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Air pollution and allergic diseases

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Abstract

Purpose of review—Exposure to traffic-related air pollutants (TRAP) 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 (1), including children since 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 substantial impact on clinical practice and research by 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

Asthma; air pollution; traffic pollution; allergy

Introduction

A recent comprehensive and systematic review of worldwide traffic emissions and health science by a Special Panel convened by the Health Effects Institute (HEI) found sufficient evidence that exposure to traffic-related air pollutants (TRAP) causes asthma exacerbation in children (1). Within the complex mixture of gaseous and particulate components of TRAP, diesel exhaust particles (DEP) are of particular concern with respect to health effects. DEP are estimated to contribute up to 90% of the particulate matter (PM) 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-

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responsiveness, 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 TRAP is also associated with reduced lung growth and the development of asthma, though recent studies have reported conflicting results (6–12). These inconsistent findings may be due to a lack of knowledge regarding the mechanistic basis of TRAP health effects and the characteristics of those most susceptibility 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 quantification of TRAP hold tremendous promise for rapid and reliable identification of individuals at-risk due to high exposure.

Epidemiology of the health impact of TRAP on allergic disease

The prevalence and incidence of allergic diseases have been increasing worldwide since the 1960's (13, 14). More recent investigators suggest that the asthma prevalence has plateaued in developed countries, while 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 (PM) of varying size, polycyclic aromatic hydrocarbons (PAHs - e.g. benzo(a)pyrene), volatile organic compounds (VOCs – e.g. benzene, acetaldehyde) and other hazardous air pollutants (HAPs). Collectively referred to as traffic-related air pollutants (TRAP), 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). 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 that 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 living within 500 meters of a freeway had significant deficits in FEV1, FVC and maximal mid-expiratory flow rate compared to those living more than 1500 meters away (19). A recent study of 5,443 Korean children aged 6–14 found that children living within 200 meters of a main road that was ≥254 meters 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 (21). ESCAPE was also comprised of five birth cohort studies including 17,041 children. While 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 (10). During this time, campaigns to reduce air pollution could have reduced exposure levels compared to 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 three years of life.

Allergic Sensitization and Eczema

Studies also support an increase of 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 PM and nitrogen oxides, act as risk factors for the development or aggravation of eczema (26). A study of 4,907 children aged 9–11 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 less than 75 meters from the main road were significantly more likely to have lifetime diagnoses and symptoms of allergic rhinitis (AR) (20). The distance to the main road and the length and proportion of the main road within 200 meters of the home were all associated with allergic sensitization, defined as positive skin prick test (SPT) 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 four by 40–83% (29, 30). Children exposed to high TRAP levels before age 1 also have an increased risk of developing food allergy by age eight, particularly those that are not sensitized at age four (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 (12). While modest associations were observed between asthma incidence/prevalence and wheeze and nitrogen oxides, PM, black carbon (BC), and road proximity, there was substantial heterogeneity observed (likely due to differences in study design, participants and exposure and outcome definitions) between the studies (12). The meta-analyses showed no association with TRAP measures and sensitization to indoor allergens (cat dog, or mold). While there was a significant association between PM and sensitization to outdoor allergens (pollen and grass), there was again high heterogeneity between studies (12). The associations between the markers of air pollution (NO_2, BC, and road proximity) and hay fever and eczema were inconsistent. With respect to 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 (12). We recently reported that a child's risk for persistent wheeze and asthma

development varies depending on the timing and duration of TRAP exposure (31). Children exposed to high levels of TRAP at time of birth were nearly twice as likely to experience persistent wheezing at age seven; however, a longer duration of exposure to high levels of TRAP (beginning early in life and continuing through age seven) was the only time period of exposure related to asthma development (31).

Collectively, there is considerable evidence that TRAP plays a role in the development, and/or 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. meta-analyses, there is substantial variability in the exposure measurements across TRAP-related studies. Land use regression (LUR) models are among the most common methods to assess TRAP exposures (12). Other methods include passive samplers, central monitoring stations and proximity to major roads. The most frequent markers of pollutants include PM, oxides of nitrogen, carbon monoxide and ozone. PM may be further reported as BC, PM_{10}, or $PM_{2.5}$. While this vast variation in the definition of TRAP exposure limit the ability to conduct sound meta-analyses, it highlights the importance of appropriate exposure assessment, as discussed below.

