The following document was submitted "for the record" to the Intermodal Container Transfer Facility (ICTF) Joint Powers Authority (JPA) during the Notice of Preparation/Initial Study (NOP/IS) comment period for the ICTF Modernization and Expansion Project.

The document was submitted by:

Andrea M. Hricko
Assoc Prof Prev Med
Keck School of Med &
Director, Community Outreach and Education
Southern CA Env Health Sciences Ctr
1540 Alcazar Street CHP 236
L.A. CA 90033
323-442-3077

---------- End Page ----------

ELSEVIER
SAUNDERS

Immunol Allergy Clin N Am
28 (2008) 577–588

IMMUNOLOGY
AND ALLERGY
CLINICS
OF NORTH AMERICA

Traffic, Outdoor Air Pollution, and Asthma

Fernando Holguin, MD, MPH

Emory University School of Medicine, Division of Pulmonary, Allergy, and Critical Care, Clinical Research Center, Davis Fisher Building, Room 2331, 550 Peachtree Street NE, Atlanta, GA 30308, USA

It is well known that outdoor air pollution can affect the health of patients with asthma. Epidemiologic studies have shown that increased levels of outdoor pollutants are associated with acute and chronic changes in lung function, increased risk for asthma exacerbations, increased risk for work or school absenteeism, and need for rescue bronchodilators. Fortunately, we have also learned that reducing ambient levels of air pollutants can decrease acute health care use for asthma and therefore improve the quality of life of these patients [1].

The epidemiology of asthma and outdoor air pollution has shown that respiratory health effects can vary in relation to different emission sources, types of pollutants, underlying nutritional status, medication use, and genetic polymorphisms. Using sophisticated exposure assessment methods in conjunction with clinical tests and biomarkers that provide mechanistic information, the study of outdoor epidemiology and asthma has evolved into a complex multidisciplinary field. This article presents an overview of the mechanisms by which outdoor air pollution and traffic-related emissions lead to changes in respiratory health and lung function in subjects with asthma.

The outdoor air pollution mix

Polluted outdoor air contains a complex mixture of particle and gas-phase pollutants. Most epidemiologic studies on asthma and air pollution have focused on understanding the health effects of criteria air pollutants, which are routinely monitored by the Environmental Protection Agency and include ozone, nitrogen dioxide, sulfur dioxide, lead, carbon monoxide,

E-mail address: fholgui@emory.edu

doi:10.1016/j.iac.2008.03.008

and particulate matter (PM) [2,3]. PM is further subdivided into coarse particulate matter or PM_{10} (PM with an aerodynamic diameter ≤ 10 μm), fine particulate matter or $PM_{2.5}$ (PM with an aerodynamic diameter ≤ 2.5 μm), and ultrafine or $PM_{1.0}$ (PM with an aerodynamic diameter ≤ 1.0 μm) [4].

The criteria pollutants are derived from different emissions sources. For example, nitrogen dioxide and ground-level ozone (which results from the effect of ultraviolet light on nitrogen dioxide) are primarily derived from vehicle exhaust, whereas sulfur dioxide derives from combustion of sulfur-containing fuels (eg, coal burning plants). Coarse particulate matter is primarily derived from dispersed ground or fugitive dust; fine and ultrafine particulate matter comes primarily from vehicular exhaust [5]. Coarse and fine particulates differ not only in their size and physical properties, but also in their chemical composition. PM_{10} is largely composed of geological materials, in contrast to $PM_{2.5}$ and $PM_{1.0}$, which have larger fractions of elemental and organic carbon [6]. These PM variations in chemical composition are associated with different toxicity profiles and can be used as tracers of vehicular emissions. For example, elemental carbon can be used for tracking traffic-related emissions [7].

The first challenge in studying the impact of air pollution on asthma status is to accurately quantify exposure. Determining that a patient with asthma may be more or less susceptible to different pollutants is easy, but trying to understand the pollution mixture actually inhaled is practically impossible. Exposure to different pollution mixtures can vary by location, proximity to roads, time of day, seasonality, and other factors. Epidemiologic research on outdoor air pollution employs different methodologies to overcome many of these limitations. This may include relating health outcomes to emission sources as the main exposure of interest (eg, proximity to roads, traffic density estimates, road densities) and use of personal air pollution monitors in smaller, better-characterized panel studies. An in-depth review of epidemiologic and exposure assessment methods used in outdoor air pollution is beyond the scope of this article. However, there are many different ways of associating air pollution exposure with respiratory health outcomes and this methodological variation is often the source inconsistent results across studies.

