

Air Pollution and Health Effects in Children

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1. Introduction

Asthma, which is characterized by reversible airway obstruction and inflammation, is the most frequent chronic disease in children. Recent global studies showed, although the rising trends in occurrence of allergic diseases in children appear to have leveled off or even reversed in many developed countries, while in many developing countries, the increase in prevalence has only recently started (Asher et al. 2006; Bjorksten et al. 2008; Pearce et al. 2007). These findings indicate that the global burden of asthma is continuing to be rising with the global prevalence differences lessening (Pearce et al. 2007). It has been suggested that this increase can not be explained by genetic factors and improvements in diagnostic methods alone. Comparative studies of the population of the same ethnic background living in different environments revealed important environmental risk factors for asthma, especially for ambient air pollution, which may play an important role in the development of asthma symptoms (Asher et al. 2010; Berhane et al. 2011; Samoli et al. 2011; McConnell et al. 2010). A systematic review concluded that, although weather, pollen, and environmental tobacco smoke (ETS) are important risk factors for asthma, each has been found to act independently of air pollution, and thus they do not explain the association between air pollution and asthma (Leikauf 2002).

Comparing with the adults, children appear to be most vulnerable to the harmful effects of air pollutants exposure due to their stage of physical growth, immature immune system, and development of lung function with increased permeability of the respiratory epithelium (Dietert et al. 2000). Children also inhale a higher volume of air per body weight compared with adults (Oyana and Rivers 2005), delivering higher doses of different compositions that may remain in the lung for a longer duration (Bateson and Schwartz 2008). Another source of increased sensitivity of children to air pollution may be the qualitative and quantitative differences in the respiratory, immune, endocrine, and nervous systems during stages of rapid growth and development (Selgrade et al. 2006). Although epidemiologic studies have shown associations between asthma outcomes and routinely monitored air pollutants including particulate matter (PM), sulfur dioxide (SO₂), nitrogen oxides (NO₂) and ozone (O₃), the contribution of ambient air pollution exposure to children's asthma seems to vary

in different parts of the world, perhaps because of the difference in spatial and temporal variability of air pollutants sources and composition between different regions (Kim et al. 2005; Kim et al. 2008; Levy et al. 2010), and also, it still remains unclear whether the association of the pollutants with increased asthma prevalence in children is independent of each other or is attributable to other toxic air pollutants, such as combustion-related organic compounds that are not routinely monitored (Delfino et al. 2006).

The purpose of this chapter is to review/summarize the evidence regarding the link between air pollution and children's asthma and asthma related symptoms. We would like to discuss gender difference for air pollution effects, as well as some other health effect susceptibilities, such as age, genetic predisposition, and disease susceptibility. Finally, the potential health effects from preventive strategies for air pollution would be also proposed.

2. Air pollution and asthma in children

2.1 Particulate Matter (PM)

Numerous studies worldwide have reported the associations between particulate matter (PM) and asthma outcomes (Berhane et al. 2011; McConnell et al. 2010; Özkaynak et al. 1987; Pope 1991; Samoli et al. 2011; Spira-Cohen et al. 2011), and most of those studies focused on fine particulate matter $< 2.5 \mu\text{m}$ in average aerodynamic diameter ($\text{PM}_{2.5}$) and thoracic particulate matter $< 10 \mu\text{m}$ in average aerodynamic diameter (PM_{10}) that dominate concentrations of fine particles in most urban areas. The health effects of the different particle sizes may differ between various areas as a result of variation in particle origin, chemical composition and biogenic content. The distinction of health effects between the fine and coarse fractions is important to define because these particles may arise from different sources (Kim et al. 2005; Kim et al. 2008; Levy et al. 2010). The coarse fraction of relatively large inhalable particles, ranging from 2.5 to $10 \mu\text{m}$ in average aerodynamic diameter ($\text{PM}_{10-2.5}$), generally consists of particles which are mainly derived from re-entrained road dust (containing soil particles, engine oil, metals, tire particles, sulfates and nitrates), construction and wind-blown dusts (mostly soil particles), and mechanical wear processes. The chemical signatures of $\text{PM}_{2.5}$ contains a mixture of particles including carbonaceous material like soot (with possibly adsorbed reactive metals and organic compounds), and secondary aerosols like acid condensates, and sulphate and nitrate particles, and is derived direct or indirect primarily from combustion of fossil fuels used in power generation, and industry, and automobile, and ultrafine particles produced by traffic, coal combustion, and metal, oil, and chemical manufacturing. This fine-mode fraction has the largest surface area and contributes also to the total particle mass concentration (Bree and Cassee 2000; Özkaynak et al. 1987; Pope 1991). Based on the previous epidemiologic studies, it was believed that $\text{PM}_{2.5}$ fraction of PM_{10} had stronger effects than the $\text{PM}_{10-2.5}$ fraction (Dreher 1996; Schwartz and Neas 2000; Tzivian 2011). However, recent analyses are somewhat more ambiguous, and inconsistent results have been reported on the association between the coarse particle fraction and asthma outcomes. Several studies compared the effects of $\text{PM}_{10-2.5}$, $\text{PM}_{2.5}$, and PM_{10} on hospitalizations of children for asthma (Dreher et al. 1996; Lin et al. 2002; Schwartz and Neas 2000; Strickland et al. 2010).

