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The Effects of Air Pollution on the Development of Atopic Disease

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Abstract

Air pollution is defined as the presence of noxious substances in the air at levels that impose a health hazard. Thus, there has been long-standing interest in the possible role of indoor and outdoor air pollutants on the development of respiratory disease. In this regard, asthma has been of particular interest but many studies have also been conducted to explore the relationship between air pollution, allergic rhinitis, and atopic dermatitis. Traffic-related air pollutants or TRAP refers to a broad group of pollutants including elemental carbon, black soot, nitrogen dioxide (NO_2), nitric oxide (NO), sulfur dioxide (SO_2), particulate matter ($PM_{2.5}$ and PM_{10}), carbon monoxide (CO), and carbon dioxide (CO_2). In this review, we aim to examine the current literature regarding the impact of early childhood exposure to TRAP on the development of asthma, allergic rhinitis, and atopic dermatitis. Although there is growing evidence suggesting significant associations, definitive conclusions cannot be made with regard to the effect of TRAP on these diseases. This conundrum may be due to a variety of factors, including different definitions used to define TRAP, case definitions under consideration, a limited number of studies, variation in study designs, and disparities between studies in consideration of confounding factors. Regardless, this review highlights the need for future studies to be conducted, particularly with birth cohorts that explore this relationship further. Such studies may assist in understanding more clearly the pathogenesis of these diseases, as well as other methods by which these diseases could be treated.

Keywords Asthma · Incident asthma · Allergic rhinitis · Atopic dermatitis · Air pollution · TRAP · Childhood

Introduction

Air pollution is defined as the presence of noxious substances in the air at levels that impose a health hazard [1]. Recognition of air pollutants as a hazard dates back to thirteenth-century London when the use of coal was prohibited due to recognized detrimental health effects. In the nineteenth century, major cities in Great Britain where covered with a dense fog of smoke coined as "smog." Recognition of smog led to the creation of the Public Health (Smoke Abatement) Act in 1926. Although this act aimed to reduce smoke emissions from industrial sources of air pollution, it did not tackle domestic sources [2]. This was followed by a series of laws to develop a national air quality strategy imposing limit values for the different outdoor air pollutants emitted into the atmosphere [2].

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In the USA, the first federal air pollution law was enacted in 1955 [3]. Currently, the United States Environmental Protection Agency (EPA) regulates air quality standards through the National Ambient Air Quality Standards (NAAQS). These standards determine the concentration thresholds for both indoor and outdoor air pollutants. Regulated pollutants are carbon monoxide (CO), lead, nitric dioxide (NO_2), ozone (O_3), sulfur dioxide (SO_2), and particulate matter [1, 4]. These pollutants are produced by vehicles, greenhouse gas emissions from gross domestic products, and population growth [5]. Regulation of these pollutants have led to a decrease in aggregate emissions of these six common pollutants, despite population growth and increased traffic distances, as shown in Fig. 1 [5]. However, the actual exposure levels determining the risk for asthma development during infancy and childhood remain uncertain.

Relevant air pollutants are measured daily as part of the Air Pollution Index (API) and include particulate matter, NOx, and O_3. Ranges of acceptable exposure limits have been defined and updated, as noted in Fig. 2. Air pollutants are emitted in two forms: gaseous compounds, such as nitric oxide (NO), sulfur oxides (SOx), carbon monoxide (CO), and carbon dioxide (CO_2), and solid particulate matter primarily from