Outdoor air pollution and mechanisms of injury pertinent to asthma

Airway inflammation

Outdoor air pollutants are known to exacerbate asthma by causing inflammation in the airways [8,9]. Even short-term exposures to vehicular traffic emissions ($PM_{2.5}$, $PM_{1.0}$, elemental carbon, and nitrogen dioxide) in subjects with asthma are associated with evidence of neutrophilic inflammation and reduced airway pH [7]. Evidence that outdoor air pollution leads to airway inflammation in asthma is also supported by studies using exhaled

nitric oxide as a biomarker. In a panel of 19 children with asthma in Seattle, a same-day increase of 10 $\mu m/m^3$ of $PM_{2.5}$ was associated with increased in exhaled nitric oxide of 4.3 ppb [95% CI 1.4–7.29] [10]. Exposure to ambient elemental carbon has also been associated with increased exhaled nitric oxide, suggesting that vehicular emissions may lead to increased airway inflammation [11].

Allergy sensitization

Outdoor air pollution may increase the risk for asthma by mechanisms that involve increased allergic sensitization. Exposure to diesel exhaust particles (DEP) before an allergen challenge has been shown to increase Th-2 cytokine levels, when compared with allergen exposure alone. Furthermore, DEP exposure favors lymphocyte-B cell differentiation and IgE production [12,13]. Short-term ambient exposure to $PM_{2.5}$ has also been associated with increased allergic inflammation by increasing the proportion of eosinophils in the nasal lavage of asthmatic children but not in healthy controls [14]. However, large-scale epidemiologic studies, such as the European Community Respiratory Health study, did not demonstrate an association between variations of annual average regional $PM_{2.5}$ and sulfur levels and allergic sensitization [15]. In contrast, the Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) found significant associations between allergic sensitization to pollen and living near streets with higher vehicular traffic [16]. Whether or not air pollution induces allergic sensitization is debatable and inconsistencies across studies may be the result of methodological differences [17].

Clinical and physiologic lung changes associated with outdoor air pollution

Acute changes in lung volumes

Subjects with asthma are far more susceptible than healthy subjects to the effects of outdoor air pollution. Most studies have found that increased concentrations of outdoor air pollution can be associated with acute reductions in forced vital capacity (FVC) and forced exhaled lung volume in one second (FEV_1) among persons with asthma. The magnitude and lag between exposure and change in lung function varies considerably according to the exposure assessment (type of pollutants being measured) and study design. Outdoor PM_{10} and $PM_{2.5}$ have been associated with acute reductions in FEV_1 and FVC. These reductions in lung volumes are observed either within the same day, a few hours after exposure, or days after exposure (lag response) [7,18].

Sulfur dioxide is oxidized in the atmosphere to sulfuric acid with resulting acid aerosol and acid rain production. Acid aerosols are associated with significant reductions in FEV_1 and FVC. Sulfur dioxide can acutely induce bronchoconstriction in subjects with asthma [19,20]. Moreover, ozone is

a strong oxidizing agent well known to reversibly reduce FEV_1 and FVC, promote bronchial hyperresponsiveness, increase airway resistance, and reduce peak expiratory flows [21,22].

Compared to subjects without chronic airway obstruction, subjects with asthma exhibit larger reductions in FEV_1 in association with exposure to ambient nitrogen dioxide [23]. In controlled exposure chamber studies, however, investigators have failed to show FEV_1 reductions in asthmatics exposed to nitrogen dioxide [24]. Discrepancies between chamber exposure and epidemiologic studies are not uncommon and may derive from the fact that, in an epidemiologic study, what we attribute to be the exposure of interest functions as a tracer or surrogate for other pollutants or a complex mixture of pollutants, such as a mixture of nitrogen dioxide, $PM_{2.5}$, and other vehicular traffic–related emissions.

