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Air pollution and childhood asthma: recent advances and future directions

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Abstract

Purpose of review—Current levels of air pollution are consistently associated with asthma development and morbidity among children, suggesting that current regulatory policies may be insufficient. This review will describe recent studies that have examined specific emission sources or components of pollutants that may be associated with pediatric asthma and identify subpopulations that may be particularly susceptible to the effects of air pollution exposure.

Recent findings—Important advances include new characterizations of the effects of traffic-related air pollution in urban areas. They also include the application of novel exposure and outcome measures such as pollution estimates derived from land use regression modeling and biological markers of airway inflammation. Additionally, studies have identified host susceptibility characteristics that may modify responses to air pollution exposure, including polymorphisms in oxidative stress genes and epigenetic alterations.

Summary—Identifying specific sources and toxic constituents of air pollution and accurately assessing air pollutant-related asthma outcomes are needed to better direct control strategies. Further research is needed to identify additional host factors that confer increased susceptibility to air pollution exposure. Future therapy to reduce the adverse effects of air pollution on respiratory disease will likely depend on targeting susceptible populations for intervention.

Keywords

air pollution; airway inflammation; asthma; oxidative stress; traffic

Introduction

Among children, acute increases in air pollution continue to be associated with asthma exacerbations [1–5]. These effects are often observed at pollutant concentrations below ambient standards, suggesting that current regulations may be insufficient or may not be targeting the responsible sources and pollutants. Recent advances in the study of air pollution and pediatric asthma include characterizing the effects of traffic-related pollutants, using novel exposure and outcome measures (Table 1Table 1 [6••,7••,8•,9••,10•,11•,12••,13•–15•,16••, 17•]), and identifying host susceptibility factors in children that may modify responses to air pollution exposure (Table 2Table 2 [18•,19•,20,21•,22••,23•,24••,25••]), including genetic polymorphisms and epigenetic alterations. With these advances, investigators have aimed to characterize air pollution-related respiratory health effects more accurately and objectively.

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Assessing traffic-related air pollution exposure and asthma outcomes

Earlier research focused primarily on pollutants for which National Ambient Air Quality Standards exist, including particulate matter, sulfur dioxide (SO_2), ozone (O_3), and nitrogen dioxide (NO_2). It is now understood that traffic emissions, especially from diesel trucks and buses, contribute a large proportion to air pollution levels in urban areas [26]. Consequently, current research attention has shifted toward improving exposure assessment and characterizing adverse health effects associated with specific sources and components of airborne traffic-related pollutants.

Whereas early epidemiologic studies relied on proxies of pollutant exposure such as traffic proximity and intensity to associate with asthma and lung function [27,28], recent advances in air pollution exposure assessment include direct measurement of black or elemental carbon to serve as indicators of ambient diesel exhaust particles (DEPs). Studies have provided evidence of long-term effects of black carbon or elemental carbon exposure, including deficits in lung development or development of asthma [29,30]. Recently, the effects of traffic-related pollutants on the development of allergy have also become apparent. In a Swedish cohort, exposures to traffic-related nitrogen oxides (NO_x) and coarse particulate matter [particles with aerodynamic diameter of 10 μm or less (PM_{10})] during the first year of life were associated with increased sensitization to inhalant allergens in addition to increased risk of wheeze and lower lung function at an age of 4 years [6••].

Current findings suggest that organic compounds and metals are additional specific components of traffic pollution that increase the risk of asthma [7••,31]. For example, in a study by our group in New York City [31], personal exposures of pregnant women to polycyclic aromatic hydrocarbons (PAHs) and environmental tobacco smoke (ETS) were associated with probable asthma and increased respiratory symptoms among their children by an age of 12 months. Hirshon *et al*. [7••] examined the association between ambient zinc and emergency department (ED) visits and hospitalizations for asthma among children in Baltimore, Maryland. They found that higher ambient air zinc levels were associated with increase in ED visits or hospital admissions for asthma on the following day.

Application of geographic information system-based measures

Until recently, investigators relied mostly on pollutant concentrations measured at central monitoring sites to assign exposures to a study population because of the prohibitive costs of monitoring persons individually. Several new asthma air pollution studies have used novel methods for assessing point and mobile source pollution exposures, including geographic information system (GIS)-based measures. For example, $PM_{2.5}$, NO_2, and elemental carbon levels measured outside 44 homes in Boston, Massachusetts were all significantly predicted by roadway length in various buffers around homes [8•]. McEntee and Ogneva-Himmelberger [13•] found that towns in Massachusetts containing major highway corridors had higher annual average levels of DEPs. These results indicate that geographic indicators of traffic may accurately represent traffic-related exposures for individual persons or populations when measured concentrations are not available.

