically active outside, especially during the warm seasons when O₃ levels are highest, this poses a greater risk of exposure to this air pollutant and subsequent adverse health effects. Because children's respiratory systems are continuously growing and developing through their early 20s,¹¹ O₃ exposure has the potential to disrupt this normal developmental process through its ability to alter structural elements of conducting airways through long-term oxidative stress of the airways.¹² These exposures may impact future lung function, airway remodeling, and airway hyperreactivity. This review focuses on how O₃ exposure(s) during early life impact lung development, lung function, and the future risk of pediatric asthma and atopic disease.

OZONE PRODUCTION

Ozone is an invisible gas that can be found in different locations in the atmosphere and can serve as both beneficial and hazardous to our health depending on whereby it is found. O₃ that is found in the upper atmosphere, or stratospheric O₃, is classified as “good O₃” and serves as protection from the sun's ultraviolet (UV) radiation. The O₃ that is located at ground-level, or tropospheric, is classified as “bad O₃.”⁴ Ground-level O₃ is created by chemical reactions that occur when oxides of nitrogen (NO_x) and volatile organic compounds (VOC) react in the presence of sunlight. Emissions from industrial facilities, farms, factories, power plants, and motor vehicle exhaust are some of the major sources of NO_x and VOC.^{4,13} Ground-level O₃ is most likely to reach dangerous and unhealthy levels on hot sunny days. O₃ levels can fluctuate due to altering weather patterns.¹ O₃ can reach the distal aspects of the human airways due to its low water solubility. Once in the airway, it has been shown to increase inflammation, increase susceptibility to viral infections, and promote remodeling of the airway epithelium.^{14,15}

SUSCEPTIBILITY OF THE DEVELOPING LUNG TO AIR POLLUTION

Exposure to early life risk factors, including environmental pollutants, plays a critical role in the development and severity of asthma.^{6,7} A child's developing respiratory system is extremely vulnerable to O₃ for several reasons. Early in life, the respiratory system is rapidly growing. At the time of birth, the human lung has about 24 million alveoli.¹⁶ This represents a fraction of the remaining alveoli that will develop into a fully functioning

respiratory system comprising roughly 257 million alveoli. It is estimated that nearly 80% of the alveoli will develop postnatally and continue to expand throughout adolescence.¹⁷ Additionally, children have a larger lung surface area per kilogram body weight ratio and increased resting respiratory rate compared with adults, corresponding to increased overall exposure.¹⁸ Finally, the smaller caliber of children's airways contributes to their increased susceptibility to air pollution's effects.¹⁸

The processes of lung growth and development along with how the tissue responds to insults are highly interlinked during early life when there are phases of rapid differentiation and growth.¹⁹ It has been hypothesized that early exposures to risk factors can alter the respiratory system, including lung development and growth, immune development and function, and inflammatory responses to oxidative stress and infections. This process is referred to as "early life programming."²⁰ The timing and nature of these events result in differing degrees of impaired maximal lung functional capacity in early adulthood, and potentially impact future long-term respiratory morbidities such as chronic asthma or chronic obstructive airway disease (COPD).

OZONE EFFECTS ON LUNG DEVELOPMENT IN PRECLINICAL STUDIES

Ozone exposure has been linked with reductions in children's lung function,²¹ but the exact pathophysiology has yet to be illustrated. Most studies that have investigated this were performed in animal models such as rodents. These studies are discussed in more detail elsewhere,²² but the results from the rodent studies showed mixed and minimal morphologic changes in the airways and lungs.^{23–25} This is most likely due to the differences between the development of the human and animal lung. The use of nonhuman primates showed more robust data on O₃ effects due to their similarities with human airway structure and postnatal lung developmental processes.

Neurogenic mechanisms are implicated in airway remodeling from O₃ exposure. A large portion of lung development occurs postnatally.^{26,27} These processes include intricate nerve connections/innervations along with the expression of neurotransmitters in the developing respiratory tract.^{28,29} Airway nerves/innervation plays a crucial role in maintaining lung function and homeostasis. This is dependent on the specific projection of axons to their targets during lung development.³⁰ Evidence suggested that the postnatal developmental period is critical for proper lung development and function. During this time the tissue is highly susceptible to exposures to mild irritants or toxicants that can markedly modify lung development.^{25,31,32} Studies using newborn rats demonstrated that early O₃ exposure (postnatal days 2–6) but not late exposure (days 19–23) increased airway sensory nerves, suggesting a narrow window of neural development and plasticity.²⁴

Primate models have shown that exposure to O₃ and allergens during early lung development alters structural components of the conducting airways, including innervation and neurokinin-1 receptor (NK-1R) expression which are linked to the development of asthma.³³ This study showed early O₃ exposure results in persistent effects within the airways which resets the steady state so that NK-1R expression is increased in airways.