A study conducted in 41 Metropolitan Atlanta hospitals indicated that the emergency department visits for asthma or wheeze among children was significantly associated only with $\text{PM}_{2.5}$ in cold season, however, only with PM_{10} and $\text{PM}_{10-2.5}$ in warm season (Strickland

et al. 2010). Lin et al. (2002) found an effect for $PM_{10-2.5}$ but not for $PM_{2.5}$ and PM_{10} after adjustment for daily weather conditions. The study in Toronto also found the $PM_{10-2.5}$ fraction to be a better predictor of asthma admissions than the $PM_{2.5}$ and PM_{10} fractions in subjects of all ages. The estimated relative risks for $PM_{10-2.5}$, $PM_{2.5}$, and PM_{10} corresponding to an increase of $10 \mu\text{g}/\text{m}^3$ with a 3-day averaging were 1.04, 1.01, and 1.01, respectively (Burnett et al. 1999). Whereas, Tecer et al. (2008) found that $PM_{2.5}$ had larger effects than did $PM_{10-2.5}$, despite that both were significantly associated with hospitalizations for asthma after adjustment for daily weather conditions. Also, a recent study found strong adverse effects of exposure to PM_{10} on emergency hospital admissions for asthma-related diagnosis among children, although analyses for $PM_{10-2.5}$ and $PM_{2.5}$ were not evaluated (Samoli et al. 2011). Besides the emergency hospital admissions for asthma mentioned above, the health effects of the different particle sizes on other asthma outcomes are also inconsistent. In the FACES cohort study of asthmatic children conducted in California of USA, wheeze was associated significantly with $PM_{10-2.5}$ but not with $PM_{2.5}$ (Mann et al. 2010). However, the results from France study conflict in this regard, no association between wheeze episodes or prevalence and $PM < 13 \mu\text{m}$ in aerodynamic diameter or black smoke in either the winter time or warm seasons among asthmatic children residing in Paris (Just et al. 2002). Results from a cohort study of school children showed that both $PM_{2.5}$ and PM_{10} were significantly associated with airway inflammation independent of asthma and allergy status, with PM_{10} effects significantly higher in the warm season, however, for the exhaled nitric oxide fraction (FeNO), the marker of important aspects of airway inflammation, the effects of $PM_{2.5}$ was higher than that of PM_{10} (Berhane et al. 2011). However, the pathophysiologic mechanism by which particles exert their health effects has not been well established. Reasons may include: (a) Variability in population characteristics and natural systems; Because populations differ markedly with respect to age, underlying health, and concomitant exposure to other insults, it is also reasonable to anticipate that different populations exposed to air pollution in different places may show a range of distinct responses. (b) Variability in the complex mixture of fine particles with a different level and composition over time and space.

Air pollution is a complex mixture whose level and composition varies over time and space according to a large number of factors ranging in scale from personal microenvironments to regional climate. Such differences in the nature of air pollution are among the possible explanations for the divergent findings about differ size of particles. For example, studies on mice and human airway cells have found that, compared with particles from wood smoke or car exhaust, particles from diesel exhaust have higher capacity to induce proallergenic Th2 cytokine production, increased major histocompatibility complex class II expression, and increased inflammatory cell proliferation (Porter et al. 2007; Samuelsen et al. 2008). Studies have also examined the relative effects of organic and inorganic fractions of particulate matter but have yielded conflicting results. In one, exposure of mice to the carbon core fraction of diesel exhaust particles (DEP) stimulated greater airway hyper-reactivity compared with the organic fraction (Inoue et al. 2007). In another, both organic and elemental carbon fractions of fine and ultrafine ambient particles were capable of stimulating proinflammatory allergic immune responses, as measured by increased secretion of Th2 cytokines and increased infiltration of eosinophils and polymorphonuclear leukocytes (Kleinman et al. 2007). The U.S. Environmental Protection Agency (EPA) has noted that $PM_{10-2.5}$ deposited in the upper airways may be more relevant for asthmatic responses and irritation (U.S. EPA 1995). Whereas, lower respiratory symptoms including respiratory infection may be the results of effects in the deep lung related to deposition of

PM_{2.5} (Loomis 2000). While investigation of the health effects of particulate matter should continue, it would be unwise to focus too narrowly to the exclusion of other components of air pollution. The preoccupation with the smallest particles may be due in part to the tendency to look where the light is: although most researchers live in North America and western Europe and most previous studies on the health effects of air pollution have been conducted in those areas, many of the world's largest cities and much of the population currently exposed to high levels of air pollution are located in developing countries. For public health purposes, it is clearly important to examine the health effects of air pollution in these areas. Research in these settings may also yield far-reaching scientific benefits by allowing the effects of air pollution to be understood in a context more representative of the world's climate and health.

