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REVIEW

# Recent Insights into the Environmental Determinants of Childhood Asthma

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## Abstract

**Purpose of Review** Ubiquitous environmental exposures, including ambient air pollutants, are linked to the development and severity of childhood asthma. Advances in our understanding of these links have increasingly led to clinical interventions to reduce asthma morbidity.

**Recent Findings** We review recent work untangling the complex relationship between air pollutants, including particulate matter, nitrogen dioxide, and ozone and asthma, such as vulnerable windows of pediatric exposure and their interaction with other factors influencing asthma development and severity. These have led to interventions to reduce air pollutant levels in children's homes and schools. We also highlight emerging environmental exposures increasingly associated with childhood asthma. Growing evidence supports the present threat of climate change to children with asthma.

**Summary** Environmental factors play a large role in the pathogenesis and persistence of pediatric asthma; in turn, this poses an opportunity to intervene to change the course of disease early in life.

**Keywords** Air pollution · Childhood asthma · Environmental exposures · Indoor air · Pediatrics · Epidemiology

## Introduction

Asthma is a common chronic childhood disease, affecting approximately one in fifteen children in the United States [1]. Characterized by airway inflammation, bronchospasm, and airflow obstruction, it presents with clinical symptoms such as wheeze, cough, and respiratory exacerbations, often in response to exposures (or "triggers") such as aeroallergens and respiratory tract viruses. Beyond these two well-known categories of exposures, however, many factors in a child's environment are linked to both asthma pathogenesis and disease activity. We review recent advances in the understanding of these associations, focusing primarily on ubiquitous airborne environmental exposures; we also discuss mechanistic insights that may suggest causal relationships and windows of vulnerability, including prenatal exposures. Increased attention has been placed on finer-scale exposure assessment; that is, more precise geographic and temporal resolution of potential environmental contaminants than what is measured regionally or locally. This includes monitoring in settings children spend the majority of their time, such as inside homes and schools. We review established airborne pollutants subject to regulation, including particulate matter (PM), ozone ($O_3$), and nitrogen dioxide ($NO_2$), referred to as "criteria" pollutants under the U.S. Clean Air Act. We also highlight other, emerging environmental exposures, including phthalates, polycyclic aromatic hydrocarbons, volatile organic compounds, radon, and organophosphates. Though tobacco smoke exposure is a well-known contributor to asthma development and morbidity, reviewing advances in that literature is beyond the scope of this article. Finally, there is increasing evidence that changes to environmental exposures related to anthropogenic climate change adversely affect children with asthma.

## Established Associations between Criteria Pollutants and Asthma Pathogenesis

The association between criteria pollutants and asthma development in children has been convincingly demonstrated (Fig. 1). A meta-analysis in 2017 summarized much of the prior literature on components of traffic-related air pollution, including black carbon, coarse PM ($PM_{10}$), fine

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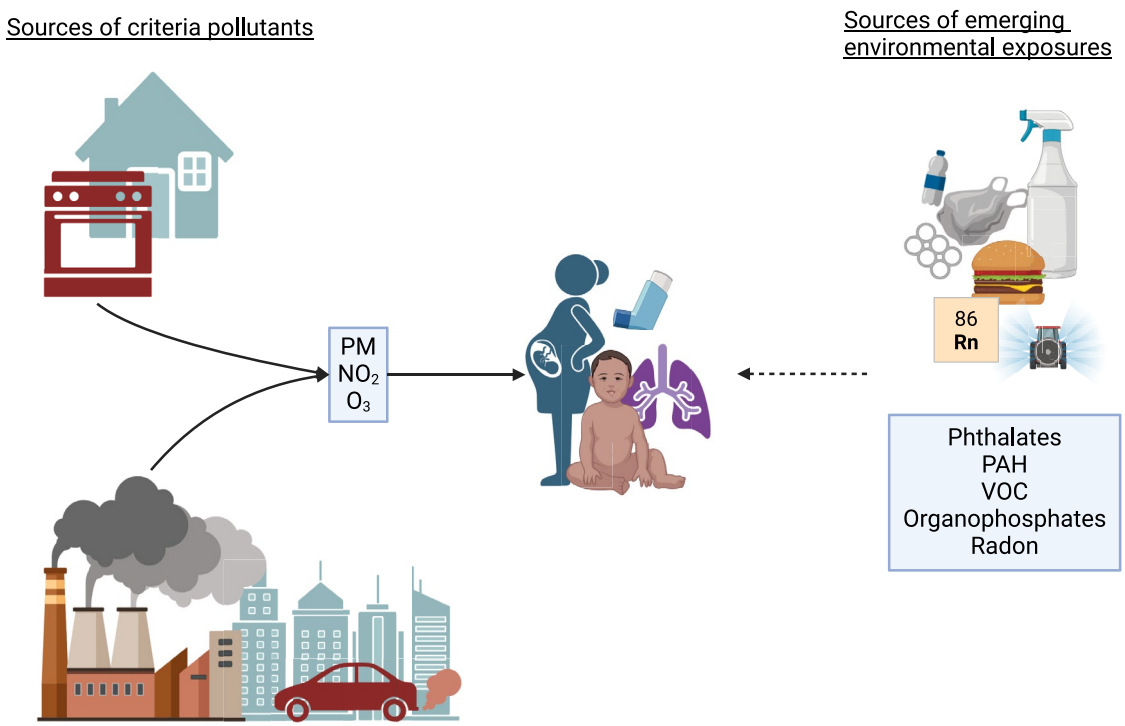