In recent cross-sectional analyses, measures such as distance to point pollution source and distance to major road or highway have been associated with asthma incidence, wheeze, and exacerbation of asthma [10•,11•,12••,13•]. As part of a longitudinal birth cohort study, infants living within 50 m of a main road had increased odds of runny nose and sneezing during the first year of life [11•] and increased odds of sensitization to inhalant allergens and asthma at an age of 4–6 years [12••]. GIS has also been applied in the development of land-use regression (LUR) models to predict concentrations of traffic-related pollutants among unmonitored individuals. In one study, elemental carbon concentrations derived from LUR models were

significantly associated with wheeze among infants in Cincinnati [9••]. The use of GIS-based indicators of traffic and LUR models represent advances in air pollution epidemiology by providing individual-level exposure estimates for pollutants that have high spatial variability, thus potentially reducing bias from exposure misclassification. Additional research is needed to identify which GIS-based indicators may predict exposure to specific pollutants.

Application of biomarkers to health outcome assessment

Biological markers of airway inflammation, including exhaled breath condensate (EBC), the liquid phase of exhaled breath, and exhaled nitric oxide (eNO) are increasingly being applied in air pollution research. Unlike subjective symptom reports, which depend on individuals' recall, these biomarkers may be objective, quantifiable indicators of asthma control. Hydrogen peroxide, 8-isoprostane, and several cytokines are consistently higher in EBC of asthmatic children than in nonasthmatic children and increase further upon acute asthma exacerbations [32,33]. eNO, however, has shown inconsistent associations with asthma symptoms among children [34,35].

Some new data support the utility of eNO and EBC measures in assessing acute effects of air pollution on airway inflammation and asthma. In a recent cross-sectional study, closer proximity to any type of roadway was associated with increases in eNO among children aged 9–11 years but not with changes in lung function parameters [15•], suggesting that eNO may be a more sensitive marker to assess children's airway responses to air pollution exposure. A panel study of both nonasthmatic and asthmatic children found that eNO levels increased in response to elevated concentrations of residential $PM_{2.5}$, nitric oxide, NO_x, and black carbon over an 11-day period, and the greatest increases in eNO occurred in association with 8-h lags in exposures [14•]. Romieu *et al*. [16••] found that increases in ambient $PM_{2.5}$ and O_3 were associated significantly with increases in EBC malondialdehyde levels among asthmatic children. Malondialdehyde, a marker of oxidative stress, was also correlated with other measures of airway inflammation, including forced expiratory volume in 1 s (FEV_1) and nasal lavage IL-8 levels. However, in a repeated-measures study by Epton *et al*. [17•], increases in ambient particulate matter had no significant effect on levels of inflammatory biomarkers in EBC of nonasthmatic or asthmatic adolescents. The findings of the aforementioned studies indicate that exhaled markers of airway inflammation and oxidative stress may be sensitive tools in linking pollutant exposure to effects in the airways that result in asthma exacerbations. The noninvasive nature of eNO and EBC and relative ease of collection in the field further support the use of these biomarkers in large epidemiologic studies. However, further development of analytical methodologies and understanding of the subject characteristics and environmental factors that modulate the levels of markers in exhaled breath are likely to improve their reliability as outcomes in studies.

Individual susceptibility: timing and host characteristics

Similar to observations regarding deleterious effects of prenatal exposure to ETS [36], growing evidence suggests that prenatal exposure to air pollution may also heighten the risk for development of asthma. For example, prenatal exposures to PAH were found to be associated with probable asthma and wheeze at an age of 12 months in a New York City birth cohort [31] and wheeze, cough, and ear infections in a Polish cohort [37]. In a recent study of asthmatic children in California, both first trimester PM_{10} and second trimester NO_2 exposures were associated with lower lung function parameters at an age of 6–11 years [19•]. These epidemiologic observations are supported by mechanistic evidence that prenatal exposures of mice to particulate matter or DEP result in higher IgE levels, skewed Th2 cytokine responses, impaired lung growth, greater airway hyperresponsiveness, and increased infiltration of inflammatory cells [38•–40•].