Assessment of TRAP exposure

Given the increasingly evident health impact of TRAP, methodologies to accurately assess exposure are needed. While 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 to 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 is also provided in Table 2.

Modeling Approaches

While regulatory air monitoring provide valuable data to link 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 alternative approach, dispersion modeling, has not been extensively utilized in epidemiologic studies due to 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 land use regression (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 characteristics of the area surrounding each sampling site (e.g. elevation, nearby roads, 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 non-sampled 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 (10, 11, 38, 40, 43–49). While initial LUR models were most often developed for NO_2 and, less commonly, PM, more recent models have been developed for additional traffic pollutants including elemental components of PM, ultrafine particles, VOCs, PAHs, and black carbon (50–54). The temporal variability of TRAP concentrations have 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 (44, 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 application of this time-weighted approach have utilized smartphones and 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 (63)

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. While 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 due to 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 PM and black carbon will lead to increased applications of personal monitoring technology in epidemiologic studies (68–70). 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). While 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 TRAP 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*.

DEP 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 pro-inflammatory cytokines including cytokines involved in T_H17 differentiation (IL1β, IL6) and neutrophil chemokines, such as IL8 (CXCL8). DEP-mediated induction of IL8 is dependent on p38 MAP kinase and NF-kB signaling (76). Upstream, IL8 secretion has been shown to be dependent on the EGFR pathway, as DEP induces secretion of endogenous EGFR ligands, and neutralizing antibodies against TGFα, heparin-binding EGF or amphiregulin decrease IL8 secretion by primary bronchial epithelial cells following DEP exposure (77). Since TGFα neutralizing antibodies or TNFα-converting enzyme (TACE; ADAM-17) inhibitors significantly decrease IL8 generation following DEP exposure, a model by which cleavage of pro-TGFα 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 GM-CSF by human bronchial epithelial cells, underscoring that these pathways are part of a broad epithelial stress response (Figure 1).

DEP 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 for T_H17 cells, especially severe steroid resistant asthma (80, 81). Immunohistochemistry on bronchial biopsies from asthmatics reveals increased IL-17A+ cells in patients with severe asthma compared to mild asthma or controls (82). In both adults and children, serum IL-17A is significantly higher in severe asthmatics compared to mild asthmatics or controls (83–85). Recent evidence demonstrates that 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 responses (86). 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 lifestages; and may contribute to 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 BALF from steroid resistant asthmatic patients (87). 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 (87). Thus, these double-producing cells may be an excellent biomarker of severe, steroid resistant patients that would benefit from additional

or alternate treatment. In a murine model, transfer of allergen-specific T_H2/T_H17 double-producing cells to naïve 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 airway hyperresponsiveness (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 aromatic hydrocarbons (PAH) 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 (HIF1β). Accordingly, a crosstalk between the hypoxia-inducible factor 1-alpha (HIF1α) and Ahr pathways has been proposed, as both might compete for ARNT binding (94). In T-cells, HIF1α driven glycolysis supports T_H17 differentiation by promoting expression of RORγt, whereas in conditions supporting T_{REG} differentiation HIF1α favors Foxp3 induction (95, 96). The respective contributions and interactions of DEP-induced Ahr signaling and oxidative stress related HIF1α signaling have not been explored.

DEP 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 co-exposure to 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 co-cultures of OVA transgenic CD4+ T cells and bone marrow derived dendritic cells (BMDC) pre-exposed to OVA with or without TRAP, demonstrated increased IFNγ, IL4, IL13, and IL17 levels in culture supernatants of OVA+TRAP exposed BMDC compared to BMDC exposed to OVA alone (99) supporting 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- 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 DCs (99). Of note, TSLP released by epithelial cells upon DEP exposure, promotes Jagged1 and OX40 ligand expression by PBMC-derived DC, favoring T_H2 differentiation (100).

The impact of early life TRAP exposure

The timing and duration of traffic-related air pollution (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 seven 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 seven were at significantly increased risk for asthma (aOR = 1.71, 95% 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, post-natal exposure to HDM and/or DEP followed by a secondary exposure to HDM 4 weeks later induced AHR only in mice that were co-exposed to HDM and DEP but not in mice that were only exposed to HDM (86). In another study where neonatal OT-II mice were repeatedly pre-exposed to TRAP before being co-exposed to OVA as adults, a secondary OVA recall response generated AHR only in mice previously co-exposed 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 (CCAAPS) birth cohort, early TRAP exposure was associated with persistent wheeze while 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 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, offspring of mice exposed to DEP were hypersensitive to OVA and developed increased OVA sensitization, airway inflammation, Th2/Th17 responses, and AHR compared to offspring with no prior *in utero* DEP exposure (106). Further, prenatal DEP exposure induced 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.

