



Air pollution and allergic diseases

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Purpose of review

Exposure to traffic-related air pollutants (TRAPs) has been implicated in asthma development, persistence, and exacerbation. This exposure is highly significant because increasingly large segments of the population worldwide reside in zones that have high levels of TRAP, including children, as schools are often located in high traffic pollution exposure areas.

Recent findings

Recent findings include epidemiologic and mechanistic studies that shed new light on the impact of traffic pollution on allergic diseases and the biology underlying this impact. In addition, new innovative methods to assess and quantify traffic pollution have been developed to assess exposure and identify vulnerable populations and individuals.

Summary

This review will summarize the most recent findings in each of these areas. These findings will have a substantial impact on clinical practice and research by the development of novel methods to quantify exposure and identify at-risk individuals, as well as mechanistic studies that identify new targets for intervention for individuals most adversely affected by TRAP exposure.

Keywords

air pollution, allergy, asthma, traffic pollution

INTRODUCTION

A recent comprehensive and systematic review of worldwide traffic emissions and health science by a Special Panel convened by the Health Effects Institute found sufficient evidence that exposure to traffic-related air pollutants (TRAPs) causes asthma exacerbation in children [1]. Within the complex mixture of gaseous and particulate components of TRAP, diesel exhaust particles (DEPs) are of particular concern with respect to health effects. DEPs are estimated to contribute up to 90% of the particulate matter derived from traffic sources, are primarily ultrafine in size (<100 nm), can be deposited in the nasal and peripheral airways, and have been shown to induce oxidative stress and airway hyper-responsiveness (AHR), and enhance allergic responses and airway inflammation [2–4]. This exposure is highly significant because in large cities in North America, up to 45% of the population resides in zones that are most impacted by TRAP [1] and over 30% of schools are located in high TRAP exposure areas [5]. Evidence from our group and others suggests that TRAP is also associated with reduced lung growth and the development of asthma, though recent studies have reported

conflicting results [6–9,10^{••},11,12^{••}]. These inconsistent findings may be because of a lack of knowledge regarding the mechanistic basis of TRAP health effects and the characteristics of those most susceptible to the harmful effects of TRAP exposure. Recent epidemiologic and mechanistic findings have started to fill gaps in knowledge regarding the health impact of TRAP exposure on allergic diseases, as well as the molecular mechanisms by which TRAP leads to adverse effects on allergic diseases such as asthma. Further, new methodologies for the quantification of TRAP hold tremendous promise for rapid and reliable identification of individuals at-risk because of high exposure.

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KEY POINTS

- Exposures to TRAP decrease lung function, trigger asthma exacerbation, and contribute to the development and aggravation of asthma, eczema, allergic rhinitis, and sensitization.
- Exposure models incorporating novel data and methodology, and new technology, including smartphones and personal sensors, have led to improved exposure estimates in epidemiologic studies.
- DEP can persist in the murine lungs for months after exposure, in association with chronic T_H17 inflammation, without triggering immune features of asthma.
- DEP exacerbates allergen-induced innate and adaptive T_H2 responses and promotes disease persistence through increased accumulation of pathogenic memory T_H2/T_H17 cells.

EPIDEMIOLOGY OF THE HEALTH IMPACT OF TRAFFIC-RELATED AIR POLLUTANT ON ALLERGIC DISEASE

The prevalence and incidence of allergic diseases have been increasing worldwide since the 1960s [13,14]. More recent investigators suggest that asthma prevalence has plateaued in developed countries, whereas in developing countries, where the prevalence was previously low, allergic diseases are on the rise [15]. Environmental changes are suspected to be the major driver of this increasing trend [16], with air pollution identified as an important extrinsic agent [17]. Motor vehicles produce a complex mixture of air pollutants including carbon monoxide, nitrogen oxides, particulate matter of varying size, polycyclic aromatic hydrocarbons [PAHs; e.g., benzo(a)pyrene], volatile organic compounds (VOCs; e.g., benzene and acetaldehyde), and other hazardous air pollutants. Collectively referred to as TRAPs, these are the primary source of intraurban variability in air pollutant concentrations [1].

Asthma and wheezing

There is sufficient evidence to suggest that TRAP can decrease lung function and trigger asthma exacerbation and hospitalizations [14,18]. Recent large studies on TRAP and respiratory outcomes substantiate these conclusions (Table 1) [10¹¹,12¹¹,19,20,21¹¹,22–25,26¹¹,27,28,29¹¹,30]. Findings from the Southern California Children's Health Study, a cohort of 11 365 schoolchildren in 16 communities, indicate that exposure to higher local nitrogen

dioxide (NO_2) concentrations and close residential proximity to a freeway increase asthma prevalence [19]. Asthmatic children in the cohort who lived in communities with higher levels of NO_2 , PM_{10} and $PM_{2.5}$ had increased chronic lower respiratory symptoms, phlegm, production, bronchitis, wheeze, and medication use [19]. Living in areas with higher air pollution markers also affected lung function and growth. Children aged 10–18 years living within 500 m of a freeway had significant deficits in forced expiratory volume in 1 second, forced vital capacity (FVC), and maximal mid-expiratory flow rate compared with those living more than 1500 m away [19]. A recent study of 5443 Korean children aged 6–14 years found that children living within 200 m of a main road that was at least 254 m long had increased lifetime wheezing, lifetime asthma diagnosis, and decreased lung function [20]. A meta-analysis of six cohorts in the European Study of Cohorts for Air Pollution Effects (ESCAPE) that included 23 704 adults found that exposure to higher NO_2 increased the incidence of adult-onset asthma, although the results did not reach significance [21¹¹]. ESCAPE was also composed of five birth cohort studies including 17 041 children. Although these birth cohorts did not find any significant associations between six traffic-related pollution metrics and childhood asthma prevalence, the land-use regression (LUR) models used to estimate exposures were carried out as long as 15 years after the asthma outcomes were collected [10¹¹]. During this time, campaigns to reduce air pollution could have reduced exposure levels compared with those present when the asthma outcomes were collected. We have also shown TRAP exposure levels at a child's birth address to be associated with wheezing [22–24] and recurrent night cough [25] in the first 3 years of life.

Allergic sensitization and eczema

Studies also support an increase in allergic sensitization and eczema with TRAP exposures (Table 1). A 2014 review of epidemiologic data on the role of air pollution in eczema concluded that a variety of air pollutants, including those related to TRAP such as particulate matter and nitrogen oxides, act as risk factors for the development or aggravation of eczema [26¹¹]. A study of 4907 children aged 9–11 years showed that lifetime eczema was significantly associated with 3-year averaged concentrations of PM_{10} , NO_2 , NO_x , and CO [27]. A Taiwanese study of 317 926 middle school students demonstrated that flexural eczema was associated with levels of CO and NO_x [28]. In the Southern California Children's Health Study, children living

Table 1. Selected epidemiologic studies of traffic-related air pollutant associations with allergic disease

