

Current reviews of allergy and clinical immunology

(Supported by a grant from GlaxoSmithKline, Inc, Research Triangle Park, NC)

Series editor: Harold S. Nelson, MD

The epidemiology and genetics of asthma risk associated with air pollution

David B. Peden, MD, MS *Chapel Hill, NC*

This activity is available for CME credit. See page 32A for important information.

The occurrence of asthma and allergic diseases has continued to increase in the United States and worldwide, despite general improvements in air quality over the past 40 years. This observation has led many to question whether air quality is truly a significant risk factor in the development and exacerbation of asthma and whether further improvement in air quality is likely to result in improved health outcomes. However, epidemiologic studies have shown that levels of pollutants of less than the current ambient air quality standards still result in exacerbations of asthma and are associated with other morbidities as well. Specific locations, such as living near a roadway, might pose a special exposure risk. Genetic factors almost certainly play a role in determining susceptibility to pollutants, such as including those involved with antioxidant defenses. The best studied of these in the context of air pollution risks are glutathione-S-transferase polymorphisms. Irrespective of whether pollutants contribute to the development of asthma or the well-documented increases in asthma results in more people having pollutant-induced disease, poor air quality in many places remains a significant problem for patients with asthma and allergic disease. A number of public health, pharmaceutical, and nutraceutical interventions might mitigate the effects of pollutant exposure and deserve further study. (*J Allergy Clin Immunol* 2005;115:213-9.)

Key words: Air pollution, asthma, genetics, antioxidants

Abbreviations used

ED: Emergency department
ETS: Environmental tobacco smoke
GST: Glutathione-S-transferase
NO₂: Nitrogen dioxide
PM: Particulate matter
SO₂: Sulfur dioxide

Air pollution results in poor air quality that can affect the entire population. Moreover, within the general population, there are subgroups that have increased susceptibility to the adverse effects of poor air quality. Such subgroups include those identified by age (children or the elderly), socioeconomic status, and the presence of diseases, such as asthma and chronic obstructive pulmonary disease. Those with specific genetic features might also be at increased risk. Air pollutants are most commonly associated with exacerbation of acute respiratory tract illnesses, such as exacerbation of asthma or hospital admission for chronic obstructive pulmonary disease.^{1,2} Chronic exposure to pollutants has been linked to impairment of normal lung growth and development of diseases such as asthma.¹ Allergic airway disorders are defined by the presence of IgE-mediated response to allergens and the resultant eosinophilic airway inflammation. However, another cardinal feature of allergic airway disease is also increased response to a number of agents that do not require IgE-dependent signaling. Environmental pollutants have been shown to enhance primary T_H2 responses to antigens, as well as to exacerbate IgE-mediated responses to subsequently encountered allergens. This review will focus on the effect of pollutants on airway diseases and IgE-mediated responses.

EPIDEMIOLOGY OF AIR POLLUTANT EXPOSURE AND ASTHMA

Epidemiologic studies of the effect of air pollution have examined both the exacerbation of lung disease associated

From the Departments of Pediatrics and Medicine and the Center for Environmental Medicine, Asthma and Lung Biology, School of Medicine, The University of North Carolina at Chapel Hill.

Disclosure of potential conflict of interest: David Peden has consultant arrangements with GlaxoSmithKline; has received grants—research support from the National Institutes of Health, the US Environmental Protection Agency, and GlaxoSmithKline; and is on the Speakers' Bureau for GlaxoSmithKline, AstraZeneca, and Merck.

Received for publication November 29, 2004; accepted for publication December 2, 2004.

Reprint requests: David B. Peden, MD, MS, The Center for Environmental Medicine, Asthma and Lung Biology, 104 Mason Farm Rd, CB#7310, The School of Medicine, The University of North Carolina at Chapel Hill, Chapel Hill, NC, 27599-7310. E-mail: peden@med.unc.edu.