2.2 Sulfur dioxide (SO₂)

Sulfur dioxide (SO₂), which is commonly from combustion of fuel containing sulfur—mostly coal and oil, metal smelting, and other industrial process, is a highly water soluble irritant gas and is rapidly taken up in the nasal passages during normal, quiet breathing. Studies in human volunteers found that, after inhalation at rest of an average of 16 ppm SO₂, less than 1% of the gas could be detected at the oropharynx (Speizer and Frank 1966). Penetration to the lungs is greater during mouth breathing than nose breathing, and also is greater with increased ventilation such as during exercise (Costa and Amdur 1996). Since individuals with allergic rhinitis and asthma often experience nasal congestion, mouth breathing is practiced at a greater frequency in these individuals perhaps making them more vulnerable to the effects of water soluble gasses such as SO₂ (Ung et al. 1990). Despite the potential for high-level SO₂ exposures to cause adverse health effects is well recognized, epidemiologic studies of children have not demonstrated convincing evidence that ambient SO₂ exposure at typical current levels are associated with asthma outcomes, even the results from the same nationality's children were also inconsistent. Four Chinese Cities study performed in 1997 did not present any associations between outdoor SO₂ exposure and asthma or asthma related symptoms (Zhang et al. 2002); also, Zhao et al. authors reported that indoor SO₂, but not outdoor SO₂, was a risk factor for wheeze, daytime breathlessness in Chinese children (Zhao et al. 2008). However, the results from the Northeast Chinese Children Health study present some evidence that ambient levels of SO₂ were positively associated with children's asthma outcomes (Dong et al. 2011). Multi-pollutant regression analyses indicated that SO₂ risk estimates for asthma outcomes were not sensitive to the inclusion of co-pollutants, including PM, NO₂, O₃ and CO, and concluded that the observed health associations for SO₂ might be attributed partly to co-pollutants, with a focus on PM and NO₂ as these pollutants tend to be moderately to highly correlated with SO₂ and have known respiratory health effects (U.S. EPA 2008). Although the studies show that co-pollutant adjustment had varying degrees of influence on the SO₂ effect estimates, among the studies with tighter confidence intervals (an indicator of study power), the effect of SO₂ on respiratory health outcomes appears to be generally robust and independent of the effects of ambient particles or other gaseous co-pollutants.

In spite of all the research investigating the relationship between SO₂ exposure and responses in individuals with asthma, the mechanism of the SO₂ response is still not very clear. SO₂ may act as an aspecific bronchoconstrictor agent, similar to inhaled histamine or methacholine: the rapid onset of bronchoconstriction after exposure suggests a neural

mechanism of action for SO₂ in asthma, but airway inflammation may result from short-term SO₂ exposure (U.S. 1998). Results from the animal studies indicated that SO₂-induced bronchoconstriction was mediated by the activation of a muscarinic (cholinergic) reflex via the vagus nerves (part of the parasympathetic branch of the autonomic nervous system (Nadel et al. 1965); However, there is some evidence from studies of human asthmatics for the existence of both muscarinic and nonmuscarinic components (Sheppard 1988), with the nonmuscarinic component possibly involving an effect of sulfur dioxide on airway mast cells. Also, injection of atropine, which counteracts the effects of the parasympathetic nervous system, prevented the increase in airway resistance and increased airway conductance in healthy subjects exposed to SO₂ but had no effect on asthmatics (Nadel et al. 1965; Snashall and Baldwin 1982). In conclusion, sulfur dioxide-induced bronchoconstriction and respiratory inhibition appear to be mediated through vagal reflexes by both cholinergic and non-cholinergic mechanisms. Non-cholinergic components include but are not limited to tachykinins, leukotrienes, and prostaglandins. The extent to which cholinergic or non-cholinergic mechanisms contribute to sulfur dioxide-induced effects is not known and may vary between asthmatic and healthy individuals and between animal species (U.S. 1998). So, the mechanism of why SO₂ elicits such a dramatic effect on the bronchial airways of subjects with asthma is still needed further study.

2.3 Nitrogen oxides (NOx)

Nitrogen oxides (NOx), a mixture of nitric oxide (NO) and nitrogen dioxide (NO₂), are produced from natural sources, motor vehicles and other fuel combustion processes. NO is colourless and odourless and is oxidised in the atmosphere to form NO₂ which is an odourous, brown, acidic, highly-corrosive gas. NO₂ are critical components of photochemical smog and produces the yellowish-brown colour of the smog. In urban areas, most of NO₂ in the ambient air arises from oxidization of emitted NOx from combustion mainly from motor engines, and it is considered to be a good marker of traffic-related air pollution.

Many epidemiological studies have reported associations between NOx, NO, NO₂ and asthma outcomes. Nordling et al. (2008) prospectively followed children in Stockholm, Sweden, from birth until 4 years of age and found that exposure to traffic-related air pollution during the first year of life was associated with an excess risk of persistent wheezing of 1.60 (95% confidence interval, 1.09–2.36) for a 44-µg/m³ increase in traffic NOx. Brauer et al. used LUR models to estimate the effect of traffic-derived pollutants on asthma incidence among 4-year-old children in the Netherlands and found odds ratios (ORs) of 1.20 per 10-µg/m³ increase in NO₂ (Brauer et al. 2007). Also, a population-based nested case-control study in southwestern British Columbia indicated, comparing with the industrial-related pollutants (PM₁₀, SO₂, black carbon), traffic-related pollutants were associated with the highest risks for asthma diagnosis: adjusted OR=1.08 (95%CI, 1.04-1.12) for a 10-µg/m³ increase of NO, and 1.12 (95%CI, 1.07-1.17) for a 10-µg/m³ increase in NO₂ (Clark et al. 2010). However, epidemiological evidence about these associations is still inconsistent. Four Chinese Cities study did not find any associations between NOx and asthma outcomes (Zhang et al. 2002); No statistically significant NO₂ effect on asthma exacerbation was provided in the study from Greece (Samoli et al. 2011). This inconsistency may be partly due to methodological problems, confounding or effect modification by other pollutants, and a lack of prospective data. To some extent, this inconsistency in epidemiological studies also relates to the differences between the groups of people who have been studied. Despite

methodological differences, a systematic review of the health effects caused by environmental NO₂ reported that there was moderate evidence that short-term exposure (24 hours) even for mean values below 50µgm³ NO₂ increased both hospital admissions and mortality. The review also reported that there was moderate evidence that long-term exposure to a NO₂ level below the World Health Organization recommended air quality annual mean guideline of 40µgm³ was associated with adverse health effects including asthma outcomes (Latza et al. 2009).