Outcome	Study type	# of studies	Sample size	Age group	TRAP markers	Main findings	References
Asthma/ wheezing	Meta-analyses	5 birth cohorts	17 041	Birth-10	NO ₂ , NO _x , PM _{2.5} , PM ₁₀ , coarse PM, traffic intensity	No significant associations between traffic-related pollution metrics and childhood asthma prevalence	Molter <i>et al.</i> [10 ^{***}]
	Review	5 cohorts	937–5603 per cohort (11 365 total)	K–10th grade	O ₃ , PM _{2.5} , PM ₁₀ , NO ₂	Higher local NO ₂ associated with increased asthma prevalence (OR 1.83, 1.04–3.22); asthmatic patients with higher NO ₂ , PM ₁₀ , and PM _{2.5} exposure had increased lower respiratory symptoms, bronchitis, phlegm production, wheeze and medication use; living within 500 m of a freeway was associated with deficits in FEV1, FVC, and MMEF	Chen <i>et al.</i> [19]
	Case-control	1	5443	6–14	Proximity	Living within 200 m of a main road increased wheeze, asthma diagnosis, and decreased lung function	Jung <i>et al.</i> [20]
	Meta-analyses	6 cohorts	23 704	Adults	NO ₂	NO ₂ exposure modestly increased incidence of adult-onset asthma (OR 1.04, 0.99–1.21)	Jacquemin <i>et al.</i> [21 ^{***}]
	Case control	1 birth cohort	762	Birth-3	Proximity, land use regression model	Higher exposures to TRAP increase wheezing and night cough	Ryan <i>et al.</i> [22–24]; Sucharew <i>et al.</i> [25]
	Meta-analyses	5 birth cohorts	272–37 401	1–12	PM _{2.5} , NO ₂ , BC	Longitudinal childhood exposure to NO ₂ (OR 1.06, 1.01–1.12), PM _{2.5} (OR 1.05, 1.01–1.08) and BC (OR 1.19, 1.07–1.32) increased asthma incidence. Substantial heterogeneity between studies for NO ₂ and PM _{2.5} .	Bowatte <i>et al.</i> [12 ^{***}]
Eczema	Review	6	400–7030	Birth-13	PM ₁₀ , NO ₂ , NO _x , CO	Traffic pollutant markers act as risk factors for the development or aggravation of eczema	Ahn <i>et al.</i> [26 [*]]
	Case-control	1	4907	9–11	Dispersion model	Eczema was significantly associated with PM ₁₀ , NO ₂ , NO _x , and CO	Penard-Morand <i>et al.</i> [27]
	Case-control	1	317 926	12–14	SO ₂ , NO _x , O ₃ , CO and PM ₁₀	Flexural eczema is associated with NO ₂ and CO	Lee <i>et al.</i> [28]
Allergic rhinitis/ sensitization	Case-control	1	5443	6–14	Proximity	Living <75 m from main road increased lifetime diagnoses and symptoms of allergic rhinitis. Distance to the main road and the length and proportion of the main road within 200 m of the home were all associated with allergic sensitization to aeroallergen or food	Jung <i>et al.</i> [20]
	Case-control	1 birth cohort	762	Birth-4	Land use regression model	High TRAP exposure modestly increased the risk of aeroallergen sensitization (OR 1.4, 0.97–2.0)	Codispoti <i>et al.</i> [29 ^{***}]
	Case-control	1 birth cohort	2545	Birth-8	Land use regression model	TRAP exposure in first year of life increased risk of pollen sensitization (OR 1.83, 1.02–3.28); TRAP increased risk of food sensitization at age 8 in those not sensitized at age 4 (OR 2.3, 1.1–4.82)	Gruzdeva <i>et al.</i> [30]
	Meta-analyses	5 birth cohorts	272–37 401	1–12	PM _{2.5} , NO ₂ , BC	Higher PM associated with increased sensitization to outdoor allergens (pollen and grass). No association with TRAP measures and sensitization to indoor allergens (cat dog, or mold)	Bowatte <i>et al.</i> [12 ^{***}]

BC, black carbon; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; MMEF, maximum mid-expiratory flow; OR, odds ratio; PM, particulate matter; TRAP, traffic-related air pollutant.

less than 75 m from the main road were significantly more likely to have lifetime diagnoses and symptoms of allergic rhinitis [20]. The distance to the main road, and the length and proportion of the main road within 200 m of the home, were all associated with allergic sensitization, defined as a positive skin prick test to an aeroallergen or food [20]. Our data and others have also shown high TRAP exposure in the first year of life to increase the risk of aeroallergen sensitization by the age of 4 by 40–83% [29²²,30]. Children exposed to high TRAP levels before age 1 also have an increased risk of developing food allergy by age 8, particularly those who are not sensitized at age 4 [30].

Insights from birth cohort studies

To evaluate the impact of TRAP on asthma and allergy development, birth cohort studies are needed (Table 1). A recent meta-analysis conducted a systematic review of birth cohort studies to understand the association between early childhood TRAP and subsequent allergies, asthma, and allergic sensitization [12²²]. Although modest associations were observed between asthma incidence/prevalence and wheeze and nitrogen oxides, particulate matter, black carbon, and road proximity, there was substantial heterogeneity observed (likely because of differences in study design, participants and exposure, and outcome definitions) between the studies [12²²]. The meta-analyses showed no association with TRAP measures and sensitization to indoor allergens (cat, dog, or mold). Although there was a significant association between particulate matter and sensitization to outdoor allergens (pollen and grass), there was again high heterogeneity between studies [12²²]. The associations between the markers of air pollution (NO₂, black carbon, and road proximity) and hay fever and eczema were inconsistent. With respect to the timing of exposure and disease development, this review suggests that TRAP exposure is associated with new onset asthma and may have an ongoing effect with a lag time of about 3 years [12²²]. We recently reported that a child's risk for persistent wheeze and asthma development varies depending on the timing and duration of TRAP exposure [31²²]. Children exposed to high levels of TRAP at the time of birth were nearly twice as likely to experience persistent wheezing at age 7; however, a longer duration of exposure to high levels of TRAP (beginning early in life and continuing through age 7) was the only time period of exposure related to asthma development [31²²].

Collectively, there is considerable evidence that TRAP plays a role in the development, and symptoms of allergic disease. However, heterogeneity in

both the definitions of TRAP exposure and outcomes, and unmeasured confounding, limit the ability to draw firm conclusions from the data. As discussed in the Bowatte *et al.* [12²²] meta-analyses, there is substantial variability in the exposure measurements across TRAP-related studies. LUR models are among the most common methods to assess TRAP exposures. Other methods include passive samplers, central monitoring stations, and proximity to major roads. The most frequent markers of pollutants include particulate matter, oxides of nitrogen, carbon monoxide, and ozone. Particulate matter may be further reported as black carbon, PM₁₀, or PM_{2.5}. Although this vast variation in the definition of TRAP exposure limits the ability to conduct sound meta-analyses, it highlights the importance of appropriate exposure assessment, as discussed below.

ASSESSMENT OF TRAFFIC-RELATED AIR POLLUTANT EXPOSURE

Given the increasingly evident health impact of TRAP, methodologies to accurately assess exposure are needed. Although TRAP affects air quality on urban and regional scales, their impact is greatest on a local scale, particularly near roadways, as their concentrations are significantly elevated within approximately 300–500 m of their source [32]. Further influencing individuals' TRAP exposure is its temporal variability combined with complex and variable personal behavior including time spent indoors/outdoors [33]. In order to meet the intrinsic challenge of accurately assessing TRAP exposure for epidemiologic studies, both modeling and personal measurement approaches have been proposed. Herein, we briefly review approaches to TRAP exposure assessment for epidemiologic studies with an emphasis on recent methodologic advances. An overview of each approach and their strengths and limitations are also provided in Table 2.