Studies using Rhesus macaques demonstrated that O₃ exposure during the first year of life resulted in structural changes in the lung along with a decrease in epithelial nerves in midlevel intrapulmonary airways.²⁷ Follow-up studies demonstrated that despite abatement of allergen and/or O₃ exposure, adaptive mechanisms were still in place that led to an exaggerated increase in airway nerve density and atypical nerve distribution compared with control animals.³⁴ This indicated that postnatal exposure to allergen and O₃ leads to the hyperinnervation of the pulmonary epithelium and disrupts processes that are important in the establishment of normal airway innervation

and may lead to the initiation and persistence of airways disease in children.³⁴ Studies by Fanucchi and colleagues also used nonhuman primates to study how O₃ alters distal airway development. Using cyclic exposures, it was shown that episodic exposure to O₃ during infancy significantly alters airway morphology and structure. Most notably it was shown that O₃-exposed animals had 4 fewer nonalveolarized airway generations, altered smooth muscle bundle orientation within the terminal and respiratory bronchioles, and hyperplastic bronchiolar epithelium.³⁵ Taken together, O₃ exposure negatively impacts the developing distal airway morphology resulting in narrower and shorter terminal bronchioles with altered smooth muscle bundles. Normal morphology and structure are critical for proper lung function. It is known that the total amount of smooth muscle is increased in asthma.^{36,37} It has also been shown that cell hyperplasia and hypertrophy are present in mild-to-moderate asthma, and even more so in severe asthmatics.³⁸ One may speculate that these cellular changes are secondary effects brought about by an already ongoing change in the lung microenvironment and immune modulation.

OZONE EFFECTS ON IMMUNE DEVELOPMENT AND FUNCTION

Airway remodeling in asthma is understood to be a response to chronic inflammation. This inflammatory assault requires continuous tissue repair and remodeling, thus a major factor in the development of asthma. Modulation/alteration of the immune cells and response including T helper cells (Th), eosinophils, neutrophils, and mast cells all play a role in the microenvironment of the lung and airway that when under inflammatory conditions result in airway remodeling.

Ozone has been shown to “prime” epithelial inflammatory responses and provokes airway hyperreactivity.²² Inhaled O₃ does not enter cells but reacts with components of the airway lining fluid to generate other reactive oxygen species (ROS) to enhance local oxidative stress, inflammation, and epithelial cell injury.³⁹ In response to O₃ exposure, epithelial cells produce proinflammatory mediators, including IL-8, IL-6, prostaglandin E₂ (PGE₂), and leukotriene C₄ (LTC₄), that recruit inflammatory cells [reviewed by¹²]. This damaged epithelial cell-airway lining fluid interface also releases damage-associated molecular patterns (DAMPs), such as heat shock proteins, oxidized lipids, fibrinogen, and low-molecular-weight hyaluronic acid that can then trigger an inflammatory response in airway macrophages. Mouse models have shown that O₃ exposure causes epithelial cell damage and death along with inducing several proinflammatory cytokines including IL-17/IL-22⁴⁰ that is mediated by TLR2/TLR4 pathways. Inflammation triggered by O₃ is linked with the development of airway hyperreactivity^{41–43} in preclinical models.

OZONE IMPACTS ON LUNG FUNCTION IN CHILDREN

Controlled human exposure studies have consistently observed O₃-associated decrements in lung function and neutrophilic inflammation. O₃-induced, pain-related symptoms may inhibit maximal inspiration due to the stimulation of airway C-fibers, leading to reduced lung function measures⁴⁴ that are not necessarily linked to airway inflammatory responses.^{44–46} Later in discussion, we review the effects of short-term and long-term ambient O₃ exposures on children’s lung function.