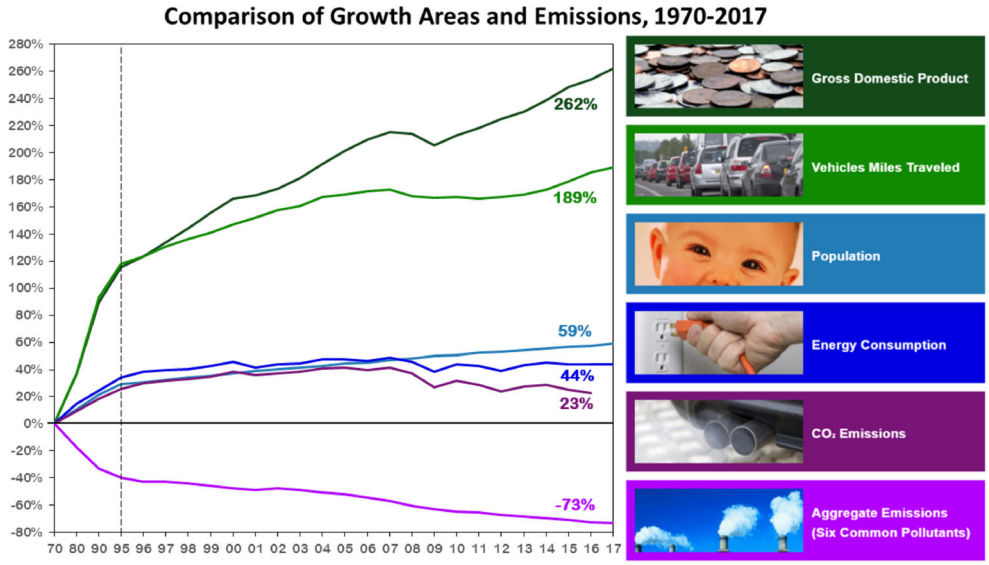

Fig. 1 Comparison of growth measurement and aggregate emissions from all sources, 1990–2007. Adapted from the US Environmental Protection Agency, 2008 [5]

traffic diesel exhaust particles (DEP) [1]. Particulate matter is classified by the size of the particles—the two most commonly referenced sizes are particles < 10 mm, referred to as PM_{10}, and particles < 2.5 mm, referred to as $PM_{2.5}$.

Among the recent epidemiologic studies examining air pollutants and asthma, nearly all have focused on traffic pollutants. The term traffic-related air pollution (TRAP) is a comprehensive term to describe all components produced by fuel combustion sources, including elemental carbon, black soot, NO_2, NO, SO_2, particulate matter ($PM_{2.5}$ and PM_{10}), ultrafine particulate matter, benzene, CO, and CO_2 [5]. Of these, certain pollutants have been chosen as surrogates to measure pollutant exposure from traffic based on four criteria from the EPA [5]: production mainly by traffic, ability to be measured at low concentrations, ability to be measured by inexpensive and accurate methods, and no independent association with health effects [5]. Nitrous oxides (NO_x), sulfur oxides (SO_x), carbon monoxide (CO), particulate matter ($PM_{2.5}$ and PM_{10}), and black carbon are the most cited pollutants in the literature as surrogates for traffic-related air pollution (TRAP).

API	Air Pollution Level
0 - 50	Good
51 - 100	Moderate
101 - 200	Unhealthy
201 - 300	Very unhealthy
301 - 500	Hazardous
500+	Emergency

Fig. 2 Air pollution index [3]

Although the incidence of asthma has significantly increased in recent decades, the rate of increase has been declining in recent years [6, 7]. Multiple environmental exposures may contribute to development of asthma: indoor and outdoor aeroallergens, viral infections, environmental tobacco smoke, the respiratory microbiome, and other airborne contaminants. There has been a longstanding interest in the possible role of indoor and outdoor air pollutants on the development of obstructive lung disease. By defining the health risks of air pollutants on respiratory health, this has enabled public health policy decisions that define safe and harmful exposure levels of outdoor air pollutants [4].

While a majority of the studies on TRAP have focused on respiratory disease, the effects of air pollutants on allergic rhinitis and eczema have also been examined. At this time, the literature remains inconclusive about a definitive relationship between the latter, perhaps due to the fact that clinical data from these studies are not comparable with regard to significant variability in the pollutants studied, models used to quantify exposure, defined outcomes, and adjustments for confounding factors are not consistent.

The Impact of Air Pollutants on Respiratory Health

Multiple cohort studies have evaluated the role of DEP ($PM_{2.5}$, PM_{10}, and black carbon) and/or gaseous air pollutants

(NO_2, NOx, O_3, and SO_2) on the development of asthma. Many studies have assessed multiple air pollutant exposures but NO_2 is the most commonly assessed individual pollutant [8].

Most studies were conducted in the pediatric age group, though a few studies examined adult/late-onset asthma. A variety of exposure models have been used for the assessment of air pollutant concentrations; the most commonly utilized land use regression (LUR) models. LUR models utilize monitoring data of air pollutant collected at multiple site locations throughout a geographic area and infer TRAP exposure concentrations in individual subjects based on geographic information systems (GIS) [9]. LUR models consider the pollutant of interest as the dependent variable and test it against other independent variables including traffic, topography, and other geographic variables, through regression analysis [10]. This allows prediction of the level of air pollutant exposure for any location [10]. These models have successfully been used to estimate annual average concentrations of traffic-related air pollutants in North American and European cities [9]. Dispersion modeling, traffic density, and distance to major roads were also used as surrogates for the concentrations of traffic-related air pollutants.