In addition to the role of exogenous NO_x on the development of asthma, the endogenous production of NO_x is also associated with the respiratory viral infection in childhood (Everard 2006). Therefore, understanding the mechanisms by which NO_x exposure contributes to allergic asthma has important global public health implications. Animal studies have demonstrated that exposure to NO₂ caused epithelial damage, reduced mucin expression, and increased tone of respiratory smooth muscle (Hussain et al. 2004). A mouse model study showed that NO₂ exposure can promote allergic sensitization and cellular damage which induces the elaboration of immunostimulatory molecules by activating TLR2 that can induce Th2 immune responses and promote experimental asthma (Bevelander et al. 2007). Morrow PE concluded that NO₂ exposure can lead to an increased inflammatory cell influx and may affect lung defense mechanisms through reduced mucociliary clearance and changes in alveolar macrophages and other immune cells (Morrow 1984). Clinical experimental studies showed that prolonged NO_x exposure induces the generation of mediators such as LTC₄ and influx of pro-inflammatory ILs (GM-CSF, TNF-α and IL-8) in the respiratory tract, with significant differences between cells produced by atopic and nonatopic subjects; In vivo exposure to NO₂ provokes BHR in exposed subjects, notably the asthmatic, with differences between exposure and symptoms of 24h for NO and of 7 days for NO₂ and increase in lymphocytes, macrophages and mast cells of BALF (Devalia et al. 1994). Whereas, contrary to the above results, a study in asthmatic subjects showed that multi-hour exposure to a high ambient concentration of NO₂ does not enhance the inflammatory response to subsequent inhaled allergen as assessed by cell distribution in induced sputum (Witten et al. 2005). So, the mechanism about NO₂-induced allergic sensitization will require future study.

2.4 Ozone (O₃)

Ozone (O₃) is a highly reactive gas that results primarily from the action of sunlight on hydrocarbons and NO_x emitted in fuel combustion. Since ozone can provoke both airway hyperreactivity and “prime” epithelial inflammatory responses, it is a likely contributor to the overall burden of asthma (Auten and Foster 2011). Despite the role of O₃ exposure in the initiation of asthma pathophysiology is controversial, it certainly acts as an exacerbating factor and chronic exposure may have durable effects on susceptibility to airway hyperreactivity. Epidemiologic and clinical studies have shown that O₃ exposure is associated with worsening of athletic performance, reductions in lung function, shortness of breath, chest pain with deep inhalation, wheezing and coughing, and asthma exacerbations among those with asthma. A cohort study performed in Mexico City, Mexico, and with a follow-up period of 22 weeks demonstrated that children living in urban high-traffic areas had a greater daily incidence of respiratory symptoms and bronchodilator use, however, in the case of co-pollutant models, only the O₃ effect continued to be significant in regard to

symptoms and medication use (Escamilla-Nunes et al. 2008). Silverman and Ito (2010) had investigated the relationship between severe asthma mortality and ozone in 74 New York City hospitals from 1999 to 2006, and found each 22-ppb increase in O₃, there was a 19% (95% CI, 1% to 40%) increased risk for intensive care unit (ICU) admissions and a 20% (95% CI, 11% to 29%) increased risk for general hospitalizations, especially for children age 6 to 18 years who consistently had the highest risk. In one recent study of the short-term associations between ambient air pollutants and pediatric asthma emergency department visits, Strickland et al. (2010) analyzed the daily counts of emergency department visits for asthma or wheeze among children aged 5 to 17 years that were collected from 41 Metropolitan Atlanta hospitals during 1993-2004 (n = 91,386 visits), and the results showed, even at relatively low ambient concentrations, ozone and primary pollutants from traffic sources independently contributed to the burden of emergency department visits for pediatric asthma. One important cohort study suggests that long-term O₃ exposure can increase the chances that children will have asthma. Although acute exposure to O₃ and other outdoor air pollutants clearly exacerbates asthma acutely, the chronic effects of air pollution have been less studied, and air pollution is not generally thought to induce new cases of asthma. However, children exercising outside receive greater doses of outdoor pollutants to the lung than those who do not and thus would be more susceptible to any chronic effects of air pollution. The California Children's Health Study carefully tested the hypothesis that air pollution can cause asthma by investigating the relation between newly diagnosed asthma and team sports in a cohort of children exposed to different concentrations of air pollutants. The relative risk of asthma development in children playing 3 or more sports in the 6 more polluted communities was 3.3 (95% CI, 1.9-5.8) compared with children in these areas playing no sports. Sports had no effect in areas of low O₃ concentration areas (relative risk, 0.8; 95% CI, 0.4-1.6), but time spent outside was associated with a higher incidence of asthma in areas of high O₃ (relative risk, 1.4; 95% CI, 1.0-2.1). Exposure to pollutants other than O₃ did not alter the effect of team sports (McConnell et al. 2002). This study needs to be replicated elsewhere, but it does suggest that higher long-term exposure to air pollution might well cause the induction of asthma.

Despite, the effects of O₃ on innate and adaptive immunologic pathways relevant to human asthma is not yet clear, but the relevance has been observed in animal models. Animal models showed that O₃ exposure has the capacity to affect multiple aspects of the "effector arc" of airway hyperresponsiveness, ranging from initial epithelial damage and neural excitation to neural reprogramming during infancy (Auten and Foster 2011). Exposed to O₃ enhanced responsiveness of airway sensory nerves in rat on specific postnatal days (PDs) between PD1 and PD29 (Hunter et al. 2010). The best evidence from non-human primates suggests that eventual development of asthma in children may also be attributable in part to remodeling of afferent airway nerves and subtle effects on airway structure and function (Auten and Foster 2011). These changes may have implications for lifelong vulnerability to other oxidative and allergic challenges that produce clinical asthma.