IMPACT OF SHORT-TERM EXPOSURES ON LUNG FUNCTION

Multiple studies have evaluated the effects of shorter-term O₃ exposure on lung function in children. A panel study of 97 children ages 10 to 11 years old living in Athens and 89

children living in Thessaloniki followed participants throughout a school year to assess the effects of O₃ exposure on respiratory outcomes, comparing the Forced Vital Capacity (FVC) and Forced Expiratory Volume in 1 Second (FEV₁) values in the fall to values in the spring–summer period.⁴⁷ Baseline asthma prevalence among these children ranged from 7% in Athens to 15% in Thessaloniki. Compared with the first spirometry value in the fall, this study found significant decreases, around 5%, in FVC and FEV₁ during the spring–summer period, which was associated with higher O₃ concentrations.⁴⁷ In addition, a growth deficit of 0.008% for FVC (~20 mL) was noted over the 6- to 8-month observation period. Additionally, a study of 10,251 healthy White children aged 8 to 12 years in several US and Canadian communities found an almost 3% decrease in FVC and FEV₁ associated with a 37 ug/m³ increase in O₃ concentrations over the prior year⁴⁸; this effect was seen in both children with and without asthma.

In 2 Austrian studies, 2153 children aged 6 to 9 years had their lung function growth assessed over approximately three 6-month periods classified according to high versus low O₃ concentrations.⁴⁹ An asthma diagnosis at the start of the study ranged between 1.2% (Heidenreichstein/Austria) and 12.8% (Amstetten/Austria), and aeroallergen sensitization ranged from 6.8% (Wiesmath/Austria, Ganserndorf/Austria) to 28.8% (Ehingen/Germany). During the summer months, children who had semiannual mean O₃ exposures between 46 and 54 parts per billion (ppb) had a growth deficit of 18.5 mL in FEV₁ and 19.2 mL in FVC compared with children with lower exposures between 22 and 30 ppb. However, over the 3.5-year study period, there was no evident lung function growth deficit; this finding was attributed to the rebound growth that occurred during the winter periods, which compensated for the growth deficits noted during the summer periods.⁴⁹

The impact of O₃ on lung function among children with asthma is also evident in both high and low ambient O₃ environments. One-hundred fifty-eight children with asthma from Mexico City, whereby the mean 1-h maximum O₃ level was 102 ppb (SD 47 ppb) participated in a double-blinded randomized trial to evaluate whether antioxidant vitamin supplementation would attenuate the effects of ambient air pollution.⁵⁰ Among children in the placebo group, elevated O₃ concentrations the day before spirometry were significantly associated with reduced forced expiratory flow (FEF_{25-75%}) of 13.32 mL/s and reduced FEV₁ of 4.59 mL for every 10 ppb increase in O₃; no association between O₃ and lung function was observed in the supplement group.⁵⁰

These transient reductions in lung function are also evident with lower O₃ exposures in children with underlying airway disease. The Childhood Asthma Management Program (CAMP) enrolled children ages 5 to 12 years from 8 North American cities who had baseline elevated airway reactivity (by methacholine challenge) at study entry. Increased 4-month averages of ambient O₃ were associated with reduced postbronchodilator FEV₁/FVC.⁵¹ Similarly, African American adolescents with persistent asthma had reduced lung function, despite the use of asthma controller medications, with low level increases of ambient air O₃ concentrations (below the 70 ppb National Ambient Air Quality Standard).⁵² Specifically, the strongest effect in the reduction of lung function measurements was observed for O₃ concentrations in the 24-h period preceding clinic visits, whereby %predicted FVC was 2.7 points lower.⁵² Similar to the transient decrements in lung function seen with controlled low-dose O₃ exposure studies among adults,^{53,54} short-term higher concentrations of O₃ are also associated with reduced lung function in children, with or without asthma.

IMPACT OF EARLY-LIFE EXPOSURES ON LUNG FUNCTION

Although studies have shown that short-term O₃ exposure is associated with reduced lung function, data surrounding the relationship between long-term O₃ exposure and

lung function over years are inconclusive.¹¹ For example, a prospective study of 1759 10-year-old children from southern California assessed the long-term effects of air pollution on children's respiratory health. There was no significant evidence that O₃ was associated with any measure of reduced lung function over an 8-year period.⁵⁵