Pathogenesis

In humans, diesel exhaust particles (DEP), specifically $PM_{2.5}$, PM_{10}, and ultrafine particulate matter, have been extensively investigated for their capacity to enhance Th2-directed immune responses. Intranasal exposure to DEP during allergen exposure (e.g., ragweed) was shown to increase local Th2 cytokine and specific IgE production, suggesting a role for DEP as an immune adjuvant [11–14]. Diaz-Sanchez et al. first demonstrated that nasal mucosal specific IgE was produced after exposure to a neoantigen, keyhole limpet hemocyanin (KLH), but only with preceding exposure to DEP [15]. These findings prompted longitudinal epidemiologic and cross-sectional studies evaluating the risk of aeroallergen sensitization associated with high TRAP exposure early in life, as listed in Table 1. Although unproven, gestational exposure to TRAP during critical periods of fetal development could elicit maternal oxidative stress, thereby impacting the fetal lungs [20, 21]. BMI status may be associated with enhanced risk of asthma associated with exposure to air pollutants. When comparing long-term exposure to TRAP on in children with high BMI versus normal BMI, TRAP was associated with a twofold greater likelihood of asthma in children with normal BMI but not high BMI [22]. The investigators speculated that children with lower BMI could spend more time outdoors and hence encounter greater exposure to TRAP compared with those with high BMIs. Dong et al., however, found an opposing effect to BMI in children age 2–15 years in seven northeastern cities in China [23]. Obese or overweight children had higher odds of respiratory symptoms defined by wheeze, phlegm, and sputum production compared with their normal BMI counterparts; furthermore, the odds ratio for respiratory symptoms increased with exposure to increasing concentrations of PM_{10}, SO_2, NO_2, and O_3[27].

Brunst et al. evaluated the effect of TRAP exposure on the development of asthma in the Cincinnati Childhood Allergy and Air Pollution Study (CCAAPS) cohort [24]. Early exposure to TRAP was associated with transient and persistent wheeze (aOR = 2.31; 95% CI, 1.28–4.15) in childhood. Children with high average TRAP exposure from birth through age 7 were at significantly increased risk for asthma at age 7 (aOR 1.71; 95% CI, 1.01–2.88). They concluded that although early exposure predicts persistent childhood wheezing, only persistent lifetime TRAP exposure significantly increased risk of asthma at age 7 [24].

A large retrospective study suggested that exposure to TRAP in the first year of life was associated with an increased likelihood for development of childhood asthma [25]. Hsu et al. further evaluated critical windows during the prenatal period and found that higher levels of exposure to $PM_{2.5}$ in the mid-gestation period, particularly at 16 to 25 weeks of gestation, carried an increased risk for asthma development in boys at 6 years of age [26].

Gehring et al. studied the effects of exposure to NO_2, $PM_{2.5}$, and "soot" in children age 0–8 years in a birth cohort study and found an increased odds ratio for asthma development for all three pollutants [27]. This relationship remained significant at age 12 years with persistent exposure to TRAP [28]. The Swedish BAMSE birth cohort determined that exposure to NO_x and PM_{10} during the first year of life was associated with increased asthma prevalence and incidence at ages 8 to 12 but not at younger ages [29].

Studies by Air Pollutant

The evidence regarding the association between TRAP and asthma development, or incidence of asthma, in the pediatric population has been conflicting (Table 2). Multiple studies have demonstrated this association [22, 24, 27, 29, 30, 32, 33, 36, 39, 40, 42], including NO_2 [27, 30, 32, 33, 39], $PM_{2.5}$ [27, 30], NO [30], black carbon [22, 27, 30, 32, 40], NOx [29], and PM_{10} [29, 42]. However, other studies have not shown a correlation between these environmental exposures and asthma [25, 31, 34, 35, 37–41]. In examining the literature, we could identify four variables that could account for this heterogeneity: duration of exposure to pollutants, a critical period of exposure, exposure to a certain cut-off level of the pollutant, and populations that are biologically at inherently increased risk.

