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 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 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.
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 airways 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•].

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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 NO2 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 O3 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 NOx during the first year of life [25••]. Significant three-way interactions were also observed among NOx 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 FEV1 with increases in PM2.5 and PM10−2.5 [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 CO₂ 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.

References and recommended reading

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

• of special interest

•• of outstanding interest

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


6. Nordling E, Berglind N, Melén E, et al. Traffic-related air pollution and childhood respiratory symptoms, function and allergies. Epidemiology 2008;19:401–408.408 [PubMed: 18379426] This study is one of the few that shows that air pollution exposure increases the risk of sensitization to inhaled allergens and also shows that early-life exposures increase the risk of respiratory disease at later ages.

7. Hirshon JM, Shardell M, Alles S, et al. Elevated ambient air zinc increases pediatric asthma morbidity. Environ Health Perspect 2008;116:826–831.831 [PubMed: 18560541] This time-series study identifies ambient zinc, which is related to combustion of fossil fuels and abrasion of vehicle brakes and tires, as an important fraction of PM$_{2.5}$ that increases the risk of asthma admissions and hospitalizations among children living in an urban area. The results make an important contribution in characterizing relative toxicities of particle constituents.

8. Clougherty JE, Wright RJ, Baxter LK, Levy JI. Land use regression modeling of intra-urban residential variability in multiple traffic-related air pollutants. Environ Health 2008;7:17. [PubMed: 18485201] The results of this study indicate that geographical indicators such as roadway length significantly predict concentrations of PM$_{2.5}$, NO$_2$, and elemental carbon outside urban residential locations and...
support the use of GIS to estimate individual-level exposures to traffic-related air pollution when measured concentrations are unavailable

9. Ryan PH, Lemasters GK, Biswas P, et al. A comparison of proximity and land use regression traffic exposure models and wheezing in infants. Environ Health Perspect 2007;115:278–284.284 [PubMed: 17384778] This study is unique in that it shows that LUR models explain a large portion of ambient elemental carbon concentrations measured outside urban residential locations and that these LUR-derived estimates are associated with infant wheezing using individual-level data


11. Morgenstern V, Zutavern A, Cyrys J, et al. Respiratory health and individual estimated exposure to traffic-related air pollutants in a cohort of young children. Occup Environ Med 2007;64:8–16.16 [PubMed: 16912084] This study is one of few that show that proximity to traffic increases the risk of allergy-related outcomes among infants

12. Morgenstern V, Zutavern A, Cyrys J, et al. Atopic diseases, allergic sensitization, and exposure to traffic-related air pollution in children. Am J Respir Crit Care Med 2008;177:1331–1337.1337 [PubMed: 18337595] These findings corroborate those from the previous study, with longer follow-up, and show that long-term exposures to traffic increase the risk of sensitization to inhalant allergens at an age of 4–6 years

13. McEntee JC, Og涅va-Himmelberger Y. Diesel particulate matter, lung cancer, and asthma incidences along major traffic corridors in MA, USA: a GIS analysis. Health Place 2008;14:817–828.828 [PubMed: 18280198] This study shows spatial clustering between distribution of highway corridors and concentrations of DEPs and makes important policy recommendations to reduce DEP emissions on the basis of findings that certain towns with elevated DEP concentrations also had elevated asthma prevalence rates

14. Murata A, Kida K, Hasunuma H, et al. Environmental influence on the measurement of exhaled nitric oxide concentration in school children: special reference to methodology. J Nippon Med Sch 2007;74:30–36.36 [PubMed: 17384475] Analysis of repeated measurements of pollutants outside people’s homes at hourly intervals and eNO over 11 consecutive days led to increased understanding of the time course of effects of air pollution exposure on markers of airway inflammation. Investigators found that eNO concentrations were most closely associated with pollutant concentrations averaged over the 8 h prior to eNO collection

15. Dales R, Wheeler A, Mahmud M, et al. The influence of living near roadways on spirometry and exhaled nitric oxide in elementary schoolchildren. Environ Health Perspect 2008;116:1423–1427.1427 [PubMed: 18941589] This cross-sectional study is unique in that it shows significant associations between increasing proximity to roadways and increases in eNO among children. No effect of roadway proximity was observed on FEV$_1$ or forced vital capacity, suggesting that eNO may be a more sensitive tool to assess responses to traffic-related air pollution than spirometry

16. Romieu I, Barraza-Villarreal A, Escamilla-Nuñez C, et al. Exhaled breath malondialdehyde as a marker of effect of exposure to air pollution in children with asthma. J Allergy Clin Immunol 2008;121:903–909.909 [PubMed: 18234317] Using a repeated-measures design, this is one of few published studies to show that increases in ambient PM$_{2.5}$ are associated with increases in oxidative stress markers in EBC of asthmatic children. The findings further support the use of EBC to assess respiratory outcomes by showing that EBC marker levels are associated with other measures of airway inflammation such as FEV$_1$ and IL-8 in nasal lavage