Conclusion

As discussed above, there is considerable evidence that exposure to TRAP is associated with childhood asthma symptoms and exacerbations (6, 7, 10, 24, 108, 109) and recent evidence suggests that TRAP is also associated with reduced lung growth and the development of asthma (31). Herein, we have reviewed the 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 new methodologies for quantification of TRAP that hold tremendous promise for rapid and reliable identification of individuals at-risk due to high exposure (Figure 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, co-morbidities, nutritional status) and environmental factors, which undoubtedly will affect the observed impact. Additional studies are needed to fill the remaining gaps including 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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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.

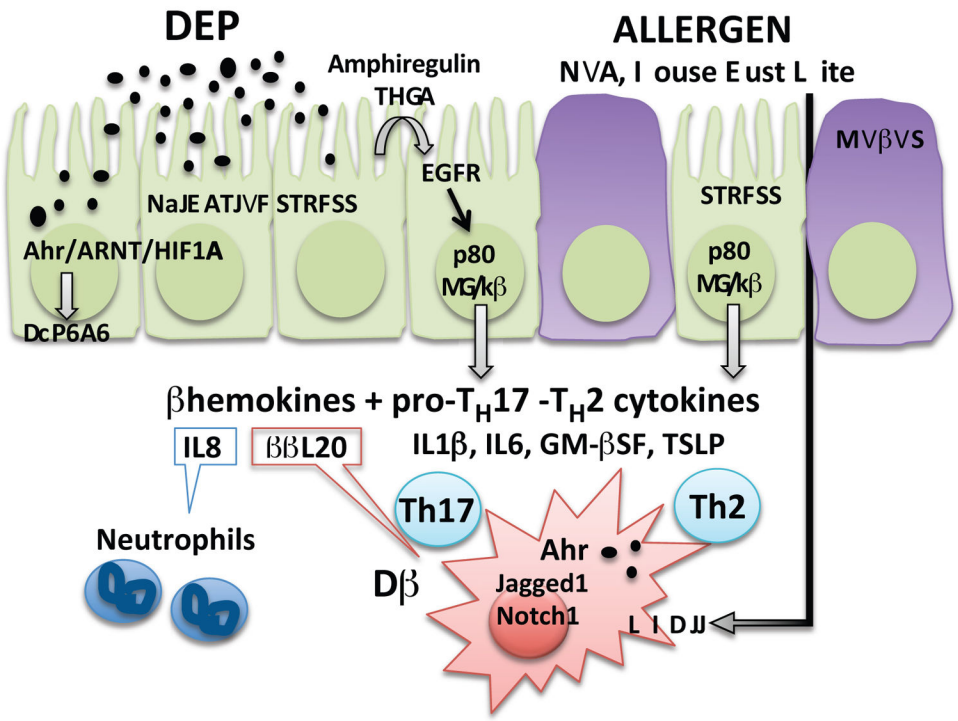

Figure 1. Mechanistic insights into DEP effects on asthma pathogenesis

Lung epithelial cells recognize polycyclic aromatic hydrocarbons present in diesel exhaust particles (DEP) 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, TGFα), which signal through the epidermal growth factor receptor (EGFR), p38 mitogen-activated protein kinase and NF-κB 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 (DC) in an AhR dependent manner in concert with allergens.

