



Motor vehicle air pollution and asthma in children: A meta-analysis

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ABSTRACT

Background: Asthma affects more than 17 million people in the United States; 1/3 of these are children. Children are particularly vulnerable to airborne pollution because of their narrower airways and because they generally breathe more air per pound of body weight than adults, increasing their exposure to air pollutants. However, the results from previous studies on the association between motor vehicle emissions and the development of childhood wheeze and asthma are conflicting. Therefore, we conducted a meta-analysis to clarify their potential relationship.

Methods: MEDLINE, Highwire, and The Cochrane Library databases were searched for relevant studies. Adjusted odds ratio (OR) with corresponding 95% confidence interval (CI) for the association between traffic air pollutants and wheeze or asthma were retrieved from individual studies and pooled to generate summary effect estimates (meta-OR) in STATA 11.1.

Results: Nineteen studies were included in the meta-analysis. Exposure to nitrogen dioxide (meta-OR: 1.05, 95% CI: 1.00–1.11), nitrous oxide (meta-OR: 1.02, 95% CI: 1.00–1.04), and carbon monoxide (meta-OR: 1.06, 95% CI: 1.01–1.12) were positively associated with a higher prevalence of childhood asthma. Exposure to sulfur dioxide (meta-OR: 1.04, 95% CI: 1.01–1.07) was positively associated with a higher prevalence of wheeze in children. Exposure to nitrogen dioxide was positively associated with a higher incidence of childhood asthma (meta-OR: 1.14, 95% CI: 1.06–1.24), and exposures to particulate matter was positively associated with a higher incidence of wheeze in children (meta-OR: 1.05, 95% CI: 1.04–1.07).

Conclusions: Living or attending schools near high traffic density roads exposes children to higher levels of motor vehicle air pollutants, and increases the incidence and prevalence of childhood asthma and wheeze.

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1. Introduction

The prevalence of asthma has increased over the past decades making it the most common chronic illness in children (Anandan et al., 2010; World Health Organization, 2008a), and the most common cause of pediatric hospitalizations in the U.S. accounting for 10.1 million missed school days per year (Mansour et al., 2000). Simultaneously, air pollution is a growing environmental concern, responsible for 2 million premature deaths per year (World Health Organization, 2008b). Children are particularly vulnerable to airborne pollution because of their narrower airways and because they generally breathe more air per pound of body weight than adults, increasing their exposure to air pollutants. Children are particularly susceptible not only because the lung is developing, but children are also often very active outdoors and have very

different ventilatory parameters compared to adults that facilitate deeper and greater lung deposition of particles and gas/cell membrane interactions (Ciencewicki et al., 2008). Children often breathe through their mouth especially when they exercise. According to Phalen (AQMD, 2007), mouth-breathing bypasses the natural filtering of air pollutants by the nose and allows large volumes of polluted air to affect the more sensitive areas of children's lungs which are still developing. Therefore, they can be subject to oxidant-induced injury to the lungs, which can lead to permanent lung changes (Gilliland et al., 1999).

The effects of traffic-related pollution exposure in the development of wheeze and asthma in children have been studied, but the results are inconsistent. For instance, particulate matter was found to increase the risk of developing childhood asthma in some studies (Gehring et al., 2010; Clark et al., 2010; Penard-Morand et al., 2010), while no association was found in other studies (Annesi-Maesano et al., 2009; Brauer et al., 2007; Kim et al., 2004; McConnell et al., 2010; Peters et al., 1999). Hwang et al. (2005) even found this exposure to be protective against asthma. Similar discrepancies were found in studies evaluating nitrogen oxide, sulfur dioxide, carbon monoxide, and ozone as potential risk factors for wheeze and asthma in children.

Abbreviations: NO, nitrogen oxides; NO₂, nitrogen dioxide; NO_x, nitrous oxide; CO, carbon monoxide; PM_{2.5}, particulate matter with aerodynamic diameter less than 2.5 μm; PM₁₀, particulate matter with aerodynamic diameter less than 10 μm; SO₂, sulfur dioxide; VOC, volatile organic compound; O₃, ozone

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Therefore, the objective of the present meta-analysis was to clarify potential associations between motor vehicle air pollutants and wheeze and asthma in children by integrating and synthesizing the results from previous studies.

2. Materials and methods

2.1. Data sources and searches

We searched MEDLINE, Highwire, and The Cochrane Library for studies published in any language up to January 2011 evaluating the relationship between motor vehicle air pollutants exposure and the incidence and/or prevalence of asthma or wheeze in children. We performed the searches using the following terms: 'traffic, asthma, children'; 'traffic-related asthma, children'; 'traffic pollution, asthma, children'; 'carbon monoxide, asthma, children'; 'oxide, asthma, children'; 'particulate matter, asthma, children'; 'ozone, asthma, children'; and 'sulfur dioxide, asthma, children'. The specific search strategies used in the different databases are presented in Appendix 1. In addition to the database search, we screened the lists of references in previous reviews and included papers to identify additional relevant studies.

2.2. Study selection

We included in the meta-analysis studies published in English that reported or contained data to calculate the odds of asthma or wheeze development with corresponding 95% confidence intervals (CI) for exposure to traffic-related air pollutants: carbon monoxide (CO), nitrogen monoxide (NO), nitrogen dioxide (NO₂), nitrogen oxides (NO_x), sulfur dioxide (SO₂), ozone (O₃), particulate matter (PM), particulate matter with aerodynamic diameter less than 10 µm (PM₁₀), and particulate matter with diameter with aerodynamic diameter less than 2.5 µm (PM_{2.5}). We excluded from the meta-analysis studies conducted with adults, and those that used the same population of another included study (only the more recent was included).