The lack of O₃ effect seen in some studies could be secondary to the timing of exposure during a child's lung development. To identify the effects of O₃ exposure during the early life period, a cross-sectional school-based survey of 1016 Taiwanese children aged 6 to 15 years without a history of asthma investigated the impact of lifetime residential exposure to intermediate levels of air pollution on spirometry.⁵⁶ Exposure to air pollution was assessed during the first year of life, age 2 to 6 years and lifetime; the lifetime annual average exposure was determined based on the residential history data of the participants and the average air pollution value in each township. Although each 1-ppb increase in O₃ was related to a 0.95% decrease in FEV₁ and 0.93% decrease in FVC when accounting for lifetime annual average exposures to O₃, the effects of O₃ became less significant after 2-pollutant adjustment for PM₁₀.⁵⁶ Additionally, a prospective birth cohort of 304 healthy term-born infants assessed the adverse effects of air pollution levels before and after birth on lung function at age 6.⁵⁷ Exposure assessment of NO₂, O₃, PM₁₀ occurred during pregnancy and during the first and sixth years of life. There were 232 children who remained in the study at the 6-year follow-up visit whereby spirometry was performed. While NO₂ exposure during pregnancy and first year of life was associated with decreased FEV₁, there were no significant associations observed for either O₃ or PM₁₀.⁵⁷

In contrast, a large prospective 2-year follow-up study of more than 1300 young children in the Korean Children's Health and Environmental Research (CHEER) cohort (mean age 6.83 ± 0.52 years at enrollment) found that exposure to elevated levels of O₃ within the past 5 years was associated with slight but significant reductions in % predicted FEV₁ and FEF_{25-75%} that was further amplified by a prior diagnosis of bronchiolitis.⁵⁸ Thus, most studies suggest that early life O₃ exposure does not by itself have long-lasting effects on lung growth and function among children. However, the CHEER cohort highlights that air pollutant exposure in the context of prior lung damage may impair future lung function. The long-term effects of O₃ on the lung function of young children with recurrent wheezing who go on to develop future asthma are unclear.

IMPACT OF PRENATAL AND EARLY LIFE EXPOSURES ON ASTHMA DEVELOPMENT

There has been growing interest surrounding the impact of air pollutant exposure during birth and early life on the development of asthma. Although multiple epidemiologic studies throughout the world have linked O₃ exposure with asthma exacerbation and increased respiratory symptoms among children and adults,¹⁰ limited studies to date have specifically examined the effect of *in utero* or early life O₃ exposure on the risk of subsequent asthma development. Herein we review the studies focused on asthma development from North America and Asia.

A large Canadian birth cohort study followed 65,254 children from birth until age 10 years using linked administrative health databases to evaluate the association between *in utero* exposure to air pollution and childhood asthma.^{59,60} This study found that higher *in utero* exposure to traffic-related air pollution was associated with increased asthma risk in preschool age children (diagnosed through age 5 years), but that O₃ exposure itself was associated with reduced risk in this age group; this finding was attributed to the negative correlation of O₃ levels with traffic-related air pollutants.^{59,60} However, higher *in utero* O₃ exposure was associated with increased

of asthma development among school-aged children (diagnosed after age 6) from this same cohort.⁶⁰ Another birth cohort study from Canada followed 1286 children from birth through age 17 to identify risk of air pollution on asthma and atopic disease.⁶¹ In a single-pollutant model, O₃ exposure at birth was not associated with asthma, allergic rhinitis, or eczema; however, in a multi-pollutant model that adjusted for NO₂, PM_{2.5} and Normalized Difference Vegetation Index (NDVI), there was a 1.2-fold higher risk of asthma per interquartile range (IQR) increase in O₃ exposure at birth. The findings were more robust when accounting for oxidant pollutants (both O₃ and NO₂) whereby for each IQR increase in oxidant pollutant exposure at birth, there was a 17% increase in the risk of developing asthma and 8% increase in risk of allergic rhinitis.⁶¹ Similarly, another population-based birth cohort study of Canadian children born in Québec between 1996 and 2011 assessed the association between outdoor air pollutant exposures at birth and the onset of childhood asthma.⁶² Asthma onset in children was associated with birth residential exposure to PM_{2.5}, O₃, and NO₂, with a Hazard Ratio (HR) of 1.06 (1.05–1.07) per interquartile range increase of O₃ levels.⁶²

Among Latino children and young adults living in the mainland United States and Puerto Rico in urban areas, the Genes-environments & Admixture in Latino Americans (GALA II) study found that for every 5 ppb increase in average O₃ exposure during the first year of life, the odds for having asthma without allergic sensitization increased by 32%.⁶³ Additionally, children with asthma without allergic sensitization were more likely to be exposed to higher levels of O₃ during the first year of life compared with children with atopic asthma, suggesting that mechanisms independent of atopy [such as airway neutrophilia seen in nonatopic children⁶⁴] may account for promoting asthma development.