Chronic lung-volume changes

Understanding the chronic respiratory health effects of outdoor air pollutants is more complex. It requires either a longitudinal approach in large study populations with repeated measures of lung function and air pollution exposure over time, or an ecological approach in which lung function values are compared in populations across a gradient of outdoor air pollution levels. The Children's Health Study is a large cohort study that enrolled children from 12 communities with varying air pollution exposure profiles across California. Results from this cohort show that children from ages 10 to 18 years exposed to higher air pollutant concentrations have reduced lung growth. Deficits in lung function were associated with nitrogen dioxide, acid vapor, and $PM_{2.5}$, but not with ozone [25]. Importantly, air pollution–related lung-growth deficits occurred in children with and without asthma. In a dynamic cohort from Mexico City that included 3120 healthy children 8 years of age at baseline and followed for 3 years, exposure to ozone, PM_{10}, and nitrogen dioxide were associated with significant deficits in lung growth [26]. Results from these studies suggest that air pollution–related deficits in lung growth prevents many children from achieving their peak lung volume.

Chronic exposure to outdoor air pollutants is also associated with increased rate of lung-volume decline over time. Results from the SAPALDIA show that long-term exposure to pollutants (nitrogen dioxide, PM_{10}, and sulfur dioxide) is associated with increased decline in FEV_1 and FVC. For FVC, an increment of 10 $\mu g/m^3$ in PM_{10} was associated with a 3.4% change in FVC [27]. The good news is that lung function can improve once exposure to air pollution is reduced, even after long-term exposure. In the same study, 9651 adults (18 to 60 years of age and assessed in 1991 and 2002), experienced an overall reduction in their outdoor PM_{10} exposure. The net effect of a decline of 10 μg of PM_{10} per cubic meter over an 11-year period was to reduce the annual rate of decline in FEV_1 by 9% and of $FEF_{25–75}$ by 16% [28]. In the California Children's Study, participants who moved to

communities with lower PM_{10} showed increased lung growth, whereas moving to higher PM_{10} environments was associated with reduced lung growth. These associations were predominantly observed in children who had been living in their new communities for at least 3 years [29].

Outdoor air pollution and asthma health status

Many epidemiologic studies have shown that increased outdoor air pollutant levels are a significant morbidity risk for subjects with asthma. Increased outdoor exposure to air pollution has been associated with increased severity of respiratory symptoms, increased risk for asthma exacerbations requiring emergency department evaluation or hospitalization, and more frequent urgent medical visits and use of asthma medications [2,4,30]. Also, higher levels of air pollution are associated with increased school and work absenteeism resulting in a large economic cost to society [31,32].

Clearly not every subject with asthma experiences adverse respiratory outcomes when exposed to higher levels of outdoor air pollutants. Several factors have been shown to either increase susceptibility or confer resistance to air pollution. The interaction between environment and genetic polymorphisms is an area of intense research and some recent studies are worth reviewing.

In asthmatics, the presence of GSTM1 (glutathione *s*-transferase null polymorphism) and GSTP1 (val/val genotype) has been associated with increased to susceptibility to ambient ozone exposure [33,34]. The GSTM1 polymorphism, which is present in approximately 40% of the general population, has been associated with increased levels of nasal biomarkers of inflammation and reduced peak expiratory flows in asthmatic children in association with ozone [33]. Both GSTM1 and GSTP1 polymorphisms are also associated with increased dyspnea in children with asthma exposed to ozone [33]. The presence of GSTM1 also increases the risk for systemic inflammation in association with traffic-related particles (black carbon and concentration of particles) [35]. Children who are GSTM1 homozygous and most susceptible to outdoor air pollution benefit the most from antioxidant supplementation. Romieu and colleagues [34] showed that, compared with placebo, children receiving antioxidant supplementation did not exhibit ozone-related reductions in lung volumes. Antioxidant supplementation was most effective in protecting children who were GSTM1 null homozygous.

Not all genetic polymorphisms have been associated with increased susceptibility. Among 3699 children participating in the children's health study in California, those who were homozygous for the tumor necrosis factor α (TNF-α) 308G polymorphism (range from 71% non-Hispanic whites to 87% in Asians) had a reduced risk for lifetime asthma prevalence and wheezing, compared with those carrying one allele. Furthermore, homozygous children living in lower-ozone communities were protected from

wheezing in relation to ozone exposure, particularly in those with the GSTM1 polymorphism [36]. It is thought that the homozygous TNF-α 308G polymorphism may protect from ozone exposure by reducing the inflammatory response to oxidative stress [36].