2.3. Data extraction and analysis

Two of the authors (A.M. and D.D.) independently extracted data from each article on study design, age of participants, and calculated the adjusted effect sizes and corresponding 95% CI for the prevalence and/or incidence of wheezing or asthma corresponding to a 10 µg/m³ increment in exposure to traffic-related pollutants (NO, NO₂, NO_x, CO, PM_{2.5}, PM₁₀, SO₂, and O₃). Discrepancies were resolved through discussion and consultation of a third author (J.G.) when necessary. Effect sizes were combined as weighted averages to generate summary estimates (Meta-OR) using random effects models. These models weight each study by its inverse variance and by the within- and between- studies variances.

Heterogeneity between study results was evaluated using the Cochran Q statistic test. This test follows a chi-square distribution with N (# of studies)–1 degrees of freedom and has a low statistical power. Therefore, the statistical significance was defined as <0.10 instead of <0.05. The percentage of variation due to heterogeneity was determined using the I² statistics. Study results were considered consistent when there was less than 50% variation due to heterogeneity. Significant heterogeneity was investigated using random effect meta-regression to determine which study-level factors explained the heterogeneity. All analyses were performed using STATA statistical software (Version 11, Stata Corporation, College Station, TX).

2.4. Quality assessment of studies

The methodological quality of the studies was assessed based on population size, study design, air pollutant exposure measures, contact time determination methods, doctor diagnosed current asthma, confounding controls used, and statistical methods utilized. Quality of reporting was evaluated by using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement checklist for cohort, case-control, and cross sectional studies, version 4 (von Elm et al., 2008). The studies were classified as having A: more than 80% of STROBE criteria fulfilled, B: 50–80% of STROBE criteria fulfilled, or C: less than 50% of STROBE criteria fulfilled.

3. Results

A total of 420 articles were identified, including 318 studies from MEDLINE, 102 from Highwire, no article from The Cochrane Library, and no new citation from reference screening (Fig. 1).

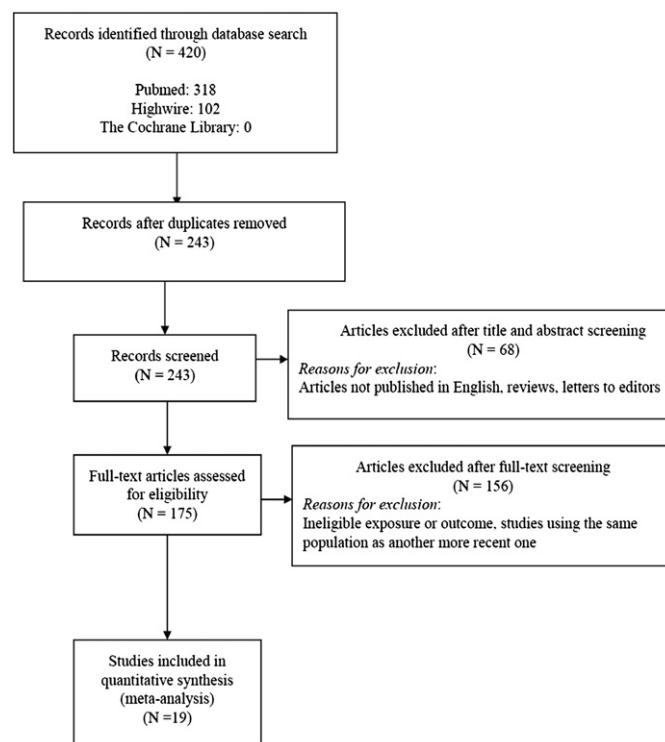


Fig. 1. Flow diagram of study selection.

Nineteen studies were included (Arnedo-Pena et al., 2009; Clark et al., 2010; Dockery et al., 1996; Gauderman et al., 2005; Gehring et al., 2002, 2010; Hirsch et al., 1999; Hwang et al., 2005; Kim et al., 2004; Linares et al., 2010; Morgenstern et al., 2007; Nicolai et al., 2003; Oftedal et al., 2009; Penard-Morand et al., 2010; Peters et al., 1999; Pikhart et al., 2001; Sahsuvaroglu et al., 2009; Shima et al., 2002; Zhang et al., 2002).

3.1. Studies' characteristics and definitions

The 19 studies that met our inclusion criteria were published between 1996 and 2010. Nine were conducted in Europe (Arnedo-Pena et al., 2009; Gehring et al., 2002, 2010; Hirsch et al., 1999; Morgenstern et al., 2007; Nicolai et al., 2003; Oftedal et al., 2009; Penard-Morand et al., 2010; Pikhart et al., 2001). Five were conducted in North America (Clark et al., 2010; Dockery et al., 1996; Gauderman et al., 2005; Peters et al., 1999; Sahsuvaroglu et al., 2009); 4 in Asia (Hwang et al., 2005; Shima et al., 2002; Zhang et al., 2002), and 1 in Latin America (Linares et al., 2010). Nine studies were cohort studies (Clark et al., 2010; Gehring et al., 2002, 2010; Linares et al., 2010; Morgenstern et al., 2007; Oftedal et al., 2009; Peters et al., 1999; Sahsuvaroglu et al., 2009; Shima et al., 2002), and 10 were cross-sectional (Arnedo-Pena et al., 2009; Dockery et al., 1996; Gauderman et al., 2005; Hirsch et al., 1999; Hwang et al., 2005; Kim et al., 2004; Nicolai et al., 2004; Penard-Morand et al., 2010; Pikhart et al., 2001; Zhang et al., 2002).

Air pollution concentrations at children addresses were estimated by measurements performed at specific sites during a year and adjusted for temporal trends to calculate long-term average concentrations or using regression models developed to relate the annual average concentrations measured at monitoring sites with the GIS variables.