**Fig. 1** Established and emerging environmental determinants of childhood asthma. "Criteria" pollutants under governmental regulation including particulate matter (PM), nitrogen dioxide ($NO_2$), and ozone ($O_3$) may arise from outdoor sources such as traffic and fossil fuel power plants or indoor sources such as cooking. Emerging ubiquitous environmental exposures in consumer plastics, combustion byproducts, food, household products, insecticides, and naturally occurring radioactive decay include phthalates, polycyclic aromatic hydrocarbons (PAH), volatile organic compounds (VOC), organophosphates, and radon

PM ($PM_{2.5}$), and $NO_2$, in relation to incident asthma [2]. Regulatory efforts have led to reduced cases of asthma: reductions in $PM_{2.5}$ and $NO_2$ from 1993 to 2014 were associated with decreased asthma incidence in a prospective cohort of children in Southern California, with ozone and $PM_{10}$ similarly trending toward an inverse association with asthma [3]. Nevertheless, ambient air pollution remains a significant contributor to asthma pathogenesis. A recent estimate of annual $NO_2$ for the decade 2010–2019, linked to the Global Burden of Disease 2019 study, found that approximately 16% of asthma cases in urban areas worldwide could be attributed to $NO_2$ [4].

Prenatal exposures to criteria pollutants, when lung development is occurring, may constitute an important window of vulnerability. Prenatal $PM_{2.5}$ and $NO_2$ are consistently associated with asthma development across various birth cohort studies [5]. Recently, Hazlehurst and colleagues have suggested that $PM_{2.5}$ exposure in the saccular phase of lung development, occurring between 24 and 36 weeks of gestation, particularly increases asthma risk [6••]. Though much of the literature has previously reported on cohort studies in the U.S., Canada, and Europe, there is increasing evidence replicating similar associations in low- and middle-income countries (LMIC), such as China and South Africa [7, 8]. The discovery that black carbon can cross the placental barrier leads to suggested mechanisms for fetal exposure to particulates [9]. $NO_2$'s injurious impact on the developing lung prenatally has also been supported by an association with decreased levels of CC16, an anti-inflammatory protein protective against factors implicated in asthma pathogenesis [10, 11]. Nonetheless, remaining variability in recent study findings, such as a registry-based study in Sweden that did not find associations between prenatal ambient air pollutant exposure and asthma in offspring, suggests further work still needs to be done to elucidate the nature of this relationship [12].