17. Epton MJ, Dawson RD, Brooks WM, et al. The effect of ambient air pollution on respiratory health of school children: a panel study. Environ Health 2008;7:16. [PubMed: 18479529] In this repeated-measures study with nonasthmatic and asthmatic children, no significant associations were observed between different size classes of ambient particulate matter and levels of EBC pH and hydrogen peroxide. Lack of associations may have resulted from large variability in measured EBC markers and low assay sensitivity, which underscores the need for further analytical improvements and characterization of sources of within-individual and between-individual variability in EBC markers

This study was unique in showing that asthma diagnosis was related to outdoor residential NO\textsubscript{2} exposures constructed using LUR modeling only among children reporting exposure to violent events. The results suggest that social stress may increase susceptibility to air pollution exposure. Exposures at different ages were evaluated, and the year of diagnosis of NO\textsubscript{2} best predicted asthma.


This retrospective study is one of few to show that prenatal exposures to carbon monoxide, PM10, and NO\textsubscript{2} are associated with adverse respiratory health outcomes in children at an age of 6–11 years.


This study aimed to separate effects of exposure to traffic-related pollutants and low income on asthma symptoms, as most low-income communities are located in high-traffic areas. Analyses with income as a confounder and effect modifier indicated that associations between traffic density and asthma symptoms were larger among individuals living in poverty.


This study is one of few to evaluate how innate immunity activation may modify associations between air pollution and asthma. The findings suggest that asthmatic children need surface expression of CD14 on neutrophils to protect themselves from exposure to bacterial and, possibly, other components of particulate matter.


This study shows that individuals with lower activity of phase II metabolizing enzyme, GSTP1, may be at increased risk of asthma if they live in close proximity to a major road.


This study found that TGFβ-1 polymorphisms associated with increased expression increased the risk of lifetime and early onset of asthma among children living within 500 m of a freeway. The findings suggest that air pollution and TGFβ-1 may interact to increase asthma risk via increasing oxidative stress.


In this large birth cohort of over 4000 children, significant three-way interactions were observed among polymorphisms in GSTP1 and TNFα and NO\textsubscript{2} exposure in increasing risk of allergic sensitization. The findings highlight the roles of both antioxidant and proinflammatory mechanisms in mediating the effects of air pollution on allergy responses.


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51. Li YJ, Takizawa H, Azuma A, et al. Disruption of Nrf2 enhances susceptibility to airway inflammatory responses induced by low-dose diesel exhaust particles in mice. Clin Immunol 2008;128:366–373.373 [PubMed: 18614404] In mice, inactivation of Nrf2, a transcription factor involved in the activation of antioxidant genes, resulted in increased airway inflammation in response to low-dose DEPs compared with wild-type mice. This study produces novel findings that moderate levels of DEPs may increase the activation of antioxidant genes.


57. Liu J, Ballaney M, Al-alem U, et al. Combined inhaled diesel exhaust particles and allergen exposure alter methylation of T helper genes and IgE production in vivo. Toxicol Sci 2008;102:76–81.81 [PubMed: 18042818] This is the first study to report that air pollutants such as DEPs may increase the susceptibility to develop asthma by altering methylation states of Th genes.


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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.
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<td>Asthmatic; Chapel Hill, North Carolina</td>
<td>PM₂·₅, PM₁₀-₂·₅</td>
<td>CD14 expression on neutrophils correlated with FEV₁ in response to increases in PM₂·₅ and PM₁₀-₂·₅</td>
<td>[22••]</td>
</tr>
<tr>
<td>GSTP1</td>
<td>Longitudinal cohort</td>
<td>Aged 10–18 years in Southern California</td>
<td>Residential proximity to major road</td>
<td>GSTP1 Val/Val associated with increased lifetime asthma if living less than 75 m from a major road</td>
<td>[23•]</td>
</tr>
<tr>
<td>TGFβ-1</td>
<td>Longitudinal cohort</td>
<td>Aged 10–18 years in Southern California</td>
<td>Residential proximity to major road</td>
<td>TGFβ−509 TT associated with asthma among if living within 500 m of a freeway</td>
<td>[24••]</td>
</tr>
<tr>
<td>GSTP1</td>
<td>Longitudinal birth cohort</td>
<td>Aged 0–4 years in Stockholm, Sweden</td>
<td>NOₓ</td>
<td>Interaction observed between GSTP1 Ile/Val and Val/Val and NOₓ on sensitization; three-way interactions observed among NOₓ, GSTP1 polymorphisms, and TNF −308</td>
<td>[25••]</td>
</tr>
<tr>
<td>Host characteristic</td>
<td>Study design</td>
<td>Cohort</td>
<td>Exposure(s)</td>
<td>Results</td>
<td>Reference</td>
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<tr>
<td>GA/AA genotypes</td>
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</table>

FEV₁, forced expiratory volume in 1 s; GSTP1, glutathione-S-transferase P1; NOₓ, nitrogen oxides; PM, particulate matter; TGFβ, transforming growth factor β; TNFα, tumor necrosis factor α.