Modeling approaches

Although regulatory air monitoring provides valuable data to link the regional and temporal variability of air pollutants to population-level health outcomes, including increased cardiopulmonary morbidity and mortality [34–37], these networks are unable to capture the high spatial variability of TRAP concentrations within an urban area. Measuring proximity (i.e., distance) to major roadways is a straightforward approach to estimate TRAP exposure, though this method does not account for traffic density and other geographic and land-use characteristics which impact TRAP concentrations [38]. An

Table 2. Summary of traffic-related air pollutant exposure assessment approaches

Category	Approach	Overview	Strengths	Limitations
Modeling	Proximity	Distance to nearby roads serves as surrogate of exposure	Straightforward, minimal data requirements, potential to incorporate traffic volume/mix	Crude estimates of exposure may result in misclassification
	Dispersion	Emission, atmospheric, meteorological, and topographic data are used to mathematically model pollutant concentrations from traffic sources	Consideration of emissions, meteorology, source-specific, high-resolution	Computationally intensive, requires assumptions regarding pollutant transport, extensive data including traffic characteristics, source emissions, fleet mix, meteorology, and topography often not available in study areas
	Land-use regression	Geographic variables measured in buffer regions surrounding multiple air sampling sites are used to estimate measured air pollutant variability, resulting regression equation used to predict pollutant concentrations at unsampled locations	Straightforward approach, able to capture high-spatial variability of TRAP, can be applied to varying measured air pollutants, potential to incorporate temporal information	Requires air sampling at sufficient density to capture TRAP variability and geographic predictors, limited transferability of developed model
	Hybrid	Combination of multiple approaches, i.e., LUR with additional spatial interpolation models or personal monitoring	Improved exposure estimates	Requires data/expertise for multiple approaches
Personal	Personal monitoring	Individuals' exposure to air pollutants is measured using wearable sampling devices	Direct measure of exposure	Requires wearable devices capable of accurately measuring exposure over long time periods, participant burden, cost of measurement devices, requires study personnel time
	Biomarkers	Concentration of internal biomarker, frequently in blood or urine, measured as marker of exposure or effect	Individual exposure assessment, potential use as measure of effect	Lack of specific markers, difficulty differentiating markers of effect from exposure, cost

LUR, land-use regression; TRAP, traffic-related air pollutant.

alternative approach, dispersion modeling, has not been extensively utilized in epidemiologic studies because of the required data (e.g., meteorology, traffic volume, and makeup) and expertise required for its use [33].

Among the most frequently used method to estimate TRAP exposure in epidemiologic studies is LUR modeling [38–41]. In the most straightforward LUR approach, a single pollutant from the TRAP mixture is measured at multiple stationary sites within a defined study region and the characteristics of the area surrounding each sampling site (e.g., elevation, nearby roads, and traffic) are used as predictors of the measured concentrations in a linear model. The resultant LUR model is then applied to estimate pollutant concentrations at nonsampled locations, including schools and homes, where significant geographic predictor variables can be determined. First described by Briggs *et al.* [42], LUR models are now among the most commonly used techniques in epidemiologic studies of respiratory

health [10²²,11,38,40,43,44²²,45–49]. Although initial LUR models were most often developed for NO₂ and, less commonly, particulate matter, more recent models have been developed for additional traffic pollutants including elemental components of particulate matter, ultrafine particles, VOCs, PAHs, and black carbon [50,51²,52,53²,54]. The temporal variability of TRAP concentrations has also been incorporated into LUR models through the addition of mobile or continuous monitoring, allowing for short term and daily estimates of TRAP exposure for study participants [44²²,55–58]. New data inputs for LUR models, including satellite-derived pollutant measurements [59,60], and the development of hybrid models combining LUR with Bayesian Maximum Entropy and other statistical approaches, have also improved the accuracy of TRAP exposure assessment [61,62]. In studies with available participant-reported time spent in locations outside the home, LUR models have been used to derive time-weighted estimates of exposure

based on location [40]. More recent applications of this time-weighted approach have utilized smartphones and global positioning system (GPS)-derived location data to improve estimates of TRAP exposure by combining LUR or other modeled TRAP estimates with individuals' location through space and time [63²²].

Personal approaches

Despite advances in modeling TRAP and the incorporation of GPS to improve estimates of individual-level exposure, personal monitoring remains the 'gold-standard' for TRAP exposure assessment. Although there have been limited applications of personal monitoring in air pollution epidemiology, usually in the context of short-term panel studies [64–66], assessing long-term exposure by personal sampling is not routinely conducted because of a current lack of wearable devices and the associated cost, time, and participant burden of personal monitoring [67]. However, new technological advances, and the miniaturization of personal sensor technology for particulate matter and black carbon, will lead to increased applications of personal monitoring technology in epidemiologic studies [68²²,69,70²²]. Another potential approach to assessing personal exposure to TRAP is the use of a measured biomarker of exposure in a biological specimen (e.g., urine or blood). Although measuring PAH metabolites as biomarkers of TRAP exposure has been conducted primarily in occupational settings, more recent studies have identified PAH metabolites specific to environmental traffic exposure making this approach more feasible for applications in environmental epidemiology [71–73].

MECHANISTIC INSIGHTS INTO TRAFFIC-RELATED AIR POLLUTANT EFFECTS ON THE PATHOGENESIS OF ALLERGIC DISEASE

Although there is strong evidence that TRAP exposure contributes to childhood asthma [1,6,7,24], the mechanistic basis of TRAP effects on asthma has been elusive. The molecular and cellular pathways triggered by exposure to TRAP and their impact on allergen-induced immune responses have been studied in human studies as well as in reductionist models *in vitro* and in animal models *in vivo*.

Diesel exhaust particle induces epithelial stress responses

As the main barrier against airway pathogens and pollutants, lung epithelial cells are commonly used

to study the toxicity of different traffic-related pollutants and their components and have been reviewed elsewhere [74,75]. The inability of epithelial cells to effectively detoxify DEP results in release of proinflammatory cytokines including cytokines involved in T_H17 differentiation [interleukin-1 beta and IL6] and neutrophil chemokines, such as IL8 (CXCL8). DEP-mediated induction of IL8 is dependent on p38 MAP kinase and nuclear factor kappa B signaling [76]. Upstream, IL8 secretion has been shown to be dependent on the epidermal growth factor receptor (EGFR) pathway, as DEP induces secretion of endogenous EGFR ligands, and neutralizing antibodies against transforming growth factor alpha (TGF α), heparin-binding epidermal growth factor or amphiregulin decreases IL8 secretion by primary bronchial epithelial cells following DEP exposure [77]. As TGF α neutralizing antibodies or TNF α -converting enzyme [tumor necrosis factor-alpha-converting enzyme, also called ADAM metalloproteinase domain 17] inhibitors significantly decrease IL8 generation following DEP exposure, a model by which cleavage of pro-TGF α by TACE leads to EGFR signaling has been proposed [78,79]. A similar cascade of events has been demonstrated for allergen (house dust mite)-mediated induction of granulocyte-macrophage colony-stimulating factor by human bronchial epithelial cells, underscoring that these pathways are part of a broad epithelial stress response (Fig. 1).

Diesel exhaust particle exposure promotes T_H17 responses including increased T_H2/T_H17 double-producing cells

Although asthma has long been characterized as a disease of dysregulated T_H2 immune responses to environmental allergens, accumulating evidence suggests a role of T_H17 cells, especially in severe steroid-resistant asthma [80,81]. Immunohistochemistry on bronchial biopsies from asthmatic patients reveals increased IL-17A⁺ cells in patients with severe asthma compared with mild asthma or controls [82]. In both adults and children, serum IL-17A is significantly higher in severe asthmatic patients compared with mild asthmatic patients or controls [83–85]. Recent evidence demonstrates that DEP exposure promotes asthma by enhancing T_H17 immune responses, and anti-IL17A treatment alleviates the negative effects of DEP on asthma in a mouse asthma model [4]. Similarly, in children, TRAP exposure is associated with increased serum IL17A levels and increased asthma severity [4]. In mice, DEP exposure results in accumulation and persistence of allergen-specific T_H2/T_H17 cells in the lungs, potentiating secondary allergen recall