Air pollution as a risk factor for asthma incidence

Outdoor air pollution not only exacerbates asthma, but is also a risk factor for developing new-onset asthma. For example, increased asthma incidence has been described in children playing outdoor sports exposed to higher ozone levels. In this study, children who played three or more outdoor sports in communities with high ozone concentrations during the summer had a relative risk of developing asthma of 3.3 [95% CI 1.9–5.8], compared with children playing no sports. Also, the risk for asthma prevalence increases proportionately with increased vehicular emission exposures, suggesting that chronic exposure to these pollutants may increase the risk of developing asthma [37,38]. In a large study of 6000 children from six French cities, the 3-year averaged concentration of ozone, PM_{10}, sulfur dioxide, and nitrogen dioxide were associated with increased odds of developing allergic rhinitis, atopy (positive skin test), and lifetime asthma [39]. A matched case control study by Zmirou and colleagues evaluated the risk for incident asthma (recent medical diagnosis within the preceding 2 years) in children of ages between 4 and 14 years and exposure to traffic density. Exposure to traffic density was calculated retrospectively and divided into an overall cumulative life exposure and an early life exposure (birth to 3 years). Early life exposure to traffic density, but not the cumulative measure, was associated with increased odds for asthma incidence [40]. Results from these studies suggest that outdoor air pollutants may play a role in increasing the risk for developing asthma and atopy, particularly early in life.

Reducing the health burden associated with outdoor air pollution

Relocating to cities with less air pollution can reduce the risk for some of the chronic lung effects and improve respiratory health. However, this option is probably not feasible or practical for most patients with asthma. Health care providers should advise their patients with asthma to follow their local air pollution forecasts to avoid outdoor exposure as much as possible during alerts. This means cutting out exercise during peak air pollution hours [41]. This advice is useful for reducing ozone exposure in subjects who live or work in air-conditioned environments. Outdoor avoidance may not provide the same degree of protection from fine and ultrafine particles, which have higher filtration coefficients and can achieve relatively high concentrations indoors.

Whether treatment with inhaled corticosteroids or other antiasthma medications can provide relief from air pollution is unclear. In a panel of 19 children with asthma, exposure to ambient $PM_{2.5}$ was associated with increased

exhaled nitric oxide. This association was not observed in children taking inhaled corticosteroids (change in exhaled nitric oxide per 10 $\mu g/m^3$ increase in $PM_{2.5}$ in children with inhaled corticosteroids: 6.3 [95% CI 2.6–10]; change in exhaled nitric oxide per 10 $\mu g/m^3$ increase in $PM_{2.5}$ in children not on inhaled corticosteroids: –0.77 [95% CI -4.6, 3]) [42]. In the California Children's Health Study, ambient ozone exposure was associated with increased prevalence of medication use and wheezing among asthmatic children, particularly in those who spent more time outdoors [43]. However, the prevalence of medication use in this study was a proxy for increased susceptibility to the exposure and no data was provided to determine whether use of inhaled corticosteroids modified the association with outdoor air pollutants. Rundell and colleagues showed that one dose of montelukast prevented bronchoconstriction in young males exercising during exposure to high PM concentrations [44]. This suggests that particulate air pollution could induce lung function deficits via leukotriene inflammatory pathways. Two other small exposure studies have shown that long-acting theophylline and salmeterol may prevent sulfur dioxide–mediated bronchoconstriction [45,46]. These results clearly need to be replicated in a larger study population. The use of antioxidant supplementation has been shown to reduce the impact of outdoor air pollution on respiratory symptoms and decline in lung volumes [34]. However, these results stem from small panel studies and do not provide the level of evidence needed to make broader clinical or public health recommendations to use antioxidants as a secondary prevention strategy.