As alveolarization of the lung continues through early childhood, early life has also been posited as an important time window for exposure to criteria pollutants. For instance, $NO_2$ exposure has been associated with onset of asthma before, but not after, age 5 in a longitudinal Canadian cohort [13]. Recent work has supported the persistence of these effects throughout childhood: $PM_{2.5}$ and $NO_2$ exposures associated with home address at birth were associated with asthma at age 20 in a Dutch birth cohort, while lung function declined in children with asthma up to age 15 in relation to $PM_{2.5}$ exposures in the first year of life [14, 15]. Indoor sources of air pollutants are

also increasingly recognized in asthma pathogenesis, both in developed countries and in LMIC [16, 17]. Though there is a substantial body of work on the relationship between indoor air pollutants and asthma morbidity, including interventions to improve indoor air quality discussed below, ascertainment of indoor criteria pollutant exposures in the prenatal and early life periods to assess their relevance to asthma pathogenesis is relatively sparse. The American Academy of Pediatrics Council on Environmental Health issued a policy statement in 2021 recognizing the adverse impact of air pollution on the child, supporting targeted interventions to reduce exposure in pregnant women and young children who may be particularly susceptible [18]. In turn, better understanding of indoor air pollutant exposures during vulnerable windows may lead to personalized interventions to reduce the risk of asthma development, complementing further policy and regulatory action to reduce ambient air pollutant levels.

## Emerging Environmental Determinants of Asthma Development

A variety of environmental exposures, including environmental chemicals, has been studied in relation to asthma development. We highlight several common exposures here because of their established links to other health effects and/or mixed findings in the literature (Fig. 1).

Phthalates are a class of plasticizer compounds in widespread use, commonly found in food storage and personal use products, leading to skin, dietary, and inhaled exposures [19]. They have been linked to perinatal health effects such as preterm birth, possibly through endocrine disruption [20, 21]. In 2014, Whyatt and colleagues first described a link between prenatal phthalate exposures and child asthma in a New York City birth cohort [22]. A meta-analysis of fourteen studies in 2020 found consistent associations between mono-benzyl phthalate (MBzP) and metabolites of di-2-ethylhexyl phthalate (DEHP) and risk of childhood asthma [23]; since then, several further prospective cohorts have reported on associations, or lack thereof, between phthalates and asthma, in both prenatal and early life exposure windows [24–27].

Children may be exposed to polycyclic aromatic hydrocarbons (PAH), produced from incomplete combustion, through inhalation from traffic-related sources and ingestion of foods with PAH. PAH have been linked to health effects including cancer, changes in neurodevelopment, early wheeze, and allergen sensitization [28–33]. In the largest cohort analysis of prenatal PAH, females but not males were at risk of asthma development [34, 35]. These inconclusive findings require further clarification.

Volatile organic compounds (VOC), gaseous at room temperature, arise from a variety of sources including household cleaners, paint, furniture, and combustion [36]. While there is evidence for prenatal VOC exposure on early life respiratory outcomes such as wheeze and decreased lung function, no data exist on persistence and transformation of these into childhood asthma [37–39]. Leveraging existing cohorts with measures of VOC during putatively vulnerable periods of exposure such as prenatally and in early life [40, 41], in addition to prospectively constructed studies, could help define any role of VOC in asthma pathogenesis.

Of note, children are exposed to phthalates, PAH, and VOC as diverse mixtures of chemicals, rather than as individual compounds, posing challenges in exposure assessment and analytical design. These challenges may contribute to the variability in associations found between these chemicals and development of asthma. We hope that analyses that thoughtfully consider mixtures of these chemicals using contemporary methods such as weighted quantile sum or Bayesian kernel machine regression will help capture the totality of exposure-outcome relationships in these emerging pollutants [42].

## Criterion Pollutant Exposures and Asthma Morbidity in Children

Similar to work on the likely causal role of criteria pollutants on asthma development, there is substantial evidence supporting a role for $PM_{2.5}$, $NO_2$, and $O_3$ in asthma morbidity, including symptomatic exacerbations and decreased lung function [43, 44]. Recent work describing links between criteria pollutants and healthcare utilization among children with asthma in LMIC complement similar literature in developed regions around the world, highlighting the global impact of air pollution on asthma severity [45–48]. In 2020, a London coroner officially implicated traffic-related air pollution in the asthma death of 9-year-old Ella Kissi-Debrah. This ruling resulted in significant public and medical discourse of the harms of air pollution to particularly vulnerable groups—including children with asthma [49, 50]. Indeed, $PM_{2.5}$ was a significant risk factor for pediatric asthma deaths in an analysis from 2001 to 2016 in North Carolina [51•]. Children with severe asthma at baseline are more significantly affected by exposures to criteria pollutants compared to those with mild asthma [52, 53]. Examination of interactions with other factors contributing to asthma severity can further help define children with asthma at particularly high risk. Among children who are obese, there is increased risk for asthma symptoms from $NO_2$ exposure and increased deposition of $PM_{2.5}$ in the lung, suggesting complex mechanistic links between asthma severity, obesity, and air pollution [54, 55]. Furthermore, the effects of air pollutants on asthma symptoms and lung function appear to persist despite baseline asthma control in children with verified maintenance use of inhaled corticosteroids [56], while