Table 1 Effects of DEP on healthy volunteers

Study	Exposures	Studies	Results
Salvi et al. [16]	15 volunteers exposed to DEP for 1 h with intermittent exercise.	• Spirometry • Blood sampling • BAL • Bronchial biopsy	• No change in lung function test • BAL showed increase in neutrophils, B lymphocytes, histamine, and fibronectin • Bronchial biopsies showed high levels of neutrophils, mast cells, CD4+ and CD8+ T lymphocytes, and upregulation of ICAM-1 and VCAM-1 at the endothelium, along with increases in the numbers of LFA-1+ cells in the bronchial tissue. • Peripheral blood showed a significant increase in neutrophil and platelet numbers
Salvi et al. [17]	15 volunteers exposed to DEP on two separate occasions for 1 h each	• BAL	• Increase gene transcription of interleukin-8 (IL-8) in bronchial tissue. • Increased expression of growth-regulated oncogene-alpha (GRO-alpha) protein • Increase in IL-5 mRNA gene transcripts • No significant changes in the levels of gene transcription of interleukin-1B (IL-1beta), tumor necrosis factor-alpha (TNF-alpha), interferon gamma (IFN-gamma), and granulocyte macrophage colony-stimulating factor (GM-CSF)
Nightingale et al. [18]	Ten participants exposed for 2 h to DEP or air in a double-blind, randomized, crossover study	• Serial spirometry • Exhaled carbon monoxide (CO), and methacholine reactivity • Sputum induction • Blood sampling	• Spirometry and Methacholine reactivity showed no significant difference between both groups. • Increased levels of exhaled CO in the DEP group compared with those exposed to air at 1 h (air, 2.9 ± 0.2 ppm [mean ± SEM]; DEP, 4.4 ± 0.3 ppm; $p < 0.001$). • Sputum induction showed increased neutrophils and myeloperoxidase (MPO) at 4 h in the DEP group compared with air (neutrophils, 41 ± 4% versus 32 ± 4%; MPO, 151 ng/ml versus 115 ng/ml, $p < 0.01$) • Sputum induction showed no significant difference in the levels of IL-8 or TNF-α • No significant difference in levels of IL-6, TNF-α and P-selectin
Sehlstedt et al. [19]	15 volunteers were exposed to DEP and air for 1 h on two separate occasions 3 weeks apart.	• Spirometry • BAL • Bronchial biopsy	• No change in lung function test • BAL showed increase in eosinophil number ($p = 0.017$) but no significant change in number of inflammatory cells • Bronchial biopsy showed increased expression of P-selectin ($p = 0.036$) and VCAM-1 ($p = 0.030$). No significant increase in ICAM-1 expression as compared with filtered air

Studies Focusing on One Pollutant

Nitrous oxide (NO_x) and nitrous dioxide (NO_2) were the most common pollutants evaluated individually. An increased risk for asthma development was noted when pediatric subjects aged 10–12 years were exposed to high annual concentrations of NO_2 [33]. More specifically, those who experienced a concentration of 29 parts per billion (ppb) had a hazard ratio of 3.25 in comparison with subjects exposed to 6.29 ppb annually (HR 1.29). However, Oftedal et al. did not find positive associations between traffic-related exposure and the onset of physician-diagnosed asthma in children [41]. Although associations for late asthma onset (defined as greater than or equal to 4 years of age) were positive, these findings were not statistically significant. Interestingly, while NO_2 did not seem to be associated with the general development of asthma, those who carried the NQO1 rs2917666 genotype demonstrated a significant association between nitrous dioxide exposure and asthma development [43].

The correlation between asthma incidence and NO_x seemed to be dependent on the cohort age. Two studies conducted by Lindgren et al. focused on NO_x exposure by

Table 2 Study evaluating asthma in the pediatric population on exposure to air pollution

Study	Location	Exposure assessment	Age group	Pollutants	Results
Brunst et al., [24]	Cincinnati, USA	LUR	1–7 years	Black carbon	Children who had high levels of TRAP exposure at birth has twofold increased risk of persistent wheeze at age 7. Those with persistent exposure from birth through 7 years of age at levels of TRAP > 75 percentile had an increased OR for development of asthma that was statistically significant (OR = 1.71; 95% CI, 1.01–2.88).
Carlsten et al. [30]	Vancouver, Canada,	LUR model	Birth, 1 and 7 years	NO, NO_2, black carbon, and $PM_{2.5}$	$PM_{2.5}$ had the highest OR for the development of asthma (OR 3.1; 95 %CI of 1.3–7.4) compared with NO_2 (OR 1.5; 95% CI 0.9–2.5), NO (OR 1.2, 95% CI 0.9–1.7), and black carbon (OR 1.1, 95% CI of 0.7–1.9). This did not hold true for bronchial reactivity, as the OR was not significant.
Clark et al. [25]	British Columbia, Canada	IDW, LUR	In utero, 1, 3–4 years	BC, CO, NO, NO_2, PM_{10}, and $PM_{2.5}$	NO was found to have an increased OR for exposure in utero and of borderline statistical significance at year 1 of life. NO_2 exposure was only statistically significant during the first year of life. Black carbon was borderline statistically significant for both periods. IDW was used to assess effects of NO, NO_2, CO, PM_{10}, $PM_{2.5}$, SO_2, and O_3. Exposure to NO, NO_2, CO, PM_{10}, and SO_2 was found to have an increased OR for exposure in utero and during first year of life but not to O_3, SO_2, and $PM_{2.5}$.
Fuertes et al. [31]	Germany	LUR	Birth, 6, 10 years	Black carbon, NO_2, and $PM_{2.5}$	No association was found between exposure to TRAP and development of asthma
Gehring et al. [27]	Netherlands	LUR	Birth–8 years	NO_2, $PM_{2.5}$, and black carbon	Statistically significant increase in incidence of asthma (OR, 1.26; 95% CI, 1.04–1.51) and wheezing across all phenotypes (OR, 1.15; 95% CI, 1.02–1.28) for the first of year of life (6%) as well as years 2–8 but at lower prevalence (1–2%) on exposure to $PM_{2.5}$. Similar associations were seen with NO_2 and soot. Exposure to any was not associated with a significantly increased risk for bronchial hyper responsiveness.
Gehring et al. [32]	Netherlands	LUR	Birth–16 years	Black carbon, NO_2, $PM_{2.5}$, and PM_{10}	Significantly increased risk of asthma at age 14–16 with increasing exposure to NO_2 ([OR] 1.13 per 10 $\mu g/m^3$ [95% CI 1.02–1.25]) and black carbon at birth (1.29 per 1 unit [1.00–1.66]) but not for $PM_{2.5}$ and PM_{10}. Incidence of asthma was apparent at age 4 years and older.
Gruzieva et al. [29]	Sweden	Dispersion modeling	Birth–12 years	NO_x and PM_{10}	Exposure to PM_{10} and NO_x in the post natal period was found to be significantly associated with occurrence of non-allergic asthma (negative IgE to aeroallergens) at 4 and 8 years of age.
Jerrett et al. [33]	CA, USA	LUR	10–12 years	NO_2	Significantly increased risk of asthma on exposure to NO_2 at an average concentration of 6.2 ppb annually (HR 1.29; 95% CI 1.07–1.56). The risk increased with exposure to higher concentrations of 28.9 ppb annually (HR 3.25; 95% CI, 1.35–7.85).
Kramer et al. [34]	Germany	LUR	0–6 years	$PM_{2.5}$ and NO_2	No association found between exposure to TRAP and development of asthma.
	USA	LUR	0–7 years		Higher levels of eNO in normal-weight vs obese children in those exposed to TRAP.