Traffic and asthma

Asthma and traffic-related emissions

Evidence that there is considerable spatial variability in the concentration of traffic-related pollutants has sparked interest in assessing the health effects associated with vehicular emissions. Several studies have found that exposure to traffic-related emissions are associated with higher rates of adverse respiratory health outcomes in comparison with background air pollution exposure [47–51]. This phenomenon may be explained by the pollutant mix properties near vehicular emission sources, including larger concentration of fine and ultrafine particles [52] and higher concentrations of carbon monoxide and nitrogen dioxide levels [53]. Although there is no clear consensus on what constitutes exposure to vehicular-related emissions, most studies have found that the rate of adverse respiratory health effects appears to increase proportionately in relation to road-proximity [38] and with increasing traffic density [54]. Proximity to major traffic roads and high traffic density has been associated with higher rates of wheezing [50], atopy [55,56], respiratory symptoms, and health care use in children [57–59].

In a cohort of 200 children aged 6 to 12 years (half of them with asthma), the author and colleagues determined the associations between road

densities (defined as total kilometers of roads within a defined area) near schools and homes and exposure to outdoor air pollution (nitrogen dioxide, elemental carbon, and $PM_{2.5}$). These exposures were then related to changes in lung volumes and exhaled nitric oxide. This study found that road density (a proxy measure for vehicular traffic) within the 50- and 100-m buffers (radius around a geographically designated area), particularly at home, was associated with reduced FEV_1 and FVC and increased exhaled nitric oxide only in children with asthma [60]. Because road density and related traffic volumes remain constant or change slowly, road density constitutes a persistent traffic exposure. In contrast, no significant associations with the ambient levels of measured pollutants (a longitudinal exposure) were observed. One possibility to explain this finding is the potential for exposure misclassification. For example, the study's pollutant exposure assessment may not accurately represent exposure during a critical time window that would be associated with changes in exhaled nitric oxide or lung volumes. Alternatively, cumulative long-term exposure may be more relevant than shorter-term peak exposures to pulmonary function in this cohort.

The effect of exposure to traffic-related emissions on respiratory health, above and beyond the background air pollution, remains controversial. Other studies have not shown significant associations [61–63]. Discrepancies among studies can be partly explained by different exposure measures, including subjective quantification of traffic density, direct measurement of traffic counts, and exposure defined at different proximity levels to roads with greater traffic densities. Also, an important source of bias when evaluating the effects of vehicular emissions is socioeconomic status position (SEP). Lower SEP has been associated with road proximity and with increased vulnerability to the effects of air pollutants [64]. Disentangling the extent of bias attributed to SEP in traffic studies can be quite difficult, as the SEP definition among studies was highly variable. Additionally, other unmeasured factors, such as noise and related stress, can be important sources of bias [65,66].

Summary

There is growing evidence that exposure to traffic-related emissions is different than that of background air pollutants in terms of the composition of the pollution mix and the health risks. However, given the broad differences in methodology and exposure assessment, it is difficult to reach a consensus on what constitutes an exposure to "traffic- or vehicle-related emission." This limitation leaves many important questions unanswered and hampers the capacity of research to translate results into community environmental improvements aimed at reducing health risks. For example, there is no consensus regarding exposure thresholds. That is, at what distance from roads or traffic emission sources would the exposure to vehicular emissions be diminished to safe levels? Should we advise patients with asthma to avoid prolonged exposure in close proximity to roads. If so, how much time

constitutes prolonged exposure? What distance is far enough away? What volume of traffic is tolerable? Should an asthmatic be advised not to reside or attend school or work based on the potential for nearby traffic exposure? The answers to these questions could have clinical implications for the caring of patients with asthma and for public health policies, urban planning and development, and other areas of society.