3. Air pollution and lung function in children

Lung function as a sensitive marker of respiratory health effects of the lower airway has been documented in previous studies (Anonymous. 1996a; Anonymous. 1996b). Most major pollutants can alter lung function in addition to other health effects when the exposure

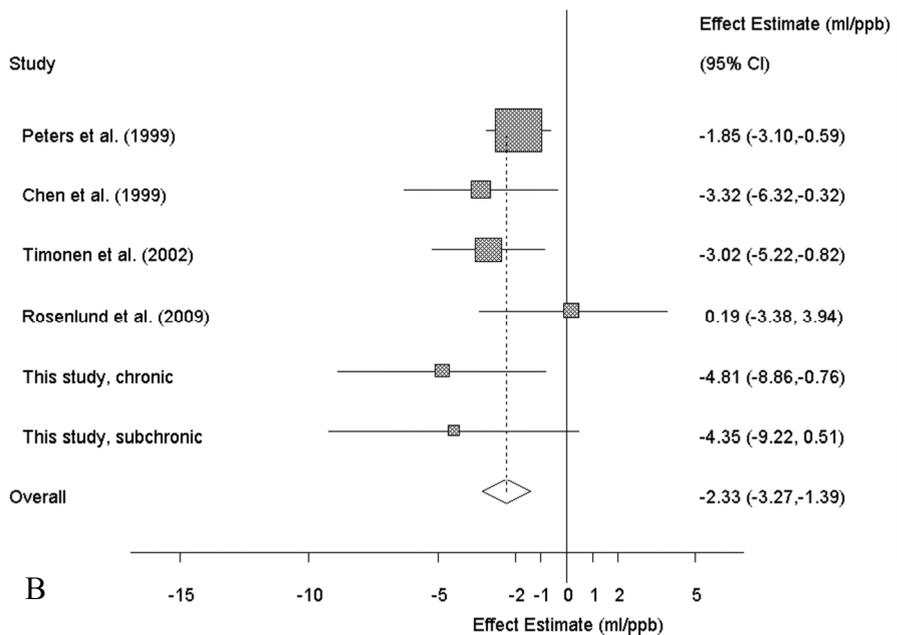
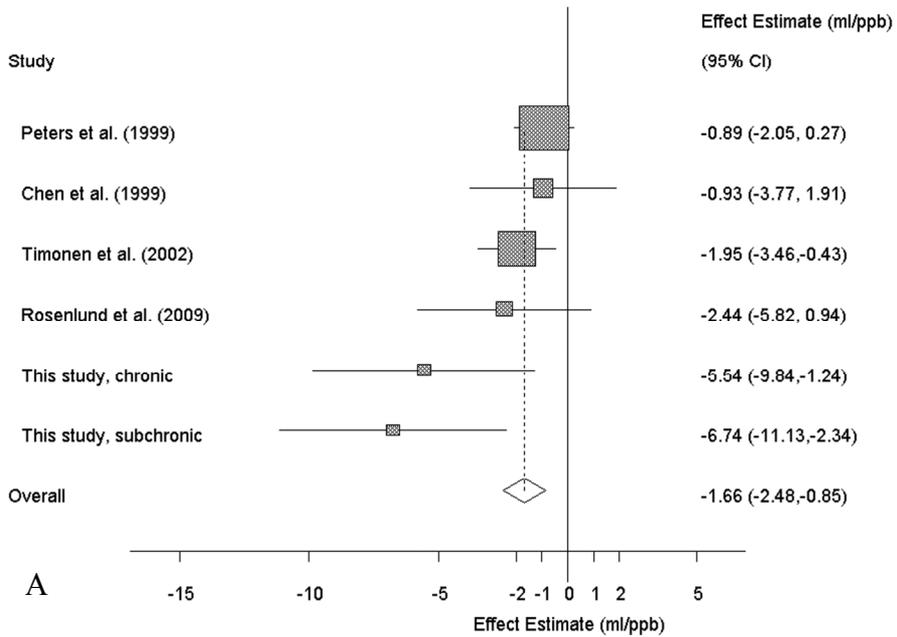
concentrations are high. However, some studies have indicated no association between ambient air pollution and lung function, especially in ambient low-dose exposure (Dockery et al. 1989; Anonymous. 1995).

Recently, our population-based epidemiologic study in Taiwanese communities was published to show that traffic-related pollutants CO, NO_x, NO₂, and NO had chronic harmful effects on lung function in children (Lee et al.). Deficits in lung function indices were not significantly related to the ambient levels of O₃, SO₂, PM_{2.5}, and PM₁₀. After adjustment for individual-level confounders, lung function differed only slightly between communities with different levels of air pollution. Our findings indicated that chronic exposure to ambient NO_x and CO significantly decreases lung function in children. These findings are in concordance with several previous epidemiologic studies concerning chronic effects of ambient air pollution from Italy (Rosenlund et al. 2009), Finland (Timonen et al. 2002), and California (Peters et al. 1999b). In present data, we found consistent effects of NO_x and CO on FVC and FEV1 that represent central airways, whereas the effects on MMEF and PEFr that provide information primarily on damage of the peripheral airways was more limited. Outdoor NO₂ is strongly influenced by local traffic density (Jerrett et al. 2005). Another recent cohort study from California revealed an adverse effect of prenatal exposure to NO₂ and CO on lung function in asthmatic children (Mortimer et al. 2008).