Questionnaire assessments and/or physician diagnosis of asthma and wheeze were used in 17 out of the 19 studies following the methodology proposed by the International Study

of Asthma and Allergy in Childhood—ISAAC (Asher et al., 1995). One study (Linares et al., 2010) used the American Thoracic Society–Division of Lung Diseases questionnaire (Ferris, 1978) to assess asthma outcome and the participants were tested using forced spirometry, and 1 study (Clark et al., 2010) identified asthma diagnoses from physician billing and hospital discharge records.

3.2. Exposure to nitrogen oxides

In relation to the exposure to nitrogen oxides, the prevalence of asthma or wheeze was estimated in 11 studies (Arnedo-Pena et al., 2009; Hirsch et al., 1999; Hwang et al., 2005; Kim et al., 2004; Nicolai et al., 2003; Oftedal et al., 2009; Penard-Morand et al., 2010; Peters et al., 1999; Sahsuvaroglu et al., 2009; Shima et al., 2010; Zhang et al., 2002) and the incidence of asthma or wheeze was reported in six studies (Clark et al., 2010; Gehring et al., 2010; Gauderman et al., 2005; Linares et al., 2010; Morgenstern et al., 2007; Shima et al., 2010).

The pooled estimates indicated a positive association between higher levels of nitrogen dioxide exposure and higher prevalence (meta-OR: 1.05, 95% CI: 1.00–1.11) and incidence of asthma in children (meta-OR: 1.14, 95% CI: 1.06–1.24) (Figs. 2 and 3). There were also positive association between higher levels of nitrous oxide exposure and higher prevalence of asthma (meta-OR: 1.02, 95% CI: 1.00–1.04).

3.3. Exposure to particulate matters (PMs)

In relation to the exposure to PMs (PM, PM_{2.5}, PM₁₀), the prevalence of asthma or wheeze was examined in 7 studies (Dockery et al., 1996; Hwang et al., 2005; Kim et al., 2004; Penard-Morand et al., 2010; Peters et al., 1999; Shima et al., 2002; Zhang et al., 2002) and the incidence of asthma or wheeze was reported in 6 studies (Clark et al., 2010; Gehring et al., 2002; Gehring et al., 2010; Linares et al., 2010; Morgenstern et al., 2007; Shima et al., 2010). Increased exposure to PMs was positively associated with increased incidence of wheeze (meta-OR: 1.05, 95% CI: 1.04–1.07) (Fig. 3).

3.4. Exposure to carbon monoxide

The prevalence of asthma or wheeze in relation to the exposure to carbon monoxide was examined in 4 studies (Arnedo-Pena et al., 2009; Hirsch et al., 1999; Hwang et al., 2005; Penard-Morand et al., 2010). Carbon monoxide exposure was positively associated with higher prevalence of asthma (meta-OR: 1.06, 95% CI: 1.01–1.12) (Fig. 2).

3.5. Exposure to sulfur dioxide

The prevalence of asthma or wheeze in relation to exposure to sulfur dioxide was evaluated in seven studies (Arnedo-Pena et al., 2009; Dockery et al., 1996; Hirsch et al., 1999; Hwang et al., 2005; Pekhart et al., 2001; Penard-Morand et al., 2010; Zhang et al., 2002). Sulfur dioxide exposure was positively associated with increased prevalence of wheeze (meta-OR: 1.04, 95% CI: 1.01–1.07) (Fig. 2).

3.6. Exposure to ozone

The prevalence of asthma or wheeze in relation to the exposure to ozone was examined in 4 studies (Dockery et al., 1996; Hirsch et al., 1999; Hwang et al., 2005; Peters et al., 1999), which were significantly heterogeneous (Cochran Q test p value=0.07 and I squared=57.1% of variation due to

heterogeneity). The random-effects meta-regression analyses including potential source of heterogeneity (covariates adjusted for, method for measurement of pollutants, method of outcome assessment, range of pollutant concentrations for which odds ratios were reported, and length of follow up in cohort studies) did not identify factors for heterogeneity between ozone and the prevalence of asthma.

4. Discussion

The results of our meta-analysis indicate that exposure to higher levels of nitrogen dioxide, nitrous oxide, carbon monoxide, particulate matter, and sulfur dioxide can increase the risk of asthma and/or wheeze in children. Traffic-related air pollutants have been suggested to promote airway sensitization by modulating the allergenicity of airborne allergens (Anderson et al., 1998; D'Amato et al., 1998, 1991; D'Amato, 2000a, 2000b; Knox, 1993; Celenza et al., 1996; Venables et al., 1997; Devalia et al., 1998). Airway mucosal damages and impairments of the mucociliary clearance functioning induced by pollutants may facilitate the penetration of inhaled allergens leading to a vicious cycle which can lead to wheeze and asthma (Devalia et al., 1998; Rusznak et al., 1996; D'Amato and Liccardi, 1998).

Nitrogen dioxide is generated most often by burning fossil-fuels. Like ozone, nitrogen dioxide is an oxidant pollutant, and exposure to them may “prime” eosinophils to subsequent activation by inhaled allergens in atopic patients (D'Amato et al., 2002). Oxidants increase augment allergic sensitization, asthma and wheeze (Krishna et al., 1998; Shima and Adachi, 2000; De Marco et al., 2002). Nitrogen dioxide is a toxic-free radical gas air pollutant; it is also formed in the lung during inflammation (Gaston et al., 1994), and can worsen asthma, particularly in children (Shima and Adachi, 2000; McConnell et al., 1999; Neas et al., 1991; Strand et al., 1997, 1998). Nitrogen dioxide can augment the degree of allergic airway inflammation and prolong allergen-induced airway hyper-responsiveness as found in rodent models of asthma (Poynter et al., 2006; Gilmour, 1995).