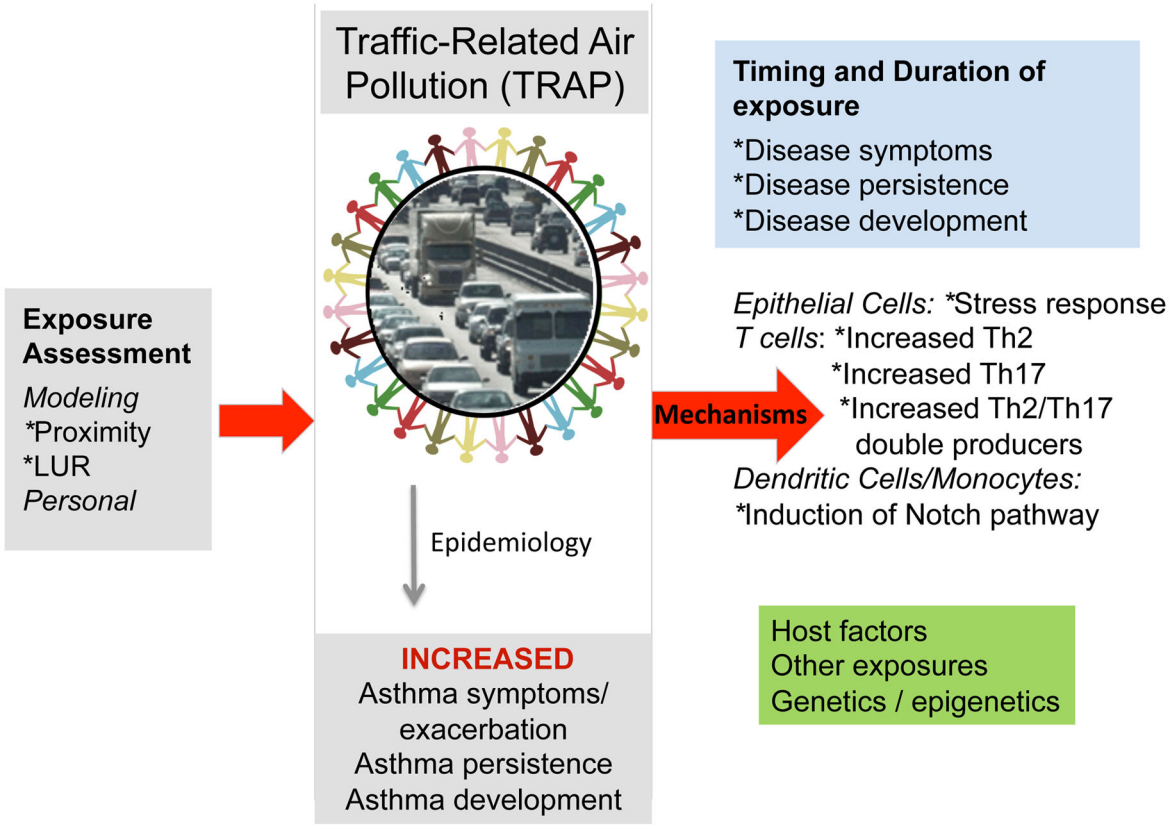

Figure 2. Overview

More accurate assessment of TRAP exposure will enable the design of epidemiologic and mechanistic studies aimed at discovery of biomarkers to identify the individuals most at-risk from the harmful effects of TRAP exposure and the design of novel targeted interventions.

Table 1

Selected epidemiologic studies of TRAP 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 et al. (10)
	Review	5 cohorts	937 – 5,603 per cohort (11,365 total)	K - 10^{th} 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); asthmatics 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 meters of a freeway was associated with deficits in FEV1, FVC and MMEF.	Chen et al. (19)
	Case-control	1	5,443	6–14	Proximity	Living within 200 meters of a main road increased wheeze, asthma diagnosis and decreased lung function.	Jung et al. (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 et al. (21)
	Case control	1 birth cohort	762	Birth-3	Proximity, land use regression model	Higher exposures to TRAP increase wheezing and night cough.	Ryan et al (22–24); Sucharew et al. (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 et al. (12)
Eczema	Review	6	400– 7,030	Birth-13	PM_{10}, NO_2, NO_X, CO	Traffic pollutant markers act as risk factors for the development or aggravation of eczema.	Ahn et al. (26)
	Case-control	1	4,907	9–11	Dispersion model	Eczema was significantly associated with PM_{10}, NO_2, NO_X and CO.	Penard-Morand et al. (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 et al. (28)
Allergic rhinitis / Sensitization	Case-control	1	5,443	6–14	Proximity	Living <75 meters from main road increased lifetime diagnoses and symptoms of AR. Distance to the main road and the length and proportion of the main road within 200 meters of the home were all associated with allergic sensitization to aeroallergen or food.	Jung et al. (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 et al. (29)

Outcome	Study Type	# of studies	Sample Size	Age Group	TRAP Markers	Main Findings	References
	Case-control	1 birth cohort	2,545	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).	Gruzieva et al. (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 et al. (12)

Table 2

Summary of TRAP 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