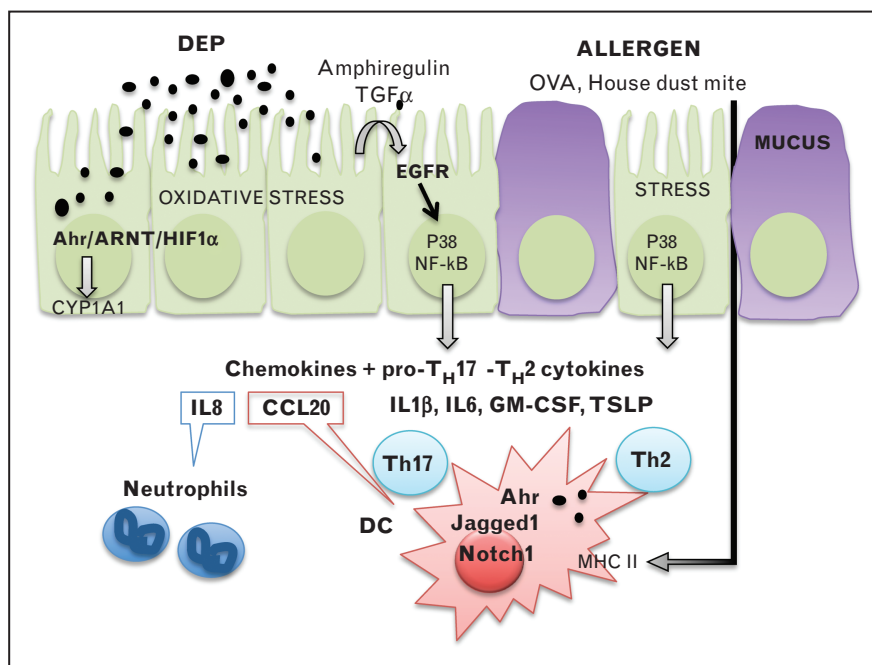


FIGURE 1. Mechanistic insights into DEP effects on asthma pathogenesis. Lung epithelial cells recognize polycyclic aromatic hydrocarbons present in diesel exhaust particles (DEPs) via the aryl hydrocarbon receptor (AhR), promoting cytochrome P450 family 1 A1 (CYP1A1)-mediated detoxification. Failure to detoxify results in oxidative stress and release of repair cytokines (amphiregulin, TGF α), which signal through the epidermal growth factor receptor (EGFR), p38 mitogen-activated protein kinase, and NF- κ B to induce secretion of chemokines, as well as cytokines involved in T_H17 and T_H2 differentiation (TSLP). DEP promotes allergic airway inflammation by upregulating the expression of the Jagged1/Notch1 pathway in dendritic cells (DCs) in an AhR-dependent manner in concert with allergens. DEP, diesel exhaust particle OVA, ovalbumin; TSLP, thymic stromal lymphopoietin.

responses [86²²]. These cells rapidly produce both T_H2 and T_H17 cytokines upon re-exposure to antigen. The induction and persistence of these resident memory cells in the lungs following TRAP exposure may be responsible, in part, for the long lasting impact of early life TRAP exposure into later life-stages, and may contribute to the persistence of asthma into adolescence. Recent studies have demonstrated that dual-positive T_H2/T_H17 cells and IL-17A were present at a higher frequency in the broncho-alveolar lavage fluid from steroid-resistant asthmatic patients [87²³]. These T_H2/T_H17 cells were resistant to dexamethasone-induced cell death and the T_H2/T_H17 predominant subgroup of patients manifested the most severe form of asthma [87²³]. Thus, these double-producing cells may be an excellent biomarker of severe, steroid-resistant patients who would benefit from additional or alternate treatment. In a murine model, transfer of allergen-specific T_H2/T_H17 double-producing cells to naive mice resulted in inflammation and exacerbated asthma [88].

Mice exposed to DEP alone develop airway neutrophilia, but do not present any of the hallmarks associated with asthma such as eosinophilia, T_H2

cytokine release, mucus production, or AHR [2,4,89]. However, chronic exposure to low doses of DEP over a 3-month period results in emphysema and accumulation of T cells [89]. DEP exposure promotes accumulation of T_{REG}, T_H17 cells, and neutrophils [2,4]. The observed increase in T_{REG} and Th17 cells may result in part from the ability of DEP to promote T_H17, T_H22, and T_{REG} differentiation through the aryl hydrocarbon receptor (AhR) [90,91]. Indeed, exposure to DEP and related polycyclic PAHs has been shown to increase T_H22 cells in an AhR-dependent manner [92,93]. AhR signaling requires dimerization with the aryl hydrocarbon receptor nuclear translocator (ARNT), also known as hypoxia-inducible factor beta. Accordingly, a cross-talk between the hypoxia-inducible factor 1- α (HIF1 α) and AhR pathways has been proposed, as both might compete for ARNT binding [94]. In T cells, HIF1 α -driven glycolysis supports T_H17 differentiation by promoting expression of ROR γ t, whereas in conditions supporting T_{REG} differentiation HIF1 α favors Foxp3 induction [95,96]. The respective contributions and interactions of DEP-induced AhR signaling and oxidative stress-related HIF1 α signaling have not been explored.

Diesel exhaust particle exposure exacerbates allergen-induced T_H2 responses

Numerous studies have demonstrated that exposure to either particulate matter or DEP can exacerbate allergic airway responses [97]. We recently demonstrated that coexposure to house dust mite (HDM) and DEP promotes a mixed T_H2/T_H17 response with increased T_H2 and T_H17 cells, as well as double-producing IL13+/IL17A+ T_H cells [2,4]. Thus, DEP exposure exacerbates T_H2 responses. Mechanisms by which DEP exposure increases allergen-induced Th2 differentiation have been reviewed elsewhere [98]. A recent study using cocultures of ovalbumin (OVA) transgenic CD4⁺ T cells and bone marrow-derived dendritic cells (BMDCs) pre-exposed to OVA with or without TRAP, demonstrated increased IFN γ , IL4, IL13, and IL17 levels in culture supernatants of OVA+TRAP exposed BMDC compared with BMDC exposed to OVA alone [99[■]] supporting the idea that TRAP exposure directly impacts dendritic cells. Further, TRAP upregulated T_H cytokine levels, IgE production, and allergic airway inflammation in mice in a Jagged1-dependent and Notch-dependent manner, and TRAP-induced Jagged1 expression was mediated by the AhR, which bound to and activated AhR response elements in the Jag1 promoter [99[■]]. AhR blockade or its lineage-specific deletion in CD11c⁺ cells abrogated the augmentation of airway inflammation by TRAP. Thus, TRAP promotes allergic airway inflammation by upregulating the expression of components of the Notch pathway in human monocytes and murine dendritic cells (DCs) [99[■]]. Of note, thymic stromal lymphopoietin (TSLP) released by epithelial cells upon DEP exposure promotes Jagged1 and OX40 ligand expression by peripheral blood mononuclear cell-derived DC, favoring T_H2 differentiation [100].

The impact of early life traffic-related air pollutant exposure

The timing and duration of TRAP exposure may be important for childhood wheezing and asthma development. This was examined in a recent article examining the relationship between TRAP exposure and longitudinal wheezing phenotypes and asthma at age 7 in a birth cohort [31[■]]. High TRAP exposure at birth was significantly associated with both transient and persistent wheezing. In contrast, only children with high average TRAP exposure continuously from birth through age 7 were at significantly increased risk for asthma [adjusted odds ratio = 1.71, 95% confidence interval (CI) 1.01–2.88]. Early-life exposure to TRAP is associated with increased risk for persistent wheezing, but only long-term exposure to high levels of TRAP throughout

childhood was associated with asthma development. In mice, postnatal exposure to HDM or DEP, followed by a secondary exposure to HDM 4 weeks later induced AHR only in mice that were coexposed to HDM and DEP but not in mice that were only exposed to HDM [86[■]]. In another study where neonatal ovalbumin-specific transgenic T cells-II mice were repeatedly pre-exposed to TRAP before being coexposed to OVA as adults, a secondary OVA recall response generated AHR only in mice previously coexposed to TRAP and OVA as neonates [101[■]]. This was associated with the accumulation of CD4⁺ T cells expressing IL4 or IL17A in the lungs. Collectively, these data strongly suggest that TRAP exposure promotes disease persistence. Indeed, in the Cincinnati Childhood Allergy and Air Pollution Study birth cohort, early TRAP exposure was associated with persistent wheeze, whereas early and sustained exposure to TRAP was associated with asthma development [31[■]]. DEP exposure has been shown to enhance allergen-specific memory, thereby potentiating secondary allergen recall responses and promoting the development of allergic asthma [86[■]].