A study by Hussain et al. (2004) showed that short-term exposure to nitrogen dioxide may cause epithelial damage, reduced mucin expression, and increased respiratory smooth muscle tone. A reduction of mucin production may happen due to long-term exposure to nitrogen dioxide. Environmental exposure to nitrogen dioxide may promote allergen sensitization, resulting in allergic airway disease in response to otherwise innocuous inhaled antigens—even when the inhalation of antigen occurs as much as several days following exposure (Bevelander et al., 2007). Whether allergic sensitization takes place even with more time lapse between exposures to the pollutant and to the antigen remains unknown. The murine model of nitrogen dioxide-induced allergic sensitization used by Bevelander et al. (2007) supported a causal role of nitrogen dioxide in the pathogenesis of asthma and provides a powerful tool to further define mechanisms underlying allergic sensitization.

Oxidative stress accompanies inflammatory diseases of the lung and correlates with disease severity. Nitrogen oxides are involved in the tyrosine nitration resulting in nitrotyrosine, which has been associated with functional abnormalities in asthmatic patients, suggesting a role in the pathophysiology of asthma (Saleh et al., 1998; Poynter et al., 2006). Nitrogen dioxide has also been suggested to augment and prolong antigen ovalbumin-induced inflammation and allergic hyper-responsiveness. Therefore, it could be an important mediator of the pathological effects seen in the allergic inflamed lung (Poynter et al., 2006). Also, Modig et al. (2009), using nitrogen dioxide as a marker for vehicle exhaust, found that it may not only worsen asthma symptoms

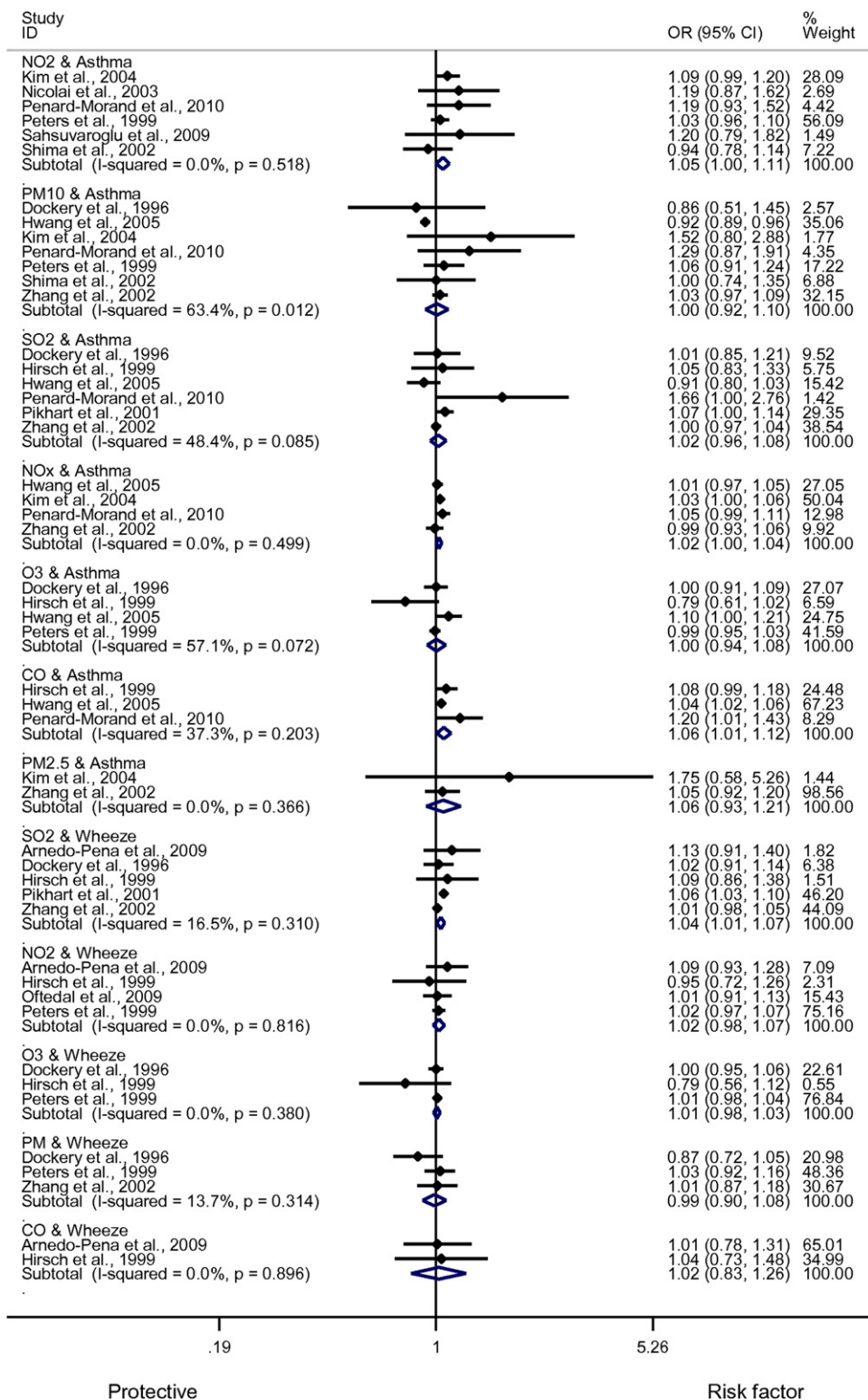


Fig. 2. Forest plot of the association between traffic-related air pollutants and the prevalence of asthma and wheeze using a random effect model. The pooled effect sizes for each exposure were obtained by a weighted average of adjusted odds ratios for a 10 $\mu\text{g}/\text{m}^3$ increase in pollutants. NO, nitrogen oxides; NO₂, nitrogen dioxide; NO_x, nitrous oxide; CO, carbon monoxide; PM_{2.5}, particulate matter with aerodynamic diameter less than 2.5 μm ; PM₁₀, particulate matter with aerodynamic diameter less than 10 μm ; SO₂, sulfur dioxide; O₃, ozone; OR, odds ratio, CI, confidence interval.