Early life cohort studies in Asia have found similarities between early life O₃ exposure and asthma development. The Prenatal Environments and Offspring Health (PEOH cohort) that followed 3725 mother–child dyads from Guangzhou, China, recently found that elevated O₃ exposure increased the risk of preschool wheezing.⁶⁵ Additionally, the risk of preschool wheezing was further amplified if maternal O₃ exposure occurred during warm weather months (when ambient O₃ exposures are elevated). A population-based cohort study of more than 30,000 children in China aged 2 to 14 years observed a significant relationship between doctor-diagnosed asthma and increases in O₃ exposure average for the preceding 3 years before assessment.⁶⁶ This positive association was seen in both normal weight (Odds Ratio, OR 1.25 (1.12, 1.40) and overweight/obese children (OR 1.41 (1.22, 1.63)). Additionally, elementary-school children from the CHEER cohort in Korea that had exposure to elevated levels of O₃ within the past 5 years and prior episodes of bronchiolitis had a significantly higher prevalence of current asthma and greater nonspecific airway reactivity assessed by methacholine challenge.⁵⁸

In summary, the available epidemiologic evidence is stronger in support of early life O₃ exposure increasing the risk of future asthma. Although O₃ exposure may not have long-lasting effects on lung function growth, by spirometry, preclinical studies support that O₃ alters airway innervation and smooth muscle bundles that would impact nonspecific bronchial reactivity, one of the hallmarks of asthma.

ALLERGIC RHINITIS

Prior studies have reported that the effects of O₃, including bronchial and bronchiolar injury and tissue hypoxia, are associated with higher risk of diseases such as allergic rhinitis. The evidence surrounding allergic rhinitis development with O₃ exposure is

mixed. A longitudinal birth cohort study of 1286 Canadian children, aged 5 to 9 years, who were followed for an average of 17 years assessed the impact of O₃ exposure in the first 3 years of life whereby O₃ exposures were estimated for the months of May to October (8-h daily maximum) using a temporally adjusted model combining modeled O₃ from the Canadian Hemispheric Regional O₃ and NO_x system operational regional air quality forecast model with ground-based observations from monitors in Canada and the US.⁶¹ Exposure to O₃ at birth was associated with 1.2-fold higher risk of allergic rhinitis when adjusting for NO₂, PM_{2.5}, and NDVI in the multi-pollutant model. Similar to what this group reported with increased risk of asthma, increased exposures to total oxidants (NO₂ and O₃) in the first 3 years of life was associated with an increasing the risk of allergic rhinitis development.⁶¹

A large cross-sectional study in China examined the effects of air pollution on children between the ages of 2 to 17 years old living in Liaoning Province, a highly industrialized region in northeastern China.⁶⁷ Four years before the investigation, ambient O₃ exposure was estimated by using a satellite-based random forest model. Long-term exposure to O₃ was significantly associated with higher risk of allergic rhinitis, which was more pronounced in children aged 7 to 17 years.⁶⁷

Additionally, the impact of O₃ exposure on the development of allergic rhinitis was evaluated in school-aged children who reside in industrial areas in Korea, whereby the O₃ concentration was higher⁵⁸ using a prospective survey of parental responses to the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaires along with an evaluation for atopic status including total and allergen-specific IgE. During the 2-year study period, there was an increased rate of newly developed sensitization to outdoor allergens in children exposed to the higher levels of O₃, and there was a significant increase in the lifetime prevalence of allergic rhinitis.⁵⁸ This could suggest that O₃ exposure may promote the development of sensitization to environmental allergens. Most pediatric studies reviewed showed a positive association between O₃ exposure and allergic rhinitis development.

FOOD ALLERGY AND ATOPIC DERMATITIS

No studies to date have examined the relationship between O₃ exposure and the development of food allergy or eosinophilic esophagitis. Overall, there are limited studies that examine the relationship between O₃ exposure and development of atopic dermatitis in children. A Korean study assessed the association between hospitalization for atopic dermatitis and ambient O₃ levels in children less than 15 years old in the years 2004 to 2005. They found a higher relative risk of childhood atopic dermatitis in Ulsan, a highly industrialized Korean city with higher O₃ concentrations, compared with Seoul, a centrally located in the Korean peninsula with lower O₃ concentrations.⁶⁸ A longitudinal birth cohort study of 1286 Canadian children, aged 5 to 9 years, assessed the impact of O₃ exposure during the first 3 years of life. While O₃ exposure at birth was not associated with eczema in single-pollutant models, they found exposures to total oxidants (NO₂ and O₃) in the first 3 years of life showed a similar trend of increasing the risk of eczema in the multi-pollutant model (similar to what was reported with increased risk of comorbid allergic rhinitis and asthma).⁶¹