References

[1] Friedman MS, Powell KE, Hutwagner L, et al. Impact of changes in transportation and commuting behaviors during the 1996 Summer Olympic Games in Atlanta on air quality and childhood asthma. JAMA 2001;285(7):897–905.
[2] Koren HS. Associations between criteria air pollutants and asthma. Environ Health Perspect 1995;103(Suppl 6):235–42.
[3] Environmental Protection Agency. Criteria air pollutants 2008. Available at: www.epa.gov. Accessed 2008.
[4] Kappos AD, Bruckmann P, Eikmann T, et al. Health effects of particles in ambient air. Int J Hyg Environ Health 2004;207(4):399–407.
[5] Harrison R. Measurements of concentrations of air pollutants. In: Holgate S, Samet J, Hillel K, et al, editors. Air pollution and health. London: Academic Press; 1999. p. 63–81.
[6] Hetland RB, Cassee FR, Lag M, et al. Cytokine release from alveolar macrophages exposed to ambient particulate matter: heterogeneity in relation to size, city and season. Part Fibre Toxicol 2005;2:4.
[7] McCreanor J, Cullinan P, Nieuwenhuijsen MJ, et al. Respiratory effects of exposure to diesel traffic in persons with asthma. N Engl J Med 2007;357(23):2348–58.
[8] Peden DB, Boehlecke B, Horstman D, et al. Prolonged acute exposure to 0.16 ppm ozone induces eosinophilic airway inflammation in asthmatic subjects with allergies. J Allergy Clin Immunol 1997;100(6 Pt 1):802–8.
[9] Aris RM, Christian D, Hearne PQ, et al. Ozone-induced airway inflammation in human subjects as determined by airway lavage and biopsy. Am Rev Respir Dis 1993;148(5):1363–72.
[10] Koenig JQ, Jansen K, Mar TF, et al. Measurement of offline exhaled nitric oxide in a study of community exposure to air pollution. Environ Health Perspect 2003;111(13):1625–9.
[11] Delfino RJ, Staimer N, Gillen D, et al. Personal and ambient air pollution is associated with increased exhaled nitric oxide in children with asthma. Environ Health Perspect 2006; 114(11):1736–43.
[12] Diaz-Sanchez D. The role of diesel exhaust particles and their associated polyaromatic hydrocarbons in the induction of allergic airway disease. Allergy 1997;52(38 Suppl):52–6.
[13] Diaz-Sanchez D, Tsien A, Fleming J, et al. Combined diesel exhaust particulate and ragweed allergen challenge markedly enhances human in vivo nasal ragweed-specific IgE and skews cytokine production to a T helper cell 2-type pattern. J Immunol 1997;158(5):2406–13.
[14] Nikasinovic L, Just J, Sahraoui F, et al. Nasal inflammation and personal exposure to fine particles PM2.5 in asthmatic children. J Allergy Clin Immunol 2006;117(6):1382–8.
[15] Bedada GB, Heinrich J, Gotschi T, et al. Urban background particulate matter and allergic sensitization in adults of ECRHS II. Int J Hyg Environ Health 2007;210(6):691–700.
[16] Wyler C, Braun-Fahrlander C, Kunzli N, et al. Exposure to motor vehicle traffic and allergic sensitization. The Swiss Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) Team. Epidemiology 2000;11(4):450–6.
[17] Polosa R, Salvi S, Di Maria GU. Allergic susceptibility associated with diesel exhaust particle exposure: clear as mud. Arch Environ Health 2002;57(3):188–93.
[18] Delfino RJ, Quintana PJ, Floro J, et al. Association of FEV1 in asthmatic children with personal and microenvironmental exposure to airborne particulate matter. Environ Health Perspect 2004;112(8):932–41.