but may also induce the disease. Carlsten et al. (2011a, 2011b) demonstrated in a high-risk birth cohort that early co-exposure to dog allergen and nitrogen dioxide (NO₂) or environmental tobacco smoke increased the risk of incident asthma. In this work, modest elevations in exposure to traffic-related air pollutants during the

year of birth were associated with new onset asthma assessed at age 7. The fact that significant associations were revealed in spite of a limited sample size emphasizes the strengths of assessing individual air pollution exposure estimates in a high-risk cohort with well-characterized data on covariates and outcomes.

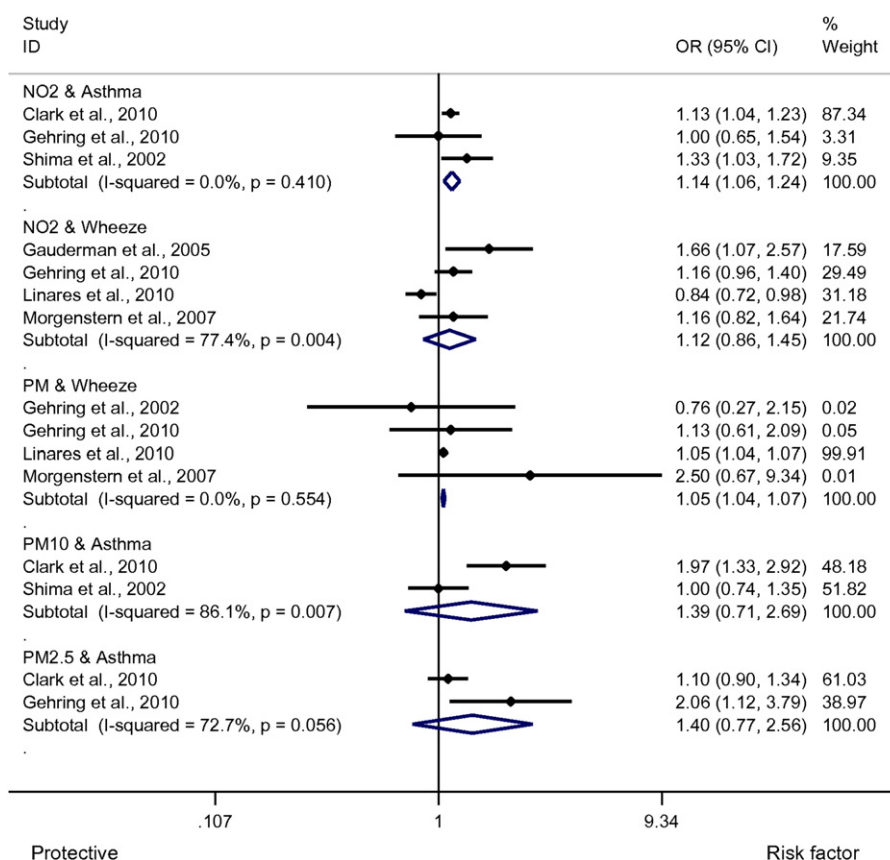


Fig. 3. Forest plot of the association between traffic air pollutants and the incidence of asthma and wheeze using a random effect model. The pooled effect sizes for each exposure were obtained by a weighted average of adjusted odds ratios for a 10 $\mu\text{g}/\text{m}^3$ increase in pollutants. NO, nitrogen oxides; NO₂, nitrogen dioxide; NOx, nitrous oxide; CO, carbon monoxide; PM_{2.5}, particulate matter with aerodynamic diameter less than 2.5 μm ; PM₁₀, particulate matter with aerodynamic diameter less than 10 μm ; SO₂, sulfur dioxide; O₃, ozone; OR, odds ratio, CI, confidence interval.

Sulfur dioxide has clearly been shown to induce acute bronchoconstriction in asthmatic subjects at concentrations well below those required to induce this response in healthy subjects (Sheppard et al., 1980; Linn et al., 1987). Unlike nitrogen dioxide and ozone, the bronchoconstrictive effect due to inhalation of sulfur dioxide in asthmatic individuals occurs after very short exposure periods, especially with oral breathing and high ventilatory rates (Horstman et al., 1986; Balmes et al., 1987). Significant effects can be observed within 2 min and maximal response can be seen within 5 to 10 min. A spontaneous recovery is possible 30 min after challenge with a refractory period of up to four hours. Pharmacological studies seem to suggest a cholinergically mediated neural mechanism (D'Amato et al., 2002).

Increased levels of particulate matters with a diameter less than 10 μm have been directly associated with a dose-dependent elevation of carbon contents in airway macrophages. In turn, increased levels of carbon in airway macrophages were associated with reduced lung function (Kulkarni et al., 2006). In vitro exposure to particulate matters with a diameter less than 10 μm may induce chromatin remodeling by histone acetylation in human lung type II alveolar cells (Gilmour et al., 2003). Diesel exhaust is the main source of particulate matters (Diesel Working Group, 1995; Sydbom et al., 2001; Nauss et al., 1995; Takafuji et al., 1987; Takenaka et al., 1995; Diaz-Sanchez et al., 1996, 1997; Bayram et al., 1998). Chronic exposure to inhaled diesel exhaust particles has been found to induce methylation changes in the interferon gamma gene promoter and the proximal promoter of interleukin 4 genes in CD4⁺ T cells in murine models of asthma sensitized to *A. fumigatus*, leading to changes in immunoglobulin E production and eosinophil counts (Liu et al., 2008).