Table 2 (continued)

Study	Location	Exposure assessment	Age group	Pollutants	Results
Le Masters et al. [22]				Black carbon	Similarly high lifetime exposure to TRAP was associated with a twofold increase in asthma in normal BMI compared with children with high BMI.
Lindgren et al. [35]	Sweden	Dispersion modeling and traffic intensity	0–6 years	NO_x	No relation between development of asthma and exposure to NO_x. No association between living close to high-traffic roads (≥ 8640 cars/day) and asthma.
McConnell et al. [36]	Southern CA, USA	Dispersion modeling for NO_x. Average annual concentrations for NO_2, $PM_{2.5}$, and PM_{10} were estimated based on the distances to the nearest freeway or other highways or arterial roads and traffic density within 150 m of each participant's residence and school and at central community sites	Kindergarten and first grade to fourth grade	NO_x, NO_2, $PM_{2.5}$, and PM_{10}	Increased risk of asthma on exposure to traffic-related air pollution at home or school. Increased association was seen when exposure to TRAP was at both locations.
Molter et al. [37]	England	Monitored levels of TRAP at participant's "microenvironments". LUR was used for outdoor exposures and INDAIR model for indoor exposures	0–11 years	PM_{10} and NO_2	No association found between the development of wheeze and asthma and exposure to PM_{10} and NO_2.
Molter et al. [38]	England, Germany, Sweden, Netherlands	LUR LUR models used were based on the measurement campaigns carried out in 2009, but the exposure timepoints specified were between 1994 and 2008	0–10 years	NO_2, NO_x, PM_{10}, $PM_{2.5}$, and black carbon	No association found between the development of wheeze and asthma and exposure to NO_2, NO_x, PM_{10}, $PM_{2.5}$, and black carbon.
Morgenstern et al. [39]	Munich, Germany	LUR	0–2 years	Black carbon, NO_2, and $PM_{2.5}$	Statistically significant association was found between wheezing and exposure to NO_2 for the first and second years of life but not for $PM_{2.5}$ or black carbon.
Morgenstern et al. [40]	Munich, Germany	LUR and distance to major roads.	4–6 years	Black carbon, NO_2, and $PM_{2.5}$	Positive associations were found for exposure to black carbon and asthma (OR, 1.56; 95% confidence interval [CI], 1.03–2.37). Living within a 50-m range from a major road was also associated with both asthma OR 1.66; 95% CI (1.01–2.59) and wheeze OR 1.24 95% CI (1.01–1.52). No associations were found for NO_2 and $PM_{2.5}$.
Oftedal et al. [41]	Oslo, Norway	Dispersion modeling and distance to major roads.	0–10 years	NO_2	No association was found between TRAP exposure and development of asthma. An interquartile range increase in the concentration of NO_2 was associated with an adjusted risk ratio of 0.82; 95% CI 0.67–1.02 for the development of asthma.
Wu et al. [42]	Southern Taiwan	Kriging method to estimate individual exposure to air pollution	School-age children	NO_2, SO_2, PM_{10}, and CO	Positive association found between high level of exposure to PM_{10} and asthma onset at > 10 years. Associations were not significant for NO_2, SO_2, or CO.