mitigating mouse allergen exposure was more effective in improving asthma symptoms among children who were less exposed to indoor $PM_{10}$ [57].

Mitigating personal exposure to criteria pollutants, particularly PM, has been an area of interest in recent years. In the last decade, landmark randomized controlled trials (RCT) of indoor air cleaners in children with asthma exposed to environmental tobacco smoke or woodstove smoke have shown decreases in symptoms and improvements in lung function [58–60]. Continued efforts to improve indoor air quality have shown varying levels of effectiveness in reducing asthma morbidity. Lung function improved with bedroom air purification and reduced $PM_{2.5}$ in a RCT in Shanghai, China [61]. An exploratory trial reducing household $NO_2$ appeared to lead to a reduction in asthma symptoms, though this effect did not reach statistical significance [62]. Though PM levels in schools, where children spend a substantial amount of time, are associated with asthma morbidity [63, 64], classroom HEPA air purifiers did not reduce symptoms in children with asthma [65••]. In a rural setting, where the makeup of airborne pollutants including the composition of particles may be different, HEPA air filters improved asthma control and reduced urinary leukotriene levels [66••]. Finally, a recent pilot RCT of ambient air pollution education for families improved asthma control [67]. We look forward to further work on fine-scale, indoor exposures to air pollution in the diverse places where children live and learn, such as the recently initiated Synair-G prospective cohort in European schools [68].

## Novel Environmental Associations with Asthma Morbidity

Emerging evidence supports the influence of a range of ubiquitous environmental factors on asthma symptoms and lung function. As discussed above, these include phthalates, PAH, and VOC. Recent work on phthalates (particularly DEHP) and a related class of plasticizer compounds, bisphenols, strengthens the link between these chemicals and asthma morbidity [69–71]. PAH exposure has been associated with increased bronchodilator and systemic corticosteroid use in the following 30 days [72]; whether these effects are causal or represent effects of confounded co-exposures, such as combustion that also produces particulates, is unclear. In contrast, the association between VOC exposures and asthma symptoms is more established, with a recent meta-analysis estimating effect sizes among