Human lung parenchyma retains particulate matters with a diameter less than 2.5 μm , while particles with diameters less than 5 μm and less than 10 μm respectively only reach the proximal airways, where they are eliminated by mucociliary clearance if the airway mucosa is intact (Churg and Brauer, 1997; Brain and Valberg 1979; Anderson et al., 1994). Seaton et al. (1995) hypothesized that fine particulate matter found in urban areas are able to induce alveolar inflammation by penetrating deep into airways, which is responsible for release of mediators that induce acute episodes of respiratory and cardiovascular diseases. To explain the acute respiratory effects associated with inhalable particulate matters the same authors suggested that transition metals in the particles damage the airways, thereby generating free radicals. Among these metals, iron has been suggested to generate hydroxyl radicals which may induce adverse respiratory effects (Smith and Aust, 1997; Ghio and Hatch, 1993). Other metals such as chromium, cobalt, copper, manganese, nickel, titanium, vanadium, and zinc have also been associated with radical activation and lung injury in animal studies (Ghio and Hatch, 1993; Donaldson et al., 1997; Costa and Dreher, 1997; Dreher et al., 1997; Costa et al., 1998). Human epithelial cells and macrophages phagocytose diesel exhaust particulates, leading to the production of the inflammatory cytokines interleukin-6, interleukin-8, and granulocyte macrophage-colony stimulating factor (Sydbom et al., 2001; Bayram et al., 1998). Interleukin 8, which is increased in lung and nasal washes of asthmatic and/or rhinitic subjects, activates the chemotaxis of lymphocytes, neutrophils and eosinophils, and causes histamine release, plasma leakage, smooth muscle contraction of airways, and increased airway hyper-responsiveness.

Table 1
Description of individual studies and summary of findings.

Study reference (Reporting quality)	Study design	Age (years)	Participants	Exposure	Exposure assessment	Outcome	Outcome assessment	Covariates adjusted for	Study Finding
Arnedo-Pena et al. (2009) (A)	Cross-sectional	6–7	20,455	SO ₂ , NO ₂ , CO	Air pollution assessed from fixed monitoring sites	Wheezing	ISAAC questionnaire	Sex. Use of antibiotic or paracetamol, parental smoking, cooking gas in home, pets in home, temperature, humidity	Annual average concentration of SO ₂ associated with a higher prevalence of recent severe asthma
Clark et al. (2010) (A)	Cohort	0–4	37,401	NO, NO ₂ , CO, O ₃ , PM, SO ₂	Regulatory monitoring data and LUR modeling	Asthma	Physician billing and hospital discharge records	Parity, breastfeeding, income, parental education, birth weight, gestational length, other traffic pollutants	Traffic-related pollution associated with respiratory infections, asthma and allergy during the first 4 years of life
Dockery et al. (1996) (B)	Cross-sectional	8–12	13,369	PM	Air pollution assessed from fixed monitoring sites	Asthma, wheeze	ISAAC questionnaire	History of allergy, parenteral asthma, parenteral education, smoking	Prevalence of bronchitis associated with particle strong acidity concentrations.
Gehring et al. (2002) (B)	Cohort	0–2	1,756	PM _{2.5} , NO ₂	LUR modeling	Asthma, Wheeze	ISAAC questionnaire	Sex, parental history of atopy (asthma and/or hayfever and/or eczema), parental education, siblings, environmental tobacco smoke	There was some indication of an association between traffic-related air pollution and symptoms of cough.
Gauderman et al. (2005) (B)	Cross-sectional	School age	208	NO ₂	Quality dispersion model based on vehicle emission rates, roadway link geometry, link traffic geometry, meteorologic conditions	Asthma	ISAAC questionnaire	Age, Sex, traffic pollutants	Lifetime history of doctor diagnosed asthma associated with outdoor NO ₂
Gehring et al. (2010) (A)	Cohort	0–8	3,863	NO ₂ , PM _{2.5} , Soot	LUR modeling	Wheeze	ISAAC questionnaire	Sex, parental allergy, parental education, maternal smoking, breastfeeding, gas stove, gas heating, siblings, smoking in home, dampness in home, pets in home, atopy	Exposure to traffic-related air pollution may cause asthma in children
Hirsch et al. (1999) (A)	Cross-sectional	5–11	5,421	SO ₂ , NO ₂ , CO, Benzene, O ₃	Air pollution assessed from fixed monitoring sites	Wheeze, asthma	ISAAC questionnaire	Sex, age, birth weight, parental education, maternal smoking, season, central heating, pets in home, dampness in home, carpet, floor level	A moderate increase in exposure to traffic-related air pollution associated with increased prevalence of cough and bronchitis, but not with atopic conditions in children
Hwang et al., 2010 (A)	Cross-sectional	School age	32,672	NO _x , CO, SO ₂ , PM ₁₀ , O ₃	Air pollution assessed from fixed monitoring sites	Asthma	ISAAC questionnaire	Age, sex, parental education, parental atopy, ETS, visible mold	The prevalence of bronchitic symptoms with asthma was positively associated with the between-community 3-year average concentrations of NO
Kim et al. (2004) (B)	Cross-sectional	School age	1,109	NO _x , NO, NO ₂ , PM _{2.5} , PM ₁₀	Air pollution assessed from fixed monitoring sites	Asthma	ISAAC questionnaire	Respiratory illness before 2, pets in home, mold, maternal asthma	Traffic-related pollution associated with respiratory symptoms in children
Linares et al. (2010) (A)	Cohort	6–14	464	O ₃ , SO ₂ , PM ₁₀ , NO ₂	Air pollution assessed from fixed monitoring sites	Wheezing	ATS questionnaire and forced spirometry	Height, BMI, Sex, age, other pollutants	Students from the school closer to major stationary air pollution sources had in general more respiratory symptoms than those from the distant school. However, in winter air pollution was generalized in this city and differences in health disappeared. PM ₁₀ levels were the most consistent factor related to pulmonary function according, to its change per 3-month period
Morgenstern et al. (2007) (A)	Cohort	0–2	5,991	PM _{2.5} , NO	Air pollution assessed from fixed monitoring sites	Wheeze, Asthma	ISAAC questionnaire	Sex, parental atopy, maternal education, siblings, ETS, cooking gas in home, home dampness, mold, pets	Effects on asthma and hay fever are subject to confirmation at older ages, when these outcomes can be more validly assessed
Nicolai et al. (2003) (B)	Cross-sectional	School age	7,509	Soot, benzene, NO ₂	Modeling using car-traffic counts and weighting function to derive pollutant estimates	Wheeze, Asthma	ISAAC questionnaire	Sex, age, traffic pollutant	High vehicle traffic associated with asthma, cough and wheeze, and in children additionally exposed to environmental tobacco smoke, with allergic sensitization