DEP, diesel exhaust particles; *TRAP*, traffic-related air pollution; *LUR*, land use regression model; *IDW*, inverse distance weighting; *NOx*, nitrogen oxides

evaluating adults aged 18–77 years old who lived within 100 m of a road with at least ten cars per minute [44, 45]. Participants with at least > 19 μg/m^3 NO_x exposure had an increased odds ratio for asthma symptoms but not necessarily an objectively confirmed diagnosis [44], though an increased prevalence of allergic asthma versus non-allergic asthma was noted among those with high NO_x exposure [43]. Unlike the aforementioned adult subjects, no relationship between NO_x and asthma development could be determined when looking at similar parameters in pediatric patients [38].

One study that focused on black carbon (BC) showed an increased odds ratio for asthma development based on pulmonary function testing in a subgroup of children persistently exposed to TRAP from birth through 7 years of age [24], and Morgenstern et al. also found positive associations between exposure to black carbon and asthma (OR, 1.56; 95% confidence interval [CI], 1.03–2.37) [39]. Another study showed that exposure to BC was significantly associated with asthma among normal-weight children but not overweight children (adjusted odds ratio of 1.8 versus 0.7), whereas the reverse was true when looking at exposure to secondhand smoke [22]. It was postulated that this could be due to the patterns of activity between both groups, particularly when comparing the amount of time these groups of children spent indoors versus outdoors.

Studies Examining Multiple Pollutants

Generally, studies that have been conducted to examine the relationship between TRAP and respiratory disease have considered multiple pollutants at the same time, as much of these pollutants are mixed together. Again, however, the results have been conflicting. While some found no association [25, 31, 34, 38], others identified a potential culprit pollutant or group of pollutants [32, 39, 40]. Of note, most of these studies focused on pediatric populations, but those done in adults are presented in Table 3.

The evidence to support asthma development among birth cohorts exposed to TRAP has not been clear-cut. When monitoring children at birth and at subsequent ages, the effect of pollutants seemed to depend on the age at which the children are exposed [14, 26, 36, 39]. One study that focused on $PM_{2.5}$ and NO_2 found that the odds ratio for asthma diagnosis was statistically significant when comparing children aged 0–12 months versus those diagnosed at 12–24 months [14]. Similar findings were noted when considering incidence of asthma or wheezing [36, 39]; however, in these cohorts, $PM_{2.5}$ seemed to have more effect at the first year of life and years 2–8 [21] versus NO_2 and BC at age 14–16 years [39]. The latter group showed a significantly increased risk of asthma with at least 1.13 per 10 μg/m^3 NO_2 and 1.29 per 1 unit of black carbon at birth.

As mentioned previously, the etiology of these associations could be partially attributed to potential genetic differences among these children. Positive association with development of asthma on exposure to NO_x and PM_{10} at older age groups has also been reported without finding associations with younger age groups [29], and asthma onset at greater than 10 years of age also seemed to correlate with high levels of PM_{10} exposure [31]. However, no significant associations were noted for NO_2, SO_2, or CO in the aforementioned study. Another study, though, found that PM_{10} and NO_2 did not have an effect of asthma development or wheeze in pediatric subjects [41].

Role of Indoor Air Pollution on the Development of Asthma

The majority of studies have focused on the effects of outdoor air pollution on the development of respiratory disease. However, indoor air pollutants have also been implicated in the development and exacerbation of asthma, and as such, there is growing interest in their role on this disease.

Indoor air pollution occurs as a product of multiple sources: transfer from outdoor sources, chemicals used in cleaning or renovation, tobacco smoking and use of gas, kerosene wood, or coal in the home. Inhaled indoor pollutants that have been studied include nitrogen dioxide, particulate matter, volatile organic compounds (VOCs), formaldehyde, and phthalates. Nitrogen dioxide and particulate matter can be found in homes as a product of outdoor pollution transferred indoors, as well as from tobacco smoking and heating devices running on gas, kerosene, wood, or coal [46].

Prior studies have shown that a drop in FEV1 in asthmatics occurs upon exposure to domestic NO_2. A drop in FEV1 was seen on exposure to 100 ppb over a duration of 1 h, and higher concentrations of NO^2 (400 ppb) were shown to cause a more profound drop in FEV1 compared with those inhaling lower concentrations [47, 48]. A meta-analysis conducted by Gehring et al. included 41 studies assessing the incidence of asthma in children exposed to NO_2 from exposure to gas cooking. Based on their analysis, there was a significant association between the two variables [49]. Nineteen of the included studies showed an increased odds ratio for current asthma as well as lifetime prevalence of asthma. However, four other studies in the meta-analysis did not show a statistically significant association.