Prenatal TRAP exposure has been linked to asthma as well [102–105]. Mothers who lived near highways during pregnancy are more likely to have children with asthma [103]. Prenatal exposure to PAHs is associated with an increased risk of allergic sensitization and early childhood wheeze [102,105]. A limited number of mechanistic studies have assessed the impact of in-utero TRAP exposure on the development of allergic disorders. In one recent study, the offspring of mice exposed to DEP were hypersensitive to OVA and developed increased OVA sensitization, airway inflammation, Th2/Th17 responses, and AHR compared with offspring with no prior in-utero DEP exposure [106[■]]. Further, prenatal DEP exposure induced the expression of genes downstream of AhR and this upregulation persisted 1 month after birth, even though mice were no longer exposed to DEP. Thus, in-utero DEP exposure appears to result in a primed state where the neonate is hypersensitive to subsequent allergen exposure. Interestingly, the Th2 and Th17 cytokines were produced primarily by natural killer (NK) cells and other non-CD3⁺ T cells. Repeated treatment with anti-NK1.1 prior to OVA challenge resulted in decreased airway inflammation [106[■]]. The importance of NK cells in allergic airway responses is supported by a recent study using NK-deficient mice [107]. The respective contribution of NK cells and other innate cells to DEP exacerbation of adaptive immune responses offers a promising new avenue of research.

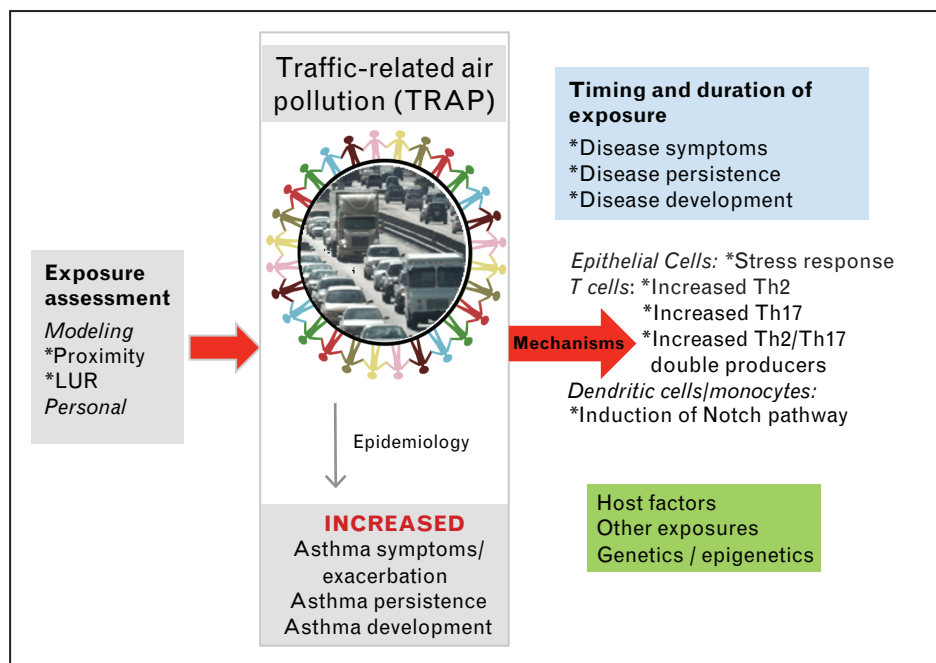


FIGURE 2. Overview. More accurate assessment of TRAP will enable the design of epidemiologic and mechanistic studies aimed at the discovery of biomarkers to identify the individuals most at-risk from the harmful effects of TRAP exposure and the design of novel-targeted interventions. LUR, land use regression; TRAP, traffic-related air pollutant.

CONCLUSION

As discussed above, there is considerable evidence that exposure to TRAP is associated with childhood asthma symptoms and exacerbations [6,7,10²²,24,108,109²²] and recent evidence suggests that TRAP is also associated with reduced lung growth and the development of asthma [31²²]. Herein, we have reviewed the recent epidemiologic and mechanistic findings that have started to fill gaps in knowledge regarding the health impact of TRAP exposure on allergic diseases, as well as new methodologies for the quantification of TRAP that hold tremendous promise for rapid and reliable identification of individuals at-risk because of high exposure (Fig. 2). These new methodologies will enable accurate assessment of exposure in real time such that interventions could be designed and implemented early in the course of exposure in vulnerable populations. The impact of TRAP exposure on allergic disease is complicated by the presence of additional host (genetic, obesity, comorbidities, and nutritional status) and environmental factors, which undoubtedly will affect the observed impact. Additional studies are needed to fill the remaining gaps, including the identification of the key host factors associated with enhanced susceptibility to TRAP exposure. These studies will have tremendous health impact and ultimately lead to design, testing, implementation, and dissemination of interventions to prevent the impact of TRAP exposure on asthma development, progression, and persistence.

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Conflicts of interest

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

1. HEI Panel on the Health Effects of Traffic-Related Air Pollution. Traffic-related air pollution: a critical review of the literature on emissions, exposure, and health effects. Boston, MA: Health Effects Institute; 2010; 45:610–624.
2. Acciani TH, Brandt EB, Khurana Hershey GK, Le Cras TD. Diesel exhaust particle exposure increases severity of allergic asthma in young mice. *Clin Exp Allergy* 2013; 43:1406–1418.
3. Takahashi G, Tanaka H, Wakahara K, *et al.* Effect of diesel exhaust particles on house dust mite-induced airway eosinophilic inflammation and remodeling in mice. *J Pharmacol Sci* 2010; 112:192–202.
4. Brandt EB, Kovacic MB, Lee GB, *et al.* Diesel exhaust particle induction of IL-17A contributes to severe asthma. *J Allergy Clin Immunol* 2013; 132:1194–1204; e2.
5. Appatova AS, Ryan PH, LeMasters GK, Grinshpun SA. Proximal exposure of public schools and students to major roadways: a nationwide US survey. *J Environ Plann Man* 2008; 51:631–646.
6. McConnell R, Islam T, Shankardass K, *et al.* Childhood incident asthma and traffic-related air pollution at home and school. *Environ Health Perspect* 2010; 118:1021–1026.

7. Jerrett M, Shankardass K, Berhane K, *et al.* Traffic-related air pollution and asthma onset in children: a prospective cohort study with individual exposure measurement. *Environ Health Perspect* 2008; 116:1433–1438.
8. Gauderman WJ, Vora H, McConnell R, *et al.* Effect of exposure to traffic on lung development from 10 to 18 years of age: a cohort study. *Lancet* 2007; 369:571–577.
9. Gauderman WJ, Avol E, Gilliland F, *et al.* The effect of air pollution on lung development from 10 to 18 years of age. *N Engl J Med* 2004; 351:1057–1067.
10. Molter A, Simpson A, Berdel D, *et al.* A multicentre study of air pollution exposure and childhood asthma prevalence: the ESCAPE project. *Eur Respir J* 2014.

This study did not find an association between air pollution exposure and childhood asthma in five European cohorts.

11. Clark NA, Demers PA, Karr CJ, *et al.* Effect of early life exposure to air pollution on development of childhood asthma. *Environ Health Perspect* 2010; 118:284–290.
12. Bowatte G, Lodge C, Lowe AJ, *et al.* The influence of childhood traffic-related air pollution exposure on asthma, allergy and sensitization: a systematic review and a meta-analysis of birth cohort studies. *Allergy* 2015; 70:245–256.

This systematic review and meta-analyses of published birth cohort studies conclude that early childhood exposures to TRAP are associated with the development of asthma in childhood as well as sensitization to aero and food allergens.