[19] Raizenne M, Neas LM, Damokosh AI, et al. Health effects of acid aerosols on North American children: pulmonary function. Environ Health Perspect 1996;104(5):506–14.
[20] Balmes JR, Fine JM, Sheppard D. Symptomatic bronchoconstriction after short-term inhalation of sulfur dioxide. Am Rev Respir Dis 1987;136(5):1117–21.
[21] Kreit JW, Gross KB, Moore TB, et al. Ozone-induced changes in pulmonary function and bronchial responsiveness in asthmatics. J Appl Physiol 1989;66(1):217–22.
[22] Higgins BG, Francis HC, Yates CJ, et al. Effects of air pollution on symptoms and peak expiratory flow measurements in subjects with obstructive airways disease. Thorax 1995; 50(2):149–55.
[23] Lagorio S, Forastiere F, Pistelli R, et al. Air pollution and lung function among susceptible adult subjects: a panel study. Environ Health 2006;5:11.
[24] Morrow PE, Utell MJ. Responses of susceptible subpopulations to nitrogen dioxide. Res Rep Health Eff Inst 1989;23:1–45.
[25] Gauderman WJ, Vora H, McConnell R, et al. Effect of exposure to traffic on lung development from 10 to 18 years of age: a cohort study. Lancet 2007;369(9561):571–7.
[26] Rojas-Martinez R, Perez-Padilla R, Olaiz-Fernandez G, et al. Lung function growth in children with long-term exposure to air pollutants in Mexico City. Am J Respir Crit Care Med 2007;176(4):377–84.
[27] Ackermann-Liebrich U, Leuenberger P, Schwartz J, et al. Lung function and long term exposure to air pollutants in Switzerland. Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) Team. Am J Respir Crit Care Med 1997;155(1):122–9.
[28] Downs SH, Schindler C, Liu LJ, et al. Reduced exposure to PM10 and attenuated age-related decline in lung function. N Engl J Med 2007;357(23):2338–47.
[29] Avol EL, Gauderman WJ, Tan SM, et al. Respiratory effects of relocating to areas of differing air pollution levels. Am J Respir Crit Care Med 2001;164(11):2067–72.
[30] von Klot S, Wolke G, Tuch T, et al. Increased asthma medication use in association with ambient fine and ultrafine particles. Eur Respir J 2002;20(3):691–702.
[31] Gilliland FD, Berhane K, Rappaport EB, et al. The effects of ambient air pollution on school absenteeism due to respiratory illnesses. Epidemiology 2001;12(1):43–54.
[32] Pope CA III, Bates DV, Raizenne ME. Health effects of particulate air pollution: time for reassessment? Environ Health Perspect 1995;103(5):472–80.
[33] Romieu I, Ramirez-Aguilar M, Sienra-Monge JJ, et al. GSTM1 and GSTP1 and respiratory health in asthmatic children exposed to ozone. Eur Respir J 2006.
[34] Romieu I, Sienra-Monge JJ, Ramirez-Aguilar M, et al. Genetic polymorphism of GSTM1 and antioxidant supplementation influence lung function in relation to ozone exposure in asthmatic children in Mexico City. Thorax 2004;59(1):8–10.
[35] Zeka A, Sullivan JR, Vokonas PS, et al. Inflammatory markers and particulate air pollution: characterizing the pathway to disease. Int J Epidemiol 2006;35(5):1347–54.
[36] Li YF, Gauderman WJ, Avol E, et al. Associations of tumor necrosis factor G-308A with childhood asthma and wheezing. Am J Respir Crit Care Med 2006;173(9):970–6.
[37] McConnell R, Berhane K, Gilliland F, et al. Asthma in exercising children exposed to ozone: a cohort study. Lancet 2002;359(9304):386–91.
[38] McConnell R, Berhane K, Yao L, et al. Traffic, susceptibility, and childhood asthma. Environ Health Perspect 2006;114(5):766–72.
[39] Penard-Morand C, Charpin D, Raherison C, et al. Long-term exposure to background air pollution related to respiratory and allergic health in schoolchildren. Clin Exp Allergy 2005;35(10):1279–87.
[40] Zmirou D, Gauvin S, Pin I, et al. Traffic related air pollution and incidence of childhood asthma: results of the Vesta case-control study. J Epidemiol Community Health 2004;58(1):18–23.
[41] Shofer S, Chen TM, Gokhale J, et al. Outdoor air pollution: counseling and exposure risk reduction. Am J Med Sci 2007;333(4):257–60.
[42] Mar TF, Jansen K, Shepherd K, et al. Exhaled nitric oxide in children with asthma and short-term PM2.5 exposure in Seattle. Environ Health Perspect 2005;113(12):1791–4.