Volatile organic compounds (VOCs) are another category of emitted gases contributing to indoor air pollution. VOCs arise from a multitude of household products that include, but are not limited to, paints, varnishes and wax, cleaning and cosmetic products, aerosol spray, pesticides, building material, glues and adhesives, and office equipment, such as copiers and printers [46]. The National Health and Nutrition Examination Survey (NHANES) conducted over a 1-year period in the USA showed higher odds of physician-diagnosed

Table 3 Studies evaluating adult onset asthma on exposure to air pollution

Castro-Giner et al. [43]	Sweden, UK, Spain Barcelona, Germany, France, Paris, Belgium	Exposures to NO_2 at each of the participants' addresses were determined using air pollution maps using focal sum techniques in a global information system model.	20–44 years	NO_2	No significant association between NO_2 exposure and development of asthma. Significant association between development of asthma and NO_2 exposure in those carrying NQO1 rs2917666 genotype.
Lindgren et al. [44]	Sweden	Self-reported exposure to traffic, traffic intensity within 100 m, modeled exposure to NO_x using modified Gaussian dispersion model.	18–77 years	NO_x	Asthma diagnosis was associated with living within 100 m of a road with greater than 10 cars/min. Participants with high exposure to NO_x (> 19 μg/m^3) had increased odds ratio for asthma symptoms but not diagnosis.
Lindgren et al. [45]	Sweden	Self-reported exposure to traffic, traffic intensity within 100 m, modeled exposure to NO_x using modified Gaussian dispersion model.	18–77 years	NO_x	Increased prevalence of allergic asthma was seen for participants living within 100 m of a road with greater than 10 cars/min but not for non-allergic asthma. No statistical significance of allergic and non-allergic asthma prevalence on exposure to NO_x at various concentrations.

asthma in patients known to have exposure to VOCs [50]. The study also reported increased odds of wheezing attacks [50].

The role of VOCs on the incidence of asthma remains unclear due to the conflicting data produced by previously conducted studies. Norback et al. demonstrated that exposure to VOCs produced asthma-like symptoms; however, concrete data confirming an association with a diagnosis of asthma through pulmonary function tests and methacholine challenge testing was not seen [51]. A population-based case-control study by Rumchev et al. with children 6 months to 3 years of age found that exposure to VOCs was an independent risk factor for the development of asthma [52]. They also showed that for every ten unit increase of toluene and benzene, both of which fall under the umbrella of VOCs, children had an increased risk of two- and threefold, respectively, for the development of asthma [52]. Other studies, however, did not report statistically significant associations between the development of asthma and indoor exposure to VOCs [53, 54].

Formaldehyde is primarily an indoor air pollutant emitted as a gas from urea. Formaldehyde resins are used as preservatives in decorative laminates, adhesives, foam in building material and household products, cotton and fiber blends, and electrical equipment [55]. The World Health Organization limits indoor levels of formaldehyde to 100 μg/m^3 due to its effects on human health. The Occupational Safety and Health Administration (OSHA) cautions against the respiratory effect of formaldehyde since concentrations above 1 ppm can lead to upper airway irritation, and when above 50 ppm, can lead to bronchial irritation and pulmonary edema [56]. Studies have shown that indoor concentration of formaldehyde can range between 9.6 and 90 μg/m^3, and some cities in Hong Kong have recorded levels greater than the recommended 100 μg/m^3 threshold [57, 58].

Multiple studies have been carried out in order to determine the effects of formaldehyde on respiratory health. In children, formaldehyde levels > 0.06 mg/m^3 have been associated with an increased risk of asthma development, but at levels of 0.1 mg/m^3, this association was not seen [59]. This study showed that even at low levels of formaldehyde, i.e., less than 100 μg/m^3, those with asthma and known dust mite allergy had increased bronchial responsiveness to mite allergen [59].

Phthalates are used to make plastic materials for improved malleability and can be found in some polyvinyl chloride products. They are also used as solvents in vinyl flooring, adhesives, detergents, plastic clothes, and personal-care products [60]. Indoor concentration of phthalates has been reported to be ten times higher indoors than they are outdoors [61]. A number of case reports have described the incidence of occupational asthma in people exposed to phthalates. An association has also been seen in children exposed to indoor phthalates, as reported by multiple studies linking high levels of fractional exhaled nitric oxide, a marker of pulmonary inflammation associated with asthma, with the presence of high

levels of urinary phthalate metabolites [62–64]. It is unclear, however, if the pulmonary inflammation can be linked immediately to phthalates, or if exposure to phthalates is an independent factor in the development of asthma.