Chronic airway inflammation could produce the decreases in lung function indices and the central airways seem to be mainly affected given the stronger signal that we detected for FVC in the present study. Plausible mechanisms of NO₂ pulmonary toxicity have been well described (Persinger et al. 2002) and may contribute to part of our findings. However, in human exposure studies, adverse pulmonary effects of NO₂ have generally been demonstrated at levels of exposure a magnitude higher than reported here (Kraft et al. 2005). The above experimental results contrast recent epidemiologic findings showing associations of asthma outcomes in children with low levels of indoor NO₂ (Belanger et al. 2006), of personal NO₂ (Chauhan et al. 2003), and of ambient NO₂. The low ambient NO₂ levels we found are more likely to have served as a surrogate for traffic-related air pollutants. Although it is difficult to discuss etiological mechanisms in our cross-sectional design, we believe these pollutants may be causally related to lung function through oxidative stress responses induced by pollutants highly correlated with NO₂ (Seaton et al. 2003; Li et al. 2003). A previous study of Californian children has showed that the acute effect of ambient NO₂ was about -0.4 ml/ppb in contrast to the chronic effect of -1.7 ml/ppb on morning FVC measurements (Linn et al. 1996). Our data also indicated that the chronic effect of NO₂ (-4.81 ml/ppb) was slightly larger than subchronic effect (-4.35 ml/ppb) on FVC. However, subchronic effects of NO₂ were significantly greater than chronic effects on MMEF and PEFr. Comparison of pollutants concentrations between studies is difficult because of differences in the atmospheres and in the measurement techniques.

We further conduct meta-analyses for the present and other available studies of ambient NO₂ effects on lung function indices in children. We accepted a priori all studies with individual as the unit of observation. The fixed-effects models were calculated using the Mantel-Haenszel method with inverse variances of individual effect estimates as weights. We also studied heterogeneity of the study-specific effect estimates by plotting the measures of effect and applying Q-statistics. Meta-analyses were undertaken of previously published studies together with the data from the present study of ambient NO₂ exposure. As shown in Figure 1, the pooled estimates for four lung indices provided consistent evidence of significantly adverse

effects. We also elaborated the heterogeneity between the specific estimates by study design and year, but none showed significant Q-statistics. Therefore, only fixed-effect models were systemically used to present pooled effect estimates (Figure 1).