13. Asher MI, Montefort S, Björkstén B, *et al.* Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006; 368:733–743.
14. Eder W, Ege MJ, von Mutius E. The asthma epidemic. *N Engl J Med* 2006; 355:2226–2235.
15. Hatzler L, Hofmaier S, Papadopoulos NG. Allergic airway diseases in childhood: marching from epidemiology to novel concepts of prevention. *Pediatr Allergy Immunol* 2012; 23:616–622.
16. Gehring U, Cyrys J, Sedlmair G, *et al.* Traffic-related air pollution and respiratory health during the first 2 yrs of life. *Eur Respir J* 2002; 19:690–698.
17. Takizawa H. Impact of air pollution on allergic diseases. *Korean J Intern Med* 2011; 26:262–273.
18. Tatum AJ, Shapiro GG. The effects of outdoor air pollution and tobacco smoke on asthma. *Immunol Allergy Clin North Am* 2005; 25:15–30.
19. Chen Z, Salam MT, Eckel SP, *et al.* Chronic effects of air pollution on respiratory health in Southern California children: findings from the Southern California Children's Health Study. *J Thorac Dis* 2015; 7:46–58.
20. Jung DY, Leem JH, Kim HC, *et al.* Effect of traffic-related air pollution on allergic disease: results of the children's health and environmental research. *Allergy Asthma Immunol Res* 2015; 7:359–366.
21. Jacquemin B, Siroux V, Sanchez M, *et al.* Ambient Air Pollution and Adult Asthma Incidence in Six European Cohorts (ESCAPE). *Environ Health Perspect* 2015; 123:613–621.

This study highlights that exposure to ambient air pollution in adults can lead to the development of adult-onset asthma.

22. Ryan PH, Bernstein DI, Lockett J, *et al.* Exposure to traffic-related particles and endotoxin during infancy is associated with wheezing at age 3 years. *Am J Respir Crit Care Med* 2009; 180:1068–1075.
23. Ryan PH, LeMasters G, Biagini J, *et al.* Is it traffic type, volume, or distance? Wheezing in infants living near truck and bus traffic. *J Allergy Clin Immunol* 2005; 116:279–284.
24. Ryan PH, Levin L, Bernstein DI, *et al.* Early life exposure to traffic pollutants and wheezing throughout childhood: the Cincinnati Childhood Allergy and Air Pollutions Study (CCAAPS). *Am J Respir Crit Care Med* 2011; 183:A3748.
25. Sucharew H, Ryan PH, Bernstein D, *et al.* Exposure to traffic exhaust and night cough during early childhood: the CCAAPS birth cohort. *Pediatr Allergy Immunol* 2010; 21 (2 Pt 1):253–259.
26. Ahn K. The role of air pollutants in atopic dermatitis. *J Allergy Clin Immunol* 2014; 134:993–999; discussion 1000.

This review highlights recent epidemiologic and experimental data that support a role of air pollution in the development and aggravation of atopic dermatitis.

27. Penard-Morand C, Raheison C, Charpin D, *et al.* Long-term exposure to close-proximity air pollution and asthma and allergies in urban children. *Eur Respir J* 2010; 36:33–40.
28. Lee YL, Su HJ, Sheu HM, *et al.* Traffic-related air pollution, climate, and prevalence of eczema in Taiwanese school children. *J Invest Dermatol* 2008; 128:2412–2420.
29. Codispoti CD, LeMasters GK, Levin L, *et al.* Traffic pollution is associated with early childhood aeroallergen sensitization. *Ann Allergy Asthma Immunol* 2015; 114:126–133.

This study supports the idea that DEP exposure enhances the risk of aeroallergen sensitization in children.

30. Gruzdeva O, Bellander T, Eneroth K, *et al.* Traffic-related air pollution and development of allergic sensitization in children during the first 8 years of life. *J Allergy Clin Immunol* 2012; 129:240–246.

31. Brunst KJ, Ryan PH, Brokamp C, *et al.* Timing and duration of traffic-related air pollution exposure and the risk for childhood wheeze and asthma. *Am J Respir Crit Care Med* 2015; 192:421–427.

This study provides the evidence that early-life exposure to high levels of TRAP is associated with wheeze symptoms during childhood and asthma development.

32. Karner AA, Eisinger DS, Niemeier DA. Near-roadway air quality: synthesizing the findings from real-world data. *Environ Sci Technol* 2010; 44:5334–5344.
33. Brauer M. How much, how long, what, and where: air pollution exposure assessment for epidemiologic studies of respiratory disease. *Proc Am Thorac Soc* 2010; 7:111–115.
34. Dockery DW, Pope CA, Xu X, *et al.* An association between air pollution and mortality in six US cities. *N Engl J Med* 1993; 329:1753–1759.
35. Bell ML, Ebisu K, Peng RD, *et al.* Hospital admissions and chemical composition of fine particle air pollution. *Am J Respir Crit Care Med* 2009; 179:1115–1120.
36. Dominici F, Peng RD, Bell ML, *et al.* Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. *JAMA* 2006; 295:1127–1134.
37. Peng RD, Bell ML, Geyh AS, *et al.* Emergency admissions for cardiovascular and respiratory diseases and the chemical composition of fine particle air pollution. *Environ Health Perspect* 2009; 117:957–963.
38. 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.
39. Ryan PH, LeMasters GK. A review of land-use regression models for characterizing intraurban air pollution exposure. *Inhal Toxicol* 2007; (19 Suppl 1): 127–133.
40. Ryan PH, LeMasters GK, Levin L, *et al.* A land-use regression model for estimating microenvironmental diesel exposure given multiple addresses from birth through childhood. *Sci Total Environ* 2008; 404:139–147.
41. Hoek G, Beelen R, de Hoogh K, *et al.* A review of land-use regression models to assess spatial variation of outdoor air pollution. *Atmos Environ* 2008; 42:7561–7578.
42. Briggs DJ, de Hoogh C, Gulliver J, *et al.* A regression-based method for mapping traffic-related air pollution: application and testing in four contrasting urban environments. *Sci Total Environ* 2000; 253:151–167.
43. 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.
44. Dons E, Van Poppel M, Int Panis L, *et al.* Land use regression models as a tool for short, medium and long term exposure to traffic related air pollution. *Sci Total Environ* 2014; 476:378–386.

This study shows LUR to be a fast and accurate means for estimating long term, and daily, black carbon and NO₂ exposure.

45. Gehring U, Wijga AH, Brauer M, *et al.* Traffic-related air pollution and the development of asthma and allergies during the first 8 years of life. *Am J Respir Crit Care Med* 2010; 181:596–603.
46. Henderson SB, Beckerman B, Jerrett M, Brauer M. Application of land use regression to estimate long-term concentrations of traffic-related nitrogen oxides and fine particulate matter. *Environ Sci Technol* 2007; 41:2422–2428.
47. Hoek G, Beelen R, Kos G, *et al.* Land use regression model for ultrafine particles in Amsterdam. *Environ Sci Technol* 2011; 45:622–628.
48. Ross Z, English PB, Scaif R, *et al.* Nitrogen dioxide prediction in Southern California using land use regression modeling: potential for environmental health analyses. *J Expo Sci Environ Epidemiol* 2006; 16:106–114.
49. Ross Z, Jerrett M, Ito K, *et al.* A land use regression for predicting fine particulate matter concentrations in the New York City region. *Atmos Environ* 2007; 41:2255–2269.
50. de Hoogh K, Wang M, Adam M, *et al.* Development of land use regression models for particle composition in twenty study areas in Europe. *Environ Sci Technol* 2013; 47:5778–5786.
51. Patton AP, Collins C, Naumova, *et al.* An hourly regression model for ultrafine particles in a near-highway urban area. *Environ Sci Technol* 2014; 48:3272–3280.

In this study, predictors of near-highway particle number concentrations were wind speed and direction, temperature, highway traffic, and distance to the highway and major roads.