Individual host characteristics may also confer greater susceptibility to air pollution-mediated asthma. In addition to atopy, sex, and nutritional status [41,42], recent studies implicate social stress [18•,20,21•] and genetic predisposition [22••,23•,24••,25••,43]. Chronic stress has been found to modify the risk of asthma associated with traffic-related air pollution exposure, although the direction of findings has been inconsistent. In one study, higher lifetime NO_2 exposures were associated with asthma only among children who reported exposure to violent events [18•]. In another study, more frequent respiratory symptoms were observed among asthmatic children living in poverty and high-traffic areas [21•]. However, a recent study reported that associations between stress and outcomes such as cytokine levels, IgE, and respiratory symptoms were stronger among children living in lower-pollution areas [20]. Mechanistic evidence to explain these contradictory epidemiologic observations is sparse.

Gene–environment interactions may provide an explanation for variability in asthma phenotypes associated with air pollution exposure. Recent studies suggest that polymorphisms in genes involved in metabolism of oxidant species [23•,25••,43], airway inflammation [24••], and innate immunity [22••] modify responses to air pollution exposures. For example, phase II enzymes such as glutathione-*S*-transferases (GSTs) facilitate the elimination of reactive oxygen species (ROS) via conjugation with glutathione. In a study of asthmatic children, the presence of the common GSTM1 null polymorphism or GSTP1 Val/Val genotype was associated acutely with difficulty breathing following increases in 6-day average ambient O_3 concentrations compared with the presence of the GSTM1 positive or GSTP1 Ile/Ile or Ile/Val genotypes, respectively [43]. In a study by Salam *et al*. [23•], GSTP1 Val/Val was associated with increased risk of lifetime asthma among children living close to major roadways or freeways compared with Ile/Val or Ile/Ile genotypes. The GSTP1 Ile/Val and Val/Val polymorphisms have also been associated with a greater risk of sensitization to any allergen in association with traffic-related NO_x during the first year of life [25••]. Significant three-way interactions were also observed among NO_x exposure, GSTP1 polymorphisms, and tumor necrosis factor α (TNFα) −308 GA/AA genotypes.

Polymorphisms in genes involved in initiating and sustaining airway inflammation have also been shown to modify respiratory responses to air pollution exposure among children. The −509 TT genotype of transforming growth factor β (TGFβ), which results in increased expression of TGFβ, was associated with a higher risk of lifetime asthma and early onset of asthma (before an age of 3 years) among children living within 500 m of a freeway as compared with the CC or CT genotype among children living greater than 1500 m from a freeway [24••].

Finally, variability in innate immune function has also been shown to alter respiratory responses to air pollution. CD14 and Toll-like receptors are pattern recognition receptors involved in the detection of pathogens, including bacterial endotoxin. In a panel study of asthmatic children, children without measurable CD14 expression on circulating neutrophils had reduced FEV_1 with increases in $PM_{2.5}$ and $PM_{10\text{-}2.5}$ [22••]. These results suggest that asthmatic children need surface expression of CD14 on neutrophils to protect themselves from exposure to bacterial constituents and, possibly, other components of particulate matter.

Mechanisms

Mechanisms implicated in the association between air pollution and pediatric asthma include the upregulation of allergic immune responses, activation of oxidative stress pathways, and epigenetic regulation. Exposure to airborne particulate matter in concert with allergen has been consistently shown to stimulate IL-4-mediated IgE pathways when compared with allergen exposure alone [44,45•,46•]. Recent advances include the identification of particle constituents that mediate this adjuvant activity. For example, studies on mice and human airway cells have

found that, compared with particles from woodsmoke or car exhaust, particles from diesel exhaust have higher capacity to induce proallergenic Th2 cytokine production, increased major histocompatibility complex class II expression, and increased inflammatory cell proliferation [46•,47•]. Studies have also examined the relative effects of organic and inorganic fractions of particulate matter but have yielded conflicting results. In one, exposure of mice to the carbon core fraction of DEP-stimulated greater airway hyperreactivity was compared with the organic fraction [45•]. In another, both organic and elemental carbon fractions of fine and ultrafine ambient particles were capable of stimulating proinflammatory allergic immune responses, as measured by increased secretion of Th2 cytokines and increased infiltration of eosinophils and polymorphonuclear leukocytes [48•].