[43] Millstein J, Gilliland F, Berhane K, et al. Effects of ambient air pollutants on asthma medication use and wheezing among fourth-grade school children from 12 Southern California communities enrolled in The Children's Health Study. Arch Environ Health 2004;59(10): 505–14.
[44] Rundell KW, Spiering BA, Baumann JM, et al. Bronchoconstriction provoked by exercise in a high-particulate-matter environment is attenuated by montelukast. Inhal Toxicol 2005; 17(2):99–105.
[45] Gong H Jr, Linn WS, Shamoo DA, et al. Effect of inhaled salmeterol on sulfur dioxide–induced bronchoconstriction in asthmatic subjects. Chest 1996;110(5):1229–35.
[46] Koenig JQ, Dumler K, Rebolledo V, et al. Theophylline mitigates the bronchoconstrictor effects of sulfur dioxide in subjects with asthma. J Allergy Clin Immunol 1992;89(4):789–94.
[47] Meng YY, Rull RP, Wilhelm M, et al. Living near heavy traffic increases asthma severity. Policy Brief (UCLA Cent Health Policy Res) 2006;1–5.
[48] Lwebuga-Mukasa JS, Oyana T, Thenappan A, et al. Association between traffic volume and health care use for asthma among residents at a U.S.-Canadian border crossing point. J Asthma 2004;41(3):289–304.
[49] Lin S, Munsie JP, Hwang SA, et al. Childhood asthma hospitalization and residential exposure to state route traffic. Environ Res 2002;88(2):73–81.
[50] Venn AJ, Lewis SA, Cooper M, et al. Living near a main road and the risk of wheezing illness in children. Am J Respir Crit Care Med 2001;164(12):2177–80.
[51] Ciccone G, Forastiere F, Agabiti N, et al. Road traffic and adverse respiratory effects in children. SIDRIA Collaborative Group. Occup Environ Med 1998;55(11):771–8.
[52] Reponen T, Grinshpun SA, Trakumas S, et al. Concentration gradient patterns of aerosol particles near interstate highways in the Greater Cincinnati airshed. J Environ Monit 2003;5(4):557–62.
[53] Sahsuvaroglu T, Arain A, Kanaroglou P, et al. A land use regression model for predicting ambient concentrations of nitrogen dioxide in Hamilton, Ontario, Canada. J Air Waste Manag Assoc 2006;56(8):1059–69.
[54] English P, Neutra R, Scalf R, et al. Examining associations between childhood asthma and traffic flow using a geographic information system. Environ Health Perspect 1999;107(9): 761–7.
[55] Nicolai T, Carr D, Weiland SK, et al. Urban traffic and pollutant exposure related to respiratory outcomes and atopy in a large sample of children. Eur Respir J 2003;21(6): 956–63.
[56] Kramer U, Koch T, Ranft U, et al. Traffic-related air pollution is associated with atopy in children living in urban areas. Epidemiology 2000;11(1):64–70.
[57] Morgenstern V, Zutavern A, Cyrys J, et al. Respiratory health and individual estimated exposure to traffic-related air pollutants in a cohort of young children. Occup Environ Med 2007;64(1):8–16.
[58] Smargiassi A, Berrada K, Fortier I, et al. Traffic intensity, dwelling value, and hospital admissions for respiratory disease among the elderly in Montreal (Canada): a case-control analysis. J Epidemiol Community Health 2006;60(6):507–12.
[59] Kim JJ, Smorodinsky S, Lipsett M, et al. Traffic-related air pollution near busy roads: the East Bay Children's Respiratory Health Study. Am J Respir Crit Care Med 2004;170(5): 520–6.
[60] Holguin F, Flores S, Ross Z, et al. Traffic-related exposures, airway function, inflammation, and respiratory symptoms in children. Am J Respir Crit Care Med 2007;176(12):1236–42.
[61] Venn A, Lewis S, Cooper M, et al. Local road traffic activity and the prevalence, severity, and persistence of wheeze in school children: combined cross sectional and longitudinal study. Occup Environ Med 2000;57(3):152–8.
[62] Wilkinson P, Elliott P, Grundy C, et al. Case-control study of hospital admission with asthma in children aged 5–14 years: relation with road traffic in north west London. Thorax 1999;54(12):1070–4.

[63] Lewis SA, Antoniak M, Venn AJ, et al. Secondhand smoke, dietary fruit intake, road traffic exposures, and the prevalence of asthma: a cross-sectional study in young children. Am J Epidemiol 2005;161(5):406–11.
[64] O'neill MS, Jerrett M, Kawachi I, et al. Health, wealth, and air pollution: advancing theory and methods. Environ Health Perspect 2003;111(16):1861–70.
[65] Ising H, Lange-Asschenfeldt H, Lieber GF, et al. Respiratory and dermatological diseases in children with long-term exposure to road traffic immissions. Noise Health 2003;5(19): 41–50.
[66] Ising H, Lange-Asschenfeldt H, Moriske HJ, et al. Low frequency noise and stress: bronchitis and cortisol in children exposed chronically to traffic noise and exhaust fumes. Noise Health 2004;6(23):21–8.