52. Gale SL, Noth EM, Mann J, *et al.* Polycyclic aromatic hydrocarbon exposure and wheeze in a cohort of children with asthma in Fresno, CA. *J Expo Sci Environ Epidemiol* 2012; 22:386–392.
53. Jedynska A, Hoek G, Wang M, *et al.* Development of land use regression models for elemental, organic carbon, PAH, and hopanes/steranes in 10 ESCAPE/TRANSPHORM European study areas. *Environ Sci Technol* 2014; 48:14435–14444.

This study developed LUR models for PAH, elemental carbon (EC), organic carbon (OC), and hopanes in 10 areas across Europe and found that predictions of the EC models correlated highly with the predictions of PM_{2.5}.

54. Weichenhals S, Van Ryswyk K, Goldstein A, *et al.* Characterizing the spatial distribution of ambient ultrafine particles in Toronto, Canada: a land use regression model. *Environ Pollut* 2015; doi: 10.1016/j.envpol.2015.04.011. [Epub ahead of print]

55. Dons E, Van Poppel M, Kochan B, *et al.* Modeling temporal and spatial variability of traffic-related air pollution: hourly land use regression models for black carbon. *Atmos Environ* 2013; 74:237–246.
 56. Larson T, Henderson SB, Brauer M. Mobile monitoring of particle light absorption coefficient in an urban area as a basis for land use regression. *Environ Sci Technol* 2009; 43:4672–4678.
 57. Smargiassi A, Brand A, Fournier M, *et al.* A spatiotemporal land-use regression model of winter fine particulate levels in residential neighbourhoods. *J Expo Sci Environ Epidemiol* 2012; 22:331–338.
 58. Saraswat A, Apte JS, Kandlikar M, *et al.* Spatiotemporal land use regression models of fine, ultrafine, and black carbon particulate matter in New Delhi, India. *Environ Sci Technol* 2013; 47:12903–12911.
 59. Lee HJ, Koutrakis P. Daily ambient NO₂ concentration predictions using satellite ozone monitoring instrument NO₂ data and land use regression. *Environ Sci Technol* 2014; 48:2305–2311.
 60. Kloog I, Nordio F, Coull BA, Schwartz J. Incorporating local land use regression and satellite aerosol optical depth in a hybrid model of spatio-temporal PM_{2.5} exposures in the Mid-Atlantic states. *Environ Sci Technol* 2012; 46:11913–11921.
 61. Beckerman BS, Jerrett M, Serre M, *et al.* A hybrid approach to estimating national scale spatiotemporal variability of PM_{2.5} in the contiguous United States. *Environ Sci Technol* 2013; 47:7233–7241.
 62. Adam-Poupard A, Brand A, Fournier M, *et al.* Spatiotemporal modeling of ozone levels in Quebec (Canada): a comparison of Kriging, land-use regression (LUR), and combined Bayesian maximum entropy-LUR approaches. *Environ Health Perspect* 2014; 122:970–976.
 63. Su JG, Jerrett M, Meng Y-Y, *et al.* Integrating smart-phone based momentary location tracking with fixed site air quality monitoring for personal exposure assessment. *Sci Total Environ* 2015; 506:518–526.
- This article applied momentary location tracking services supplied by smartphones to identify an individual's location in space-time over Wi-Fi and found that integrating these services with fixed site field monitoring, and indoor-outdoor air exchange calibration, makes exposure assessment of a very large population over extended periods of time feasible.
64. Delfino RJ, Quintana PJ, Floro J, *et al.* Association of FEV₁ in asthmatic children with personal and microenvironmental exposure to airborne particulate matter. *Environ Health Perspect* 2004; 112:932–941.
 65. Delfino RJ, Staimer N, Gillen D, *et al.* Personal and ambient air pollution is associated with increased exhaled nitric oxide in children with asthma. *Environ Health Perspect* 2006; 114:1736–1743.
 66. Dons E, Int Panis L, Van Poppel M, *et al.* Personal exposure to black carbon in transport microenvironments. *Atmos Environ* 2012; 55:392–398.
 67. Zou B, Wilson JG, Zhan FB, Zeng Y. Air pollution exposure assessment methods utilized in epidemiological studies. *J Environ Monit* 2009; 11:475–490.
 68. Ryan PH, Son SY, Wolfe C, *et al.* A field application of a personal sensor for ultrafine particle exposure in children. *Sci Total Environ* 2015; 508:366–373.
- This study conducted a field test of a personal sensor for ultrafine particles and found that the sensor can measure near-real time exposures to UFP with high spatiotemporal resolution.
69. Cai J, Yan B, Ross J, *et al.* Validation of MicroAeth® as a black carbon monitor for fixed-site measurement and optimization for personal exposure characterization. *Aerosol and Air Quality Research* 2014; 14:1–9.
 70. Nieuwenhuijsen MJ, Donaire-Gonzalez D, Rivas I, *et al.* Variability in and agreement between modeled and personal continuously measured black carbon levels using novel smartphone and sensor technologies. *Environ Sci Technol* 2015; 49:2977–2982.
- This study used smartphones with tracking software and personal sensors to measure black carbon exposure in children. They found that personal black carbon levels vary substantially throughout the day and that the correlation of modeled and measured black carbon levels was generally good, except for commuting times.
71. Neophytou AM, Hart JE, Chang Y, *et al.* Short-term traffic related exposures and biomarkers of nitro-PAH exposure and oxidative DNA damage. *Toxics* 2014; 2:377–390.
 72. Nethery E, Wheeler AJ, Fisher M, *et al.* Urinary polycyclic aromatic hydrocarbons as a biomarker of exposure to PAHs in air: a pilot study among pregnant women. *J Expos Sci Environ Epidemiol* 2012; 22:70–81.
 73. Adetona O, Sjodin A, Zheng L, *et al.* Personal exposure to PM_{2.5} and urinary hydroxy-PAH levels in bus drivers exposed to traffic exhaust, in Trujillo, Peru. *J Occup Environ Hyg* 2012; 9:217–229.
 74. Schwarze PE, Totlandsdal AI, Lag M, *et al.* Inflammation-related effects of diesel engine exhaust particles: studies on lung cells *in vitro*. *BioMed Res Int* 2013; 2013:685142.
 75. Li YJ, Kawada T, Azuma A. Nrf2 is a protective factor against oxidative stresses induced by diesel exhaust particle in allergic asthma. *Oxid Med Cell Longev* 2013; 2013:323607.
 76. Totlandsdal AI, Cassee FR, Schwarze P, *et al.* Diesel exhaust particles induce CYP1A1 and pro-inflammatory responses via differential pathways in human bronchial epithelial cells. *Part Fibre Toxicol* 2010; 7:41.
 77. Parnia S, Hamilton LM, Puddicombe SM, *et al.* Autocrine ligands of the epithelial growth factor receptor mediate inflammatory responses to diesel exhaust particles. *Respir Res* 2014; 15:22.
 78. Ovreik J, Refsnes M, Totlandsdal AI, *et al.* TACE/TGF- α /EGFR regulates CXCL8 in bronchial epithelial cells exposed to particulate matter components. *Eur Respir J* 2011; 38:1189–1199.
 79. Skuland T, Ovreik J, Lag M, *et al.* Silica nanoparticles induce cytokine responses in lung epithelial cells through activation of a p38/TACE/TGF- α /EGFR-pathway and NF- κ B signalling. *Toxicol Appl Pharmacol* 2014; 279:76–86.
 80. McKinley L, Alcorn JF, Peterson A, *et al.* TH17 cells mediate steroid-resistant airway inflammation and airway hyperresponsiveness in mice. *J Immunol* 2008; 181:4089–4097.
 81. Chesne J, Braza F, Mahay G, *et al.* IL-17 in severe asthma. Where do we stand? *Am J Respir Crit Med* 2014; 190:1094–1101.
 82. Al-Ramli W, Prefontaine D, Chouiali F, *et al.* T(H)17-associated cytokines (IL-17A and IL-17F) in severe asthma. *J Allergy Clin Immunol* 2009; 123:1185–1187.
 83. Agache I, Ciobanu C, Agache C, Anghel M. Increased serum IL-17 is an independent risk factor for severe asthma. *Respir Med* 2010; 104:1131–1137.
 84. Chien JW, Lin CY, Yang KD, *et al.* Increased IL-17A secreting CD4⁺ T cells, serum IL-17 levels and exhaled nitric oxide are correlated with childhood asthma severity. *Clin Exp Allergy* 2013; 43:1018–1026.
 85. Alyasin S, Karimi MH, Amin R, *et al.* Interleukin-17 gene expression and serum levels in children with severe asthma. *Iranian J Immunol* 2013; 10:177–185.
 86. Brandt EB, Biagini Myers JM, Acciani TH, *et al.* Exposure to allergen and diesel exhaust particles potentiates secondary allergen-specific memory responses, promoting asthma susceptibility. *J Allergy Clin Immunol* 2015; 136:295–303.
- This study demonstrates that DEP persists in murine lungs for months with increased airway neutrophil and IL17A levels. DEP coexposure with HDM results in increased accumulation of allergen-specific T_H2/T_H17 cells in the lungs, potentiating HDM recall responses. Exposure to TRAP at birth is associated with earlier sensitization in young children and the development of allergic asthma at age 7.
87. Irvin C, Zafar I, Good J, *et al.* Increased frequency of dual-positive TH2/TH17 cells in bronchoalveolar lavage fluid characterizes a population of patients with severe asthma. *J Allergy Clin Immunol* 2014; 134:1175–1186; e7.
- This study highlights that an increased frequency of BALF T_H2/T_H17 cells is associated with more severe asthma and in-vitro glucocorticoid resistance.
88. Wang YH, Voo KS, Liu B, *et al.* A novel subset of CD4(+) T(H)2 memory/effector cells that produce inflammatory IL-17 cytokine and promote the exacerbation of chronic allergic asthma. *J Exp Med* 2010; 207:2479–2491.
 89. Yoshizaki K, Brito JM, Moriya HT, *et al.* Chronic exposure of diesel exhaust particles induces alveolar enlargement in mice. *Respir Res* 2015; 16:18. doi: 10.1186/s12931-015-0172-z.
 90. Quintana FJ, Basso AS, Iglesias AH, *et al.* Control of T(reg) and T(H)17 cell differentiation by the aryl hydrocarbon receptor. *Nature* 2008; 453:65–71.
 91. Ramirez JM, Brembilla NC, Sorg O, *et al.* Activation of the aryl hydrocarbon receptor reveals distinct requirements for IL-22 and IL-17 production by human T helper cells. *Eur J Immunol* 2010; 40:2450–2459.
 92. Ple C, Fan Y, Ait Yahia S, *et al.* Polycyclic aromatic hydrocarbons reciprocally regulate IL-22 and IL-17 cytokines in peripheral blood mononuclear cells from both healthy and asthmatic subjects. *PLoS One* 2015; 10:e0122372.
 93. van Voorhis M, Knopp S, Juliard W, *et al.* Exposure to atmospheric particulate matter enhances Th17 polarization through the aryl hydrocarbon receptor. *PLoS One* 2013; 8:e82545.
 94. Vorrink SU, Domann FE. Regulatory crosstalk and interference between the xenobiotic and hypoxia sensing pathways at the AhR-ARNT-HIF1 α signaling node. *Chem Biol Interact* 2014; 218:82–88.
 95. Dang EV, Barbi J, Yang HY, *et al.* Control of T(H)17/T(reg) balance by hypoxia-inducible factor 1. *Cell* 2011; 146:772–784.
 96. Palazon A, Goldrath AW, Nizet V, Johnson RS. HIF transcription factors, inflammation, and immunity. *Immunity* 2014; 41:518–528.
 97. Maes T, Provoost S, Lanckacker EA, *et al.* Mouse models to unravel the role of inhaled pollutants on allergic sensitization and airway inflammation. *Respir Res* 2010; 11:7.
 98. Li N, Buglak N. Convergence of air pollutant-induced redox-sensitive signals in the dendritic cells contributes to asthma pathogenesis. *Toxicol Lett* 2015; 237:55–60.
 99. Xia M, Viera-Hutchins L, Garcia-Lloret M, *et al.* Vehicular exhaust particles promote allergic airway inflammation through an aryl hydrocarbon receptor-notch signaling cascade. *J Allergy Clin Immunol* 2015; 136:441–453; doi: 10.1016/j.jaci.2015.02.014. [Epub ahead of print]
- This study demonstrates that traffic-related ambient fine and ultrafine particles increase expression of Notch1 and Jagged1 in bone marrow-derived dendritic cells in an Ahr-dependent but TLR4, Nrf2, and Nlrp3 independent way. In mice, activation of this cascade exacerbated allergen-induced airway inflammation.
100. Bleck B, Tse DB, Gordon T, *et al.* Diesel exhaust particle-treated human bronchial epithelial cells upregulate Jagged-1 and OX40 ligand in myeloid dendritic cells via thymic stromal lymphopoietin. *J Immunol* 2010; 185: 6636–6645.

- 101.** Saravia J, You D, Thevenot P, *et al.* Early-life exposure to combustion-derived particulate matter causes pulmonary immunosuppression. *Mucosal Immunol* 2014; 7:694–704.

This study demonstrates that exposure to traffic-related particulate matter during the first few weeks of life abrogates HDM-induced allergic airway responses. However, mice exposed to particulate matter and OVA as neonates and rechallenged with OVA as adults display exacerbated allergic responses.

- 102.** Perzanowski MS, Chew GL, Divjan A, *et al.* Early-life cockroach allergen and polycyclic aromatic hydrocarbon exposures predict cockroach sensitization among inner-city children. *J Allergy Clin Immunol* 2013; 131:886–893.
- 103.** Patel MM, Quinn JW, Jung KH, *et al.* Traffic density and stationary sources of air pollution associated with wheeze, asthma, and immunoglobulin E from birth to age 5 years among New York City children. *Environ Res* 2011; 111:1222–1229.
- 104.** Rosa MJ, Jung KH, Perzanowski MS, *et al.* Prenatal exposure to polycyclic aromatic hydrocarbons, environmental tobacco smoke and asthma. *Respir Med* 2011; 105:869–876.

- 105.** Jedrychowski WA, Perera FP, Mauger U, *et al.* Intrauterine exposure to polycyclic aromatic hydrocarbons, fine particulate matter and early wheeze. Prospective birth cohort study in 4-year olds. *Pediatr Allergy Immunol* 2010; 21 (4 Pt 2):e723–e732.

- 106.** Manners S, Alam R, Schwartz DA, Gorska MM. A mouse model links asthma susceptibility to prenatal exposure to diesel exhaust. *J Allergy Clin Immunol* 2014; 134:63–72.

In this study, mice exposed first to DEP *in utero* and then sensitized and challenged with OVA as neonates developed increased allergic airway responses mediated by NK cells.

- 107.** Mathias CB, Guernsey LA, Zammit D, *et al.* Pro-inflammatory role of natural killer cells in the development of allergic airway disease. *Clin Exp Allergy* 2014; 44:589–601.
- 108.** Spira-Cohen A, Chen LC, Kendall M, *et al.* Personal exposures to traffic-related air pollution and acute respiratory health among Bronx schoolchildren with asthma. *Environ Health Perspect* 2011; 119:559–565.
- 109.** Guarnieri M, Balmes JR. Outdoor air pollution and asthma. *Lancet* 2014; 383:1581–1592.

This article is a great overall review of outdoor air pollution and its detrimental effect on asthma.