SUMMARY

Preclinical studies and more recent epidemiologic studies support that early life exposure to O₃ increases susceptibility to developing chronic airway disease including asthma and allergic rhinitis (Fig. 1). Once asthma is established, elevated O₃ levels are well known to cause asthma exacerbations in both children and adults. In addition

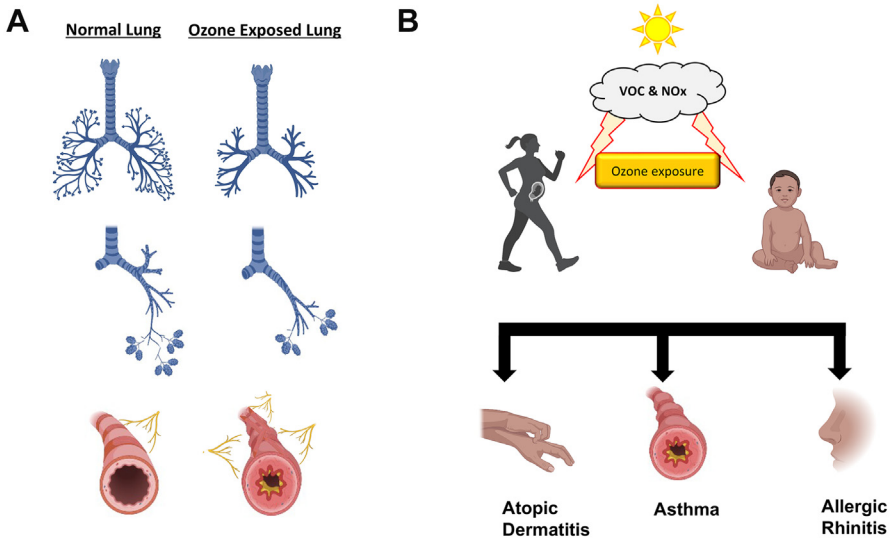


Fig. 1. Ozone exposure and the development of asthma and atopic disease. (A). Ozone exposure during lung development causes morphologic and structural changes: decreases bronchial branching and alveoli number, alterations in smooth muscle bundle orientation, and hyperinnervation of pulmonary epithelium. (B). Ozone exposure during early life increases the risk of developing asthma, allergic rhinitis, and atopic dermatitis. (Created with [BioRender.com](https://www.biorender.com).)

to promoting neutrophil-predominant airway inflammation, O₃ may increase the risk of allergic sensitization⁵⁸ and enhance the response to environmental allergens⁶⁹ that further perpetuate a prolonged airway inflammatory response. Such chronic inflammation may contribute to airway remodeling seen with chronic respiratory diseases such as asthma and COPD.¹²

The evidence underlying the impact of O₃ on adverse health effects compelled the US Environmental Protection Agency (EPA) to lower the primary and secondary National Ambient Air Quality Standard (NAAQS) for O₃ to 70 ppb in 2015.⁷⁰ Primary standards are meant to provide protective for “sensitive” populations who may have increased susceptibility to air pollution, namely children, the elderly, and those with underlying respiratory diseases such as asthma, while secondary standards are meant to provide widespread protection and promote public welfare. Based on our review, much work still needs to be conducted to address the potential effects of prolonged O₃ exposure at levels below the NAAQS on pregnant persons and infants that would impact early life lung development, asthma inception, and the development of other allergic diseases such as atopic dermatitis, food allergy, and eosinophilic esophagitis. These data are needed to develop robust, evidence-based policies that will reduce the overall burden of ambient air pollution for future generations throughout the globe.

CLINICS CARE POINTS

- O₃ is the most common noninfectious environmental cause of asthma exacerbations: it is imperative to minimize O₃ exposure among children and adults with underlying respiratory disease.

- Ozone exposure of pregnant persons and young children should be minimized to reduce the risk of developing asthma, allergic rhinitis, and atopic dermatitis.
- Clinical studies are needed to evaluate any links between O₃ exposure and risk of developing other atopic diseases such as food allergy and eosinophilic esophagitis.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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