Role of Air Pollution on the Development of Aeroallergen Sensitization and Atopic Dermatitis

In addition to asthma, a number of studies have looked into the relationship between TRAP exposure and the development of atopic dermatitis and aeroallergen sensitization. Gruzieva et al. found that children in the BAMSE cohort exposed to nitrogen oxides and PM_{10} in the first year of life had an increased risk of pollen sensitization at 4 years of age (odds ratio, 1.83; 95% confidence interval 1.02–3.28), though this did not hold true at 8 years of age [65]. Codispoti et al. showed similar findings in that the risk of early aeroallergen sensitization was enhanced by DEP exposure, and the aeroallergen wheal area noted at 2 and 3 years of age was associated with allergic rhinitis by the age of 4 [66]. Another study explored the relationship between an increased risk for atopic disease and living near a main road [67]. It was found that children who lived within 75 m of a main road were at an increased risk of lifetime allergic rhinitis. Also, the distance to the main road, the length of the main road, and the proportion of the main road area were associated with allergic sensitization.

Along with allergic rhinitis, recent evidence has suggested that air pollutants may be risk factors for the development of atopic dermatitis due to their possible ability to induce oxidative stress in the skin and cause barrier dysfunction. Lee et al. found that following adjustment for possible confounders, flexural eczema was associated with nitrogen oxides and carbon monoxide in school-aged Taiwanese children going to school within 2 km of 55 stations [68]. Another study that utilized a dispersion model determined that eczema symptoms in 9–11-year-old children were associated with exposure to 3-year averaged concentrations of CO, NOx, PM_{10}, and benzene [69]. Two other studies done in birth cohorts in Munich demonstrated strong positive associations between eczema and distance to main roads [70].

It should be noted that while there seems to be a great amount of evidence supporting the development or aggravation of atopic disease with air pollutants, definitive statements cannot necessarily be made. The small number of studies, inherent challenges in study design, varying definitions of TRAP and the diseases in question, differing methods of exposure assessment and health outcomes, the presence of confounding variables (e.g., obesity, genetics, and comorbidities), and other factors all present limitations in making a firm conclusion about the causative link between air pollution and atopic disease.

Current Recommendations Regarding Travel to Areas of High Pollution

The current literature does not support a definitive causative role for traffic-related air pollution on the development of asthma; however, potential hazards of high air pollution levels on health remain a concern. The most notable indication of public concern regarding this issue was in relation to athletes and their performance levels during the 2008 Beijing Olympics. Beijing's environment authorities took swift action prior to the opening ceremony to decrease the levels of air pollution in order to meet national air quality standards. They focused their efforts on decreasing vehicle emissions and industrial emissions, as they are the major contributors to poor air quality recorded in the city. Pressure from international communities and athletes forced authorities to impose a 30% reduction in industrial emissions by closing down major industries and pulling 1.3 million cars off the roads every day prior to the event [71].

The CDC advises travelers to familiarize themselves with the air quality of their destination, especially those with preexisting pulmonary or cardiovascular disease, children, and the elderly, as these groups are the most susceptible to poor air quality [72]. The CDC recommends limiting exertion and time spent outdoors in cities with high levels of air pollution. The use of face masks is also encouraged, though they do not make final recommendations on the matter due to lack of evidence that the use of regular face masks will provide protection against traffic-related air pollution [72]. The use of valved dust respirators has been shown to decrease the effects of air pollution on heart rate and blood pressure in a small study conducted in Beijing [72]. The US Environmental Protection Agency recommends checking the level of air pollution at travel destinations, as well as the day-to-day levels of air pollution in hometowns using the airnow.gov website. The quality of air can be assessed using Fig. 2 [73]. They deem an air pollution index of 150 as unhealthy. At that level, the EPA concurs with the CDC's recommendation to limit excessive and prolonged outdoor activity [73].

Conclusion

The current state of literature indicates that the development of asthma, allergic rhinitis, and atopic dermatitis from exposure to traffic-related air pollutants remains inconclusive. The reason for this may be attributed to a number of factors related to study design. In some of the reported studies, participants were assessed for brief periods of time that were not sufficient to observe the development of these conditions. An absence of correlation could also be secondary to low levels of pollutant concentrations in the areas assessed, thus not reaching critical levels as defined by the World Health Organization. It should also be noted that in younger age groups, it is often difficult to

accurately diagnose asthma, as case definitions may vary among researchers. Also, the number of studies looking specifically at allergic rhinitis and atopic dermatitis is much smaller. This review highlights the need for further research to understand the potential role of air pollutants on atopic disease.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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