Airborne pollutants such as DEPs have been reported to increase intracellular ROS levels and increase the expression of proinflammatory cytokines via regulation of redox-sensitive transcription factors, nuclear factor κB and activation protein-1, and signaling via the mitogen-activated protein kinase pathway [49]. Recent evidence suggests that additional intracellular signaling pathways may also be activated in response to DEP-generated ROS. In a study by Cao *et al*. [50••], DEP exposure of human airway epithelial cells activated the transcription factor, Stat3, via ROS-dependent activation of the epidermal growth factor receptor. In addition to stimulating oxidative stress pathways, DEPs may also stimulate antioxidant mechanisms. Li *et al*. [51••] showed that DEP treatment in mice resulted in increased expression of antioxidant enzymes such as GSTs, superoxide dismutase, and heme-oxygenase-1 via activation of the transcription factor, Nrf2. Nrf2 knockout mice had diminished antioxidant expression, higher cytokine production, and increased airway hyperresponsiveness in response to DEPs, suggesting that individuals with diminished antioxidant capacity may be more susceptible to DEP-induced airway inflammation.

Epigenetic regulation of genes, which refers to heritable changes in gene expression in the absence of alterations in DNA sequences, is a growing field of study of air pollution and asthma research [52]. Epigenetic changes in gene expression have been used to explain mechanisms underlying DEP-induced airway inflammation [53••,54••]. For example, DEP exposure of human airway cell-stimulated expression of the proinflammatory cyclooxygenase-2 (*COX-2*) gene by stimulating COX-2 promoter activity and increasing mRNA stability [53••]. DEPs also stimulated *COX-2* gene expression by increasing acetylation of promoter-associated histones, stimulating degradation of histone deacetylase 1 and recruiting histone acetyltransferase to the COX-2 promoter, all of which culminate in chromatin remodeling around DNA and activation of gene expression [54••]. Altered DNA methylation represents another mechanism by which airborne pollutants may induce airway inflammation. Experimental studies provide substantial in-vitro data indicating that DNA methylation of genes critical to T-helper cell differentiation may influence polarization toward or away from an allergic phenotype [55,56]. In a recent study, mice sensitized to the mold *Aspergillus fumigates* and exposed to DEPs had hypermethylation of CpG sites in the IFN-γ promoter and hypomethylation of CpG sites in the IL-4 promoter, and these altered patterns of methylation correlated with sera IgE levels [57•].

Conclusion

As our understanding of asthma pathogenesis increases, findings may translate into testable potential therapies for pollution-induced asthma. These may include pharmaceutical interventions that reduce oxidative stress by stimulating phase II enzymes such as GSTs or enhancing antioxidant responses or both. Future research directions should also include a greater study of the impact of climate change on airborne pollutant levels and on asthma and allergy risk. Already, it is apparent that increasing temperatures and CO_2 concentrations may

be associated with increased pollen concentrations and increased allergenicity of pollens [58].

Although concentrations of many airborne pollutants have decreased over time as a result of emissions control regulations [59,60], current levels of pollutants remain associated with asthma development and acute asthma morbidity. Identifying source contributions and toxic constituents of air pollution and accurately assessing air pollutant-related health outcomes are needed to direct pollutant-control strategies toward those sources responsible for the greatest burden of risk to asthma development and morbidity and to target interventions to susceptible populations.

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There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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Table 1