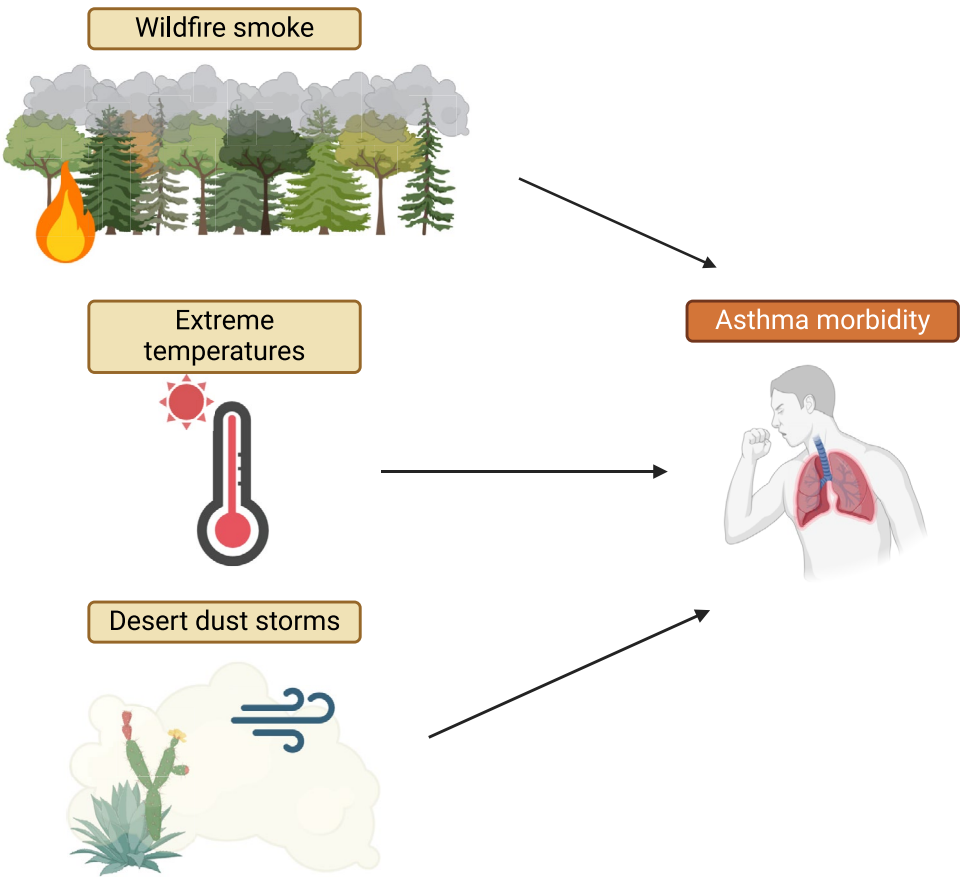


**Fig. 2** The impact of anthropogenic climate change on childhood asthma morbidity

children with asthma approximately double that of criteria pollutants [73]. This builds on prior work suggesting children are more vulnerable than adults to the respiratory effects of VOC exposure [74, 75].

Other emerging environmental determinants of asthma morbidity include organophosphates, present in insecticides and therefore important for children with asthma living in non-urban areas, [76, 77] and radon, a noble gas that can accumulate inside poorly ventilated buildings, including homes and schools [78]. High summer ambient temperatures, independent of air pollutant, aeroallergen, or respiratory viral levels, also contribute to asthma exacerbations in children [79].

## Children with Asthma are Vulnerable to the Effects of Climate Change

Rising ambient temperatures are but one consequence of anthropogenic climate change that is likely to adversely affect children with asthma. Wildfire smoke, a complex environmental hazard that is an important source of ambient fine and ultrafine PM, is becoming more intense and more widespread, including outside traditionally wildfire-prone areas [80–82]. For instance, in 2023, smoke from wildfires of unprecedented size in Canada was associated with increased asthma-related healthcare utilization in New York City [83]. The harmful effects of wildfire smoke exposure on pediatric asthma seem to extend beyond "background" exposures to traffic-related air pollution [84]. In addition to efforts to reduce wildfire activity, there is an urgent need to develop personal interventions to mitigate exposures among vulnerable populations such as children with asthma [85]. We also highlight here recent work attempting to mitigate exposure to another source of particulates linked to climate change—desert dust storms—in which an intervention with home air purifiers and decreased home ventilation successfully reduced indoor infiltration of dust storm PM [86]. Furthermore, continued fossil fuel extraction, with consequent production of air pollution due to activities such as gas flaring, is associated with pediatric asthma morbidity [87]. A warming climate may lead to increases in environmental exposures known to be determinants of asthma and pose new challenges for children with asthma (Fig. 2).

## Conclusions

Though the associations between PM, $NO_2$, and $O_3$ and childhood asthma are well-established, we continue to learn about the complexity of these relationships. Recent investigations have identified vulnerable windows of exposure and subgroups at particularly high risk. At the same time, more needs to be done to understand the causal pathways in order to continue developing interventions to mitigate exposure-related asthma morbidity. Increasing evidence is emerging to support ubiquitous chemicals in children's indoor environments such as phthalates, PAH, and VOC as determinants of asthma. These environmental hazards, which are likely to evolve and increase in a changing climate, require a multi-pronged approach of regulatory action, translational research, and individual mitigation to protect children with asthma.

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**Data Availability** No datasets were generated or analysed during the current study.

## Compliance with Ethical Standards

**Conflict of Interest** Dr. Sun declares no conflicts of interest. Dr. Gaffin reports personal fees from medical-legal consulting, outside the submitted work.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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