0091-6749/\$30.00

© 2005 American Academy of Allergy, Asthma and Immunology

doi:10.1016/j.jaci.2004.12.003

TABLE I. Primary national ambient air quality standards, United States

Carbon monoxide	Lead	NO ₂	Ozone	Sulfur oxides	PM ₁₀	PM _{2.5} (1997 proposed standards)
9 ppm (8-h average)	1.5 µg/m ³ (quarterly average)	0.053 ppm (annual mean)	0.08 ppm (8-h standard)	0.14 ppm (24-h mean)	50 µg/m ³ (annual mean)	15 µg/m ³ (annual mean)
35 ppm (1-h average)			0.12 ppm (1-h average)	0.03 ppm (annual mean)	150 µg/m ³ (24-h mean)	65 µg/m ³ (24-h mean)

Adapted from the US Environmental Protection Agency Web site: <http://epa.gov/air/criteria.html>.

with acute exposure to pollutants and the development of lung disease or impairment associated with chronic pollutant exposure. Air pollutants implicated in these effects include those regulated by the US Environmental Protection Agency under the Clean Air Act, including nitrogen dioxide (NO₂), ozone, and particulate matter (PM; Table I),¹ as well as other agents, including organic carbon and volatile organic compounds.³⁻⁵ Monitoring of these pollutants is conducted primarily at the state and local level. These monitoring programs generally rely on fixed monitoring stations, providing an overview of air quality for a given area.¹

For research applications, investigators frequently use both regional monitoring data and data from personal monitoring devices, in which an individual carries portable pollutant detection instruments (usually for ozone and PM). Correlation between health and biologic outcomes and pollutant levels is often much stronger with personal monitoring data than with regional monitoring data. Individuals exposed to outdoor pollutants for prolonged periods of time will have a greater exposure burden than those who spend the majority of the day indoors. Regional monitoring alone might underestimate the exposure burden of such individuals. Conversely, for regulatory purposes, it should be noted that regional monitors are less likely to overestimate pollutant levels because of contaminants derived from nonregulated sources (eg, indoor sources of particles).

NO₂ is an important component of indoor and outdoor ambient air pollution, and oxides of nitrogen (NO_x, including NO₂) are precursors for production of ambient air ozone.⁶ Increased levels of NO₂ in domestic buildings are associated with respiratory symptoms (cough, wheeze, phlegm, and report of bronchitis) in children.⁷⁻⁹ In 2004, van Strien et al¹⁰ examined a cohort of infants living in New England identified on the basis of having at least one older sibling with asthma (suggesting increased genetic risk for asthma in this cohort). One-time NO₂ measurements were made in the home, and symptoms were monitored, revealing that infants exposed to more than 17.4 ppb NO₂ had significantly increased risk for respiratory disease compared with those experiencing low-level (<5.1 ppb) NO₂ exposure. This finding is consistent with a 2003 report by McConnell et al¹¹ showing that outdoor NO₂ exposure is associated with bronchitic symptoms in asthmatic children in Southern California. Chauhan et al¹² observed that increased indoor NO₂

exposure was associated with increased severity of viral-induced exacerbation of asthma. Together, these studies and others show that NO₂ is a risk factor for exacerbation of asthma.

The effect of exposure to ozone on lung disease, development, and asthma has been extensively studied. Asthma and respiratory tract disease morbidity (emergency department [ED] visits, hospitalizations, and rescue medication use) are clearly associated with exposure to increased levels of ambient air ozone.² A notable risk population for ozone-induced exacerbation of respiratory illness is asthmatic children.^{1,2} In a study based in Atlanta, White et al¹³ reported increased ED visits by schoolchildren for asthma when 1-hour ozone levels exceeded 0.11 ppm. Similar observations have been made in Mexico City and Los Angeles.^{1,14-16} A 2003 report by Gent et al¹⁷ involving 271 children in southern New England demonstrated that levels of ozone less than the current 1- and 8-hour ozone standards (0.12 and 0.085 ppm, respectively) were associated with exacerbation of asthma in children requiring chronic therapy for asthma. It is also likely that ozone augments response to allergen. Delfino et al¹⁸