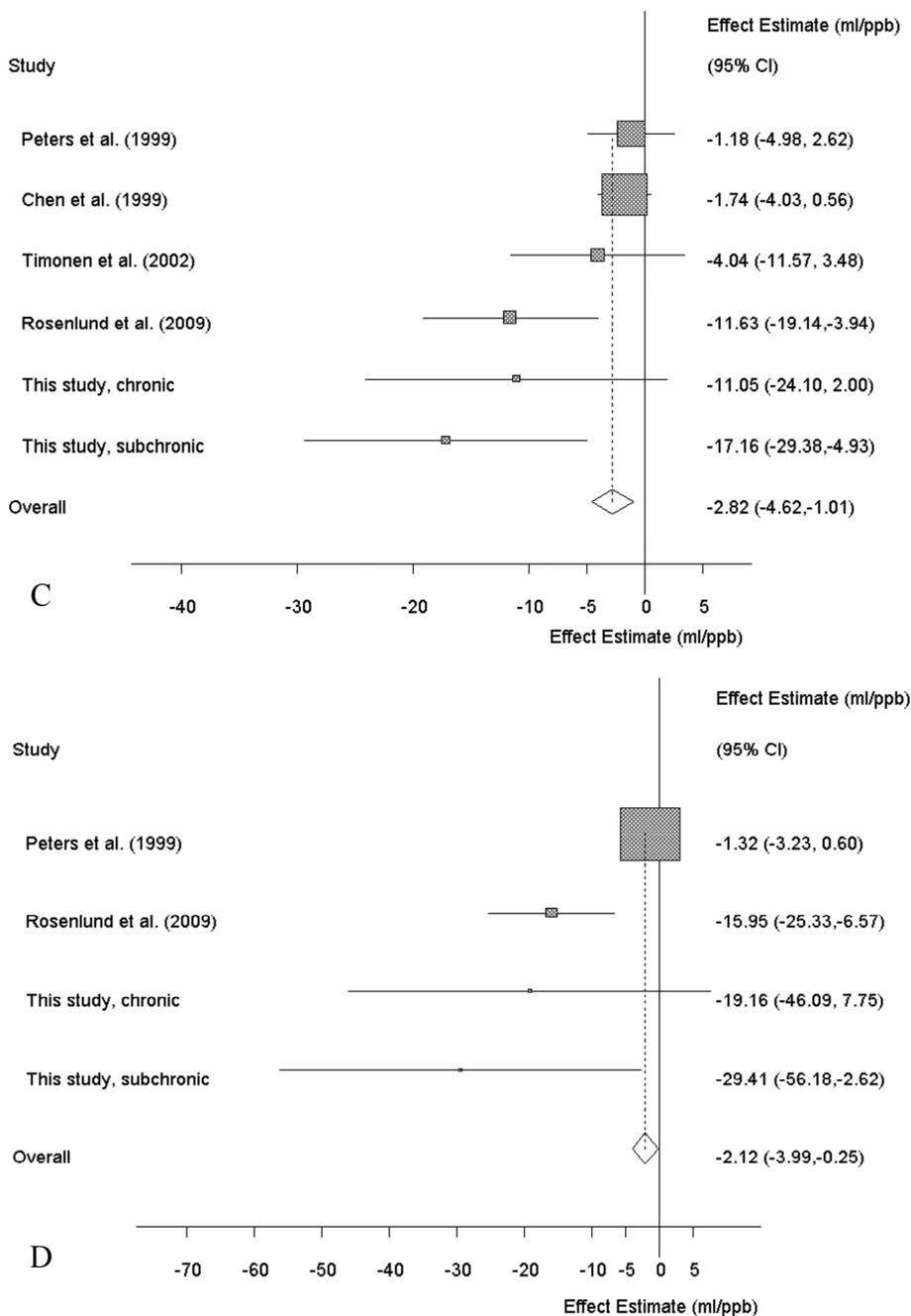


Fig. 1. Meta-analyses of ambient NO₂ effects on lung function in children. (A) FVC (B) FEV₁ (C) MMEF (D) PEF.

4. Gender difference for the air pollution effects in children

Despite the literature is far from consistent, there is growing epidemiological evidence of the differing associations between air pollution and respiratory health for males and females (Clougherty 2010; Keitt et al. 2004). Generally, many investigations were focused on the differences of gender or sex, however, there is also the distinction between definition of gender and sex (Clougherty 2010). As a social construct, Krieger et al. (2003) had expatiated that gender includes cultural norms, roles, and behaviors shaped by relations among women and men and among girls and boys; however, sex, a biological construct, is based on physiologic differences enabling reproduction, defined by physiologic characteristics (especially reproductive organs) or chromosomal complement. Also, Clougherty et al. (2010) have given recently a summary account that gender, inherently social, varies continuously over multiple dimensions over the life course, whereas sex is normally dichotomous. Gender is shaped at the societal level and varies across nation, culture, class, race, ethnicity, nationality, sexuality, and religion. Gender describes patterns of behavior, place, and role, determining where people spend time and their activities, thereby shaping exposure distributions. Sex-linked traits (e.g., hormonal status, body size) influence biological transport of environmentally derived chemicals (Clougherty 2010).

The gender analyses are more common in occupational epidemiology than in environmental health, because persistent job stratification by gender has produced marked differences in occupational exposures to chemical agents, ergonomic demands, injury, and psychosocial stressors (Clougherty 2010). Compared with the studies among adults, disentangling gender effects in air pollution-health associations among children may be more complicated, because lung function growth rates (critical periods for pollution effects) differ by sex (Berhane et al. 2000). Most air pollution epidemiology studies among children examine chronic exposures, although outcomes considered vary widely, including lung function growth, wheeze, asthma onset and exacerbation, and symptoms.

It has been reported elsewhere that boys were more susceptible than girls to the effects of environmental factors including the effects of ambient air pollution. A 10-yr prospective cohort study of Southern California children in grade 4, 7 and 10 indicated that, based on the 1986–1990 exposure data, prevalence of wheeze was associated with exposure to NO₂ (OR=1.48; 95% CI: 1.08–2.02) and acid (OR=1.55; 95% CI: 1.09–2.21) in males only; also, based on the 1994 exposure measurements, again see a positive association of NO₂ (OR=1.54; 95% CI: 1.08–2.19) and acid (OR=1.45; 95% CI: 1.14–1.83) with wheeze in boys only (Peters et al. 1999a). The results from an international collaborative study on the impact of Traffic-Related Air Pollution on Childhood Asthma (TRAPCA) showed, when stratified analysis by gender, significant associations between residential PM_{2.5}, NO₂ and respiratory symptoms (e.g., cough without infection, cough at night) only among boys but not among girls 0–2 years of age (Gehring et al. 2002). In a prospective cohort study of annual mean total suspended particle (TSP) and SO₂ exposures among preadolescent children in Krakow, Poland, Jedrychowski et al. (1999) reported stronger associations with FVC and FEV₁ among boys than among girls. The authors noted sex-differing lung growth rates, producing different critical periods for pollution effects. Also, the cohort study from Southern California suggested that the relation between FEV₁ growth and traffic air pollution was noticeably larger in boys than in girls, although a test of effect modification by sex was non-significant (p=0.10) (Gauderman et al. 2007). Some authors have ever explained that the

greater effect in boys may be due to greater time spent outdoors and more physical activity, both of which are factors that would increase exposure to and the respiratory dose of ambient air pollution (Tager et al. 1998). Also, this is plausible as there are differences between male and female airways from early in fetal lung development and throughout life (Becklake and Kauffmann 1999), for example female lungs mature earlier with regard to surfactant production. Throughout life women have smaller lungs than men, but their lung architecture is more advantageous with a greater airway diameter in relation to the volume of the lung parenchyma. Thus, in childhood, airway hyper-responsiveness and asthma are more common among boys than girls.

Despite the existed evidence that boys may be more susceptible to air pollution than girls as mentioned above, however, many studies reported the stronger effects among girls. Using the hospital records for 2768 children aged 0 to 18 years from northern Orange County, California, Delfino et al. authors (2009) estimated the association of local traffic-generated air pollution (CO, NO₂, NO_x) with repeated hospital encounters for asthma, and found that associations were stronger for girls but were not significantly from boys. In a dynamic cohort study among Mexican children 8 years of age, Rojas-Martinez et al. (2007) found that negative association of O₃ with lung function growth was stronger on girls than boys in multipollutant models. Also, among Roman children 9–14 years of age, Rosenlund et al. (2009) found associations between chronic residential NO₂ exposure and lung function to be stronger among Roman girls than boys; mean FEV₁ and FEF_{25–75} decrements were approximately four times greater in girls than boys. The authors indicated complexities in comparing childhood cohorts differing by age, pubertal status, pollution mixtures, study designs, and susceptibilities and noted that the consistency of results across reporting stronger air pollution effects among girls, meriting further investigation.