Ofstedal et al. (2009) (A)	Cohort	9–10	2,871	NO ₂	Combined 3-dimensional Eulerian/Lagrangian dispersion model to estimate concentration of pollutants	Asthma	ISAAC questionnaire	Sex, parental atopy, parental education, maternal smoking during pregnancy.	No positive associations of long-term traffic-related exposures with asthma onset or with current respiratory symptoms in 9- to 10-year-old children in Oslo
Penard-Morand et al. (2010) (A)	Cross-sectional	9–11	6,683	Benzene, PM10, VOC, CO, NOx, NO, NO ₂ , SO ₂	Dispersion model combining data on both regional and local components depending on traffic emissions and local dispersion conditions	Asthma	ISAAC questionnaire	Age, sex, siblings, family atopy, parental education, race/ethnicity, smoking in home, mold, dampness, gas for heating or cooking, pets in home	Urban air pollution was associated with some measures of childhood asthma and allergies
Peters et al. (1999) (A)	Cohort	School age	3,676	O ₃ , PM10, NO ₂	Air pollution assessed from fixed monitoring sites	Asthma, Wheeze	ISAAC questionnaire	Race, parental asthma and atopy, water damage, pets, smoking, cockroaches.	Current levels of ambient air pollution in Southern California may be associated with effects on schoolchildren's respiratory morbidity as assessed by questionnaire
Pikhart et al. (2001) (B)	Cross-sectional	7–10	8,013	SO ₂	Air pollution assessed from fixed monitoring sites	Asthma Wheeze	ISAAC questionnaire	Age, sex, traffic pollutants	In these 2 central european cities, with relatively high levels of air pollutants, small area based indicators of long term outdoor winter concentrations of SO ₂ were associated with wheeze and with asthma diagnosed by the doctor.
Sahsuvarglu et al. (2009) (A)	Cohort	School age	1,467	NO ₂	Exposure to air pollution estimated using a kriged NO ₂ surface based on a network of passive NO ₂ monitors and LUR modeling derived from the same monitoring network	Asthma	ISAAC questionnaire	Household income, dwelling, smoking, rate of home repair	Traffic-related pollutants, such as NO ₂ associated with asthma without overt evidence of other atopic disorders among female children living in a medium sized Canadian city
Shima et al. (2002) (A)	Cohort	School age	3,048	NO ₂ , PM10	Air pollution assessed from fixed monitoring sites	Asthma	ISAAC questionnaire	Sex, history of allergy, respiratory diseases before 2, parental atopy, maternal smoking, heater in winter, other pollutants	Air pollution, including nitrogen dioxide, may be an important factor in the development of asthma among children in urban districts
Zhang et al. (2002) (B)	Cross-sectional	School age	7,621	SO ₂ , NO ₂ , PM2.5	Air pollution assessed from fixed monitoring sites	Asthma,	ISAAC questionnaire	Age, sex, traffic pollutants	Positive associations between morbidity and outdoor levels of PM. Ambient levels of NOx and SO ₂ positively associated with respiratory symptoms, but the evidence for these two gaseous pollutants appeared to be weaker than that for the PM

NO: nitrogen oxides; NO₂: nitrogen dioxide; NOx: nitrous oxide; CO: carbon monoxide; PM2.5: particulate matter with aerodynamic diameter less than 2.5 µm; PM10: particulate matter with aerodynamic diameter less than 10 µm; SO₂: sulphur dioxide; VOC: volatile organic compounds; O₃: ozone. Reporting quality: A, more than 80% of STROBE criteria fulfilled; B, 50–80% of STROBE criteria fulfilled, and C, less than 50% of STROBE criteria fulfilled.

Penard-Morand et al. (2010) showed that associations between asthma and motor vehicle air pollutants are most noticeable among children living in closest proximity to major roads (McConnell et al., 2002; Zmirou et al., 2004; Brauer et al., 2007). In this study, a significant relationship of asthma to sulfur dioxide was found. Results illustrate that individuals living near or attending school in close proximity to areas of high motor vehicle traffic have reduced lung function and increased prevalence of respiratory illness. Populations living within urban areas with increased motor vehicle density are more likely to be exposed to higher levels of these compounds (Kim and American Academy of Pediatrics Committee on Environmental Health, 2004) and have increased incidence of respiratory problem hospitalizations and deaths. The results of a study conducted by Dales et al. (2009) found that the concentration of exhaled nitric oxide, a measure of asthma related airway inflammation, was positively and significantly related to increased roadway density within a 200-meter buffer area around a neighborhood (Dales et al., 2009). Experimental studies indicate that chemicals found in diesel and the toxic auto exhaust mix may actually trigger allergic reactions and aggravate respiratory conditions (Delfino et al., 2009).