Traffic-related air pollution exposure and childhood asthma

Approach	Study design	Cohort	Exposure(s)	Results	Reference
Meaured traffic-related pollutants	Longitudinal birth cohort	Aged 0–4 years in Sweden	NO_x and PM_{10}	NO_x and PM_{10} during first year of life associated with increased sensitization, wheeze, and lower lung function at an age of 4 years	[6••]
	Population-level time series	Aged 0–17 years in Baltimore, Maryland	Ambient $PM_{2.5}$–Zinc	Increases in ambient zinc associated with increase in ED asthma visits or hospital admissions	[7••]
	Exposure assessment	Homes in Boston, Massachusetts	$PM_{2.5}$, NO_2, (EC)	$PM_{2.5}$, NO_2, and EC predicted by roadway length	[8•]
GIS	Cross-sectional analysis	Aged 0–1 years in Cincinnati, Ohio	EC	EC concentrations derived from LUR models associated with wheeze among infants	[9••]
	Case–control study	Aged 0–17 years in Puerto Rico	Proximity to point emission sources	Symptomatic children more likely to reside in proximity to point emission sources	[10•]
	Longitudinal birth cohort	Aged 0–1 years in Munich, Germany	Proximity to a major road	Infants living within 50 m of a main road had increased odds of runny nose and sneezing	[11•]
	Longitudinal birth cohort	Aged 0–6 years in Munich, Germany	Proximity to a major road	Residence within 50 m of a main road associated with increased odds of sensitization at an age of 4–6 years	[12••]
	Spatial analysis	Towns or census tracts in Massachusetts	DEP	Towns containing major highway corridors had higher levels of DEP and asthma incidence	[13•]
Biomarkers of airway inflammation	Panel study	Nonasthmatic and asthmatic children aged 5–10 years in Tokyo, Japan	$PM_{2.5}$, NO, NO_x, organic black carbon	eNO levels correlated with $PM_{2.5}$, NO, NO_x, and organic black carbon	[14•]
	Cross-sectional analysis	Aged 9–11 years in Windsor, Ontario	Proximity to roadway	Residence closer to any roadway associated with higher eNO levels	[15•]

Approach	Study design	Cohort	Exposure(s)	Results	Reference
	Panel study	Asthmatic children with mean age of 9 years in Mexico City, Mexico	$PM_{2.5}$, ozone	Increases in 8-h moving averages of $PM_{2.5}$ and ozone associated with increases in EBC malondialdehyde	[16••]
	Panel study	Nonasthmatic and asthmatic males aged 12–18 years in Christchurch, New Zealand	PM_{10}, $PM_{2.5}$, $PM_{1.0}$	Increases in PM had no effect on exhaled biomarkers	[17•]

DEP. diesel exhaust particle; EBC, exhaled breath condensate; EC, elemental carbon; ED, emergency department; eNO, exhaled nitric oxide; LUR, land-use regression; NO, nitric oxide; PM, particulate matter.

Table 2

Host characteristics, air pollution, and pediatric asthma

Host characteristic	Study design	Cohort	Exposure(s)	Results	Reference
Exposure to violent events	Longitudinal birth cohort	Aged 0–18 years in Boston, Massachussets	NO_2	Higher levels of lifetime NO_2 associated with asthma only among those exposed to violent events	[18•]
Trimester of exposure	Retrospective analysis	Asthmatic children aged 6–11 years in San Joaquin Valley, California	O_3, PM_{10}, CO, NO_2	Prenatal and early-life exposures to CO, PM10, and NO_2 associated with decreased lung function	[19•]
Chronic stress	Cross-sectional analysis	Mean age 12.8 years in Vancouver, Canada	NO_2	Effects of chronic stress on airway inflammation, symptoms higher among children with lower NO_2 exposures	[20]
Poverty	Cross-sectional analysis	Aged 1–65+ years	Residential traffic density	Effects of residence in high-traffic-density areas larger among individuals living in poverty	[21•]
CD14	Panel study	Asthmatic; Chapel Hill, North Carolina	$PM_{2.5}$, $PM_{10\text{-}2.5}$	CD14 expression on neutrophils correlated with FEV_1 in response to increases in $PM_{2.5}$ and $PM_{10\text{-}2.5}$	[22••]
GSTP1	Longitudinal cohort	Aged 10–18 years in Southern California	Residential proximity to major road	GSTP1 Val/Val associated with increased lifetime asthma if living less than 75 m from a major road	[23•]
TGFβ-1	Longitudinal cohort	Aged 10–18 years in Southern California	Residential proximity to major road	TGFβ −509 TT associated with asthma among if living within 500 m of a freeway	[24••]
GSTP1	Longitudinal birth cohort	Aged 0–4 years in Stockholm, Sweden	NO_x	Interaction observed between GSTP1 Ile/Val and Val/Val and NO_x on sensitization; three-way interactions observed among NO_x, GSTP1 polymorphisms, and TNF −308	[25••]

Host characteristic	Study design	Cohort	Exposure(s)	Results	Reference
				GA/AA genotypes	

FEV_1, forced expiratory volume in 1 s; GSTP1, glutathione-*S*-transferase P1; NO_X, nitrogen oxides; PM, particulate matter; TGFβ, transforming growth factor β; TNFα, tumor necrosis factor α.