In fact, some authors suggested, when focused on the gender difference of the health responses to air pollution, the types of air pollutants should be fully considered. For example, boys may be more susceptible to some kind of pollutants, whereas, girls may be more susceptible to some other pollutants. Results from the Canada showed that respiratory hospitalizations were significantly associated with PM_{2.5–10} among boys and girls, with PM₁₀ among boys, and with NO₂ among girls (Lin et al. 2005). Also, Rojas-Martinez et al. (2007) associated elevated PM₁₀, NO₂, and O₃ with reduced lung function among boys and girls. Interquartile range increases in NO₂ predicted FEV₁ declines in girls, whereas increases in PM₁₀ predicted FEV₁ declines among boys. Interesting, results from the Northeast Chinese Children Health Study showed, when stratified by allergic predisposition, amongst children without an allergic predisposition, air pollution effects on asthma were stronger in boys compared to girls; Current asthma prevalence was related to PM₁₀ (ORs=1.36 per 31 µg/m³; 95% CI, 1.08-1.72), SO₂ (ORs=1.38 per 21µg/m³; 95%CI, 1.12-1.69) only among boys. However, among children with allergic predisposition, more positively associations between air pollutants and respiratory symptoms and diseases were detected in girls; An increased prevalence of doctor-diagnosed asthma was significantly associated with SO₂ (ORs=1.48 per 21µg/m³; 95%CI, 1.21-1.80), NO₂ (ORs=1.26 per 10µg/m³; 95%CI, 1.01-1.56), and current asthma with O₃ (ORs=1.55 per 23µg/m³; 95%CI, 1.18-2.04) only among girls (Dong et al. 2011).

The difference of health response to air pollution between boys and girls remains unclear and needs to be explored further. Just as Clougherty (2010) elaborated that careful

consideration of gender and sex effects and exploration of nascent methods for quantitative gender analysis may help to elucidate sources of difference. More broadly, exploring the role for gender analysis in environmental epidemiology may provide a model for exploring other social factors that can shape population responses to air pollution.

5. Health effect susceptibility and prevention of air pollution

Air pollution has shown significant effects on asthma development and exacerbation. In a recent Indian study, it was suggested that asthma admissions increased by almost 21% due to the ambient levels of pollutants exceeding the national air quality standards (Pande et al. 2002). In Israel, outdoor air pollution revealed significant correlation with ER visits and 61% of the variance could be explained by air pollutants including NO_x, SO₂, and O₃ (Garty et al. 1998). Ambient air pollution was also estimated to attribute 13-15% of the prevalence of childhood asthma in Taiwan, after adjustment for hereditary and indoor factors (Lee et al. 2003). In Central Jakarta and Tangerang, where the average NO₂ concentrations were highest, reduction of NO₂ to a proposed level of 25 ppb could yield savings in mean 15,639-18,165 Indonesian rupiah (6.80-7.90 US dollars) per capita for treatment of the respiratory symptoms, and reduce average work/school days lost per capita by 3.1-5.5 days (Duki et al. 2003). The overall economic cost (both direct and indirect) of air pollution might be higher than what has been estimated in the study.

The worldwide variation in asthma prevalence indicates that environmental factors may be critical. There is now growing evidence to suggest that air pollution is probably responsible, at least in part, for the increasing prevalence of asthma in children. Outdoor ambient air pollutants in communities are relevant to the acute exacerbation and possibly the onset of asthma. From some children's studies, asthma prevalences were different despite of similar prevalences of atopic sensitization. This supported the hypothesis that outdoor air pollution with unchanged levels of allergen could be a risk factor for the increasing prevalence of asthma observed over the past two decades. However, the ecological association with known outdoor air pollutants and asthmatic morbidities remains suggestive. Outdoor air pollutants at levels below the current standards were shown harmful to susceptible individuals. There might be serious public health consequences if small decreases in lung function were associated causally with chronic exposure to air pollution, especially if the size of the exposed population is large. It is possible that some permissible levels of ambient air pollutants in children are not sufficiently low for human health protection. Better technology and public policy are needed to help prevent the enormous suffering and human loss associated with air pollution. What has yet to be documented is whether reduced outdoor pollution will result in decreased morbidities from children's health. Studies to investigate this hypothesis are currently under way.

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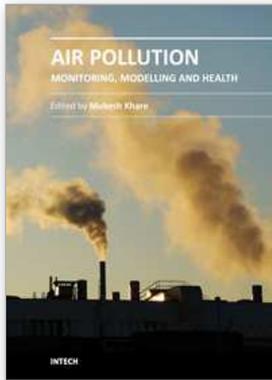
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Air pollution has always been a trans-boundary environmental problem and a matter of global concern for past many years. High concentrations of air pollutants due to numerous anthropogenic activities influence the air quality. There are many books on this subject, but the one in front of you will probably help in filling the gaps existing in the area of air quality monitoring, modelling, exposure, health and control, and can be of great help to graduate students professionals and researchers. The book is divided in two volumes dealing with various monitoring techniques of air pollutants, their predictions and control. It also contains case studies describing the exposure and health implications of air pollutants on living biota in different countries across the globe.

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