There is a lack of consistent epidemiological data available on air pollutants as causal instruments in the development of asthma (Nordling et al., 2008). These inconsistencies may be a result of using different indicators to measure air pollution (Penard-Morand et al., 2010). Brauer et al. (2007) found an association between motor vehicle air pollution and incidence of wheeze and diagnosis of asthma in children aged up to 4 years (Brauer et al., 2007). Delfino et al. (2009) reported that exposure to nitrous oxide and carbon monoxide has a role in exacerbating asthma symptoms, as evidenced by hospital admissions in asthmatic children (Delfino et al., 2009). Penard-Morand et al. (2010) found diesel exhaust to be associated with allergic responses and inflammatory effects. A case control study in France found an association between asthma incidence and early-life exposure to motor vehicle air pollution (Zmirou et al., 2004). In terms of specific pollutions, Jerrett et al. (2008) saw an association between asthma incidence and residential exposure to nitrogen dioxide (Jerrett et al., 2008). According to our results, it is not clear if these pollutants contribute to the onset of asthma. Family history of asthma and childhood allergies are also strong risk factors for developing asthma independent from exposure to air pollution (London et al., 2001; Peden et al., 1995).

This meta-analysis has several limitations. Six of the 16 studies were cross-sectional, thus did not allow assessing temporality between asthma and wheeze and exposure to the pollutants. Exposure was assessed differently in individual studies, using dispersion models or background air pollution. The outcomes asthma or wheeze were reported based on questionnaires and confirmed in only 2 studies which used hospital data (Clark et al., 2010) or performed spirometry (Linares et al., 2009). Combining effect sizes adjusted for different covariates and for different increases in pollutant ranges may have reduced the consistency across studies and reduced the precision of our summary estimates. Most papers reported the odds of wheeze or asthma for an interquartile increase in pollutants. However, Clark et al., 2010, Hirsh et al., 1999, and Linares et al., 2009 presented results for a 10 µg/m³ increase in nitrogen oxides, ozone, sulfur dioxide while Sahsuvaroglu et al. (2009) and Shima et al. (2002) presented results for a unit increment. Articles included in the meta-analysis were published in English and may not be representative of all studies on wheeze, asthma, and exposure to traffic air pollutants Table 1.

In summary, this meta-analysis shows an association between several traffic-related air pollutants and the incidence and

prevalence of asthma and wheeze in children living or attending school in close proximity to areas of high motor-vehicle traffic. These findings underscore the need for more comprehensive air quality policies in order to protect sensitive populations, and the importance of continuously revising existing regulations in light of new findings from recent studies.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.envres.2012.05.001>.

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Appendix 1 -

In Medline ("Traffic"[Journal] OR "traffic"[All Fields]) AND ("asthma"[MeSH Terms] OR "asthma"[All Fields]) AND ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields]) using the key words traffic, asthma, children. Traffic-related[All Fields] AND ("asthma"[MeSH Terms] OR "asthma"[All Fields]) AND ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields]) using key words traffic – related asthma, children. ("Traffic"[Journal] OR "traffic"[All Fields]) AND pollution[All Fields] AND ("asthma"[MeSH Terms] OR "asthma"[All Fields]) AND ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields]) using key words traffic pollution asthma, children. ("carbon monoxide"[MeSH Terms] OR ("carbon"[All Fields] AND "monoxide"[All Fields]) OR "carbon monoxide"[All Fields]) AND ("asthma"[MeSH Terms] OR "asthma"[All Fields]) AND ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields]) using key words carbon monoxide, asthma, children. ("oxides"[MeSH Terms] OR "oxides"[All Fields] OR "oxide"[All Fields]) AND ("asthma"[MeSH Terms] OR "asthma"[All Fields]) AND ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields]) using key words oxide, asthma, children. ("particulate matter"[MeSH Terms] OR ("particulate"[All Fields] AND "matter"[All Fields]) OR "particulate matter"[All Fields]) AND ("asthma"[MeSH Terms] OR "asthma"[All Fields]) AND ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields]) using key words particulate matter, asthma, children. ("ozone"[MeSH Terms] OR "ozone"[All Fields]) AND ("asthma"[MeSH Terms] OR "asthma"[All Fields]) AND ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields]) using the key words ozone, asthma, children. sulfurdioxide[All Fields] AND ("asthma"[MeSH Terms] OR "asthma"[All Fields]) AND ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields]) using the key words sulfur dioxide, asthma and children.

In Highwire: “traffic* asthma* child*(all words in title or abstract) and traffic- related asthma* child* (all words in title or abstract)”, “traffic pollution* asthma* child*(all words in title or abstract) and carbon monoxide* asthma* child (all words in title or abstract)”, oxide* asthma* child* (all words in title or abstract) particulate matter* asthma * child*(all words in title or abstract), “ ozone* asthma * child* (all words in title or abstract) sulfur dioxide* asthma * child*(all words in title or abstract)”

In Cochrane Library: “traffic related asthma* child* (Title, Abstract, or key words)” and “children” (Title, Abstract, or Keywords)”, “traffic pollution* asthma * child* (Title, Abstract, or key words)” and “carbon monoxide* asthma * child* (Title, Abstract or key words), “oxide* asthma* child* (Title, Abstract, or key words)” and “sulfur dioxide* asthma * child*(Title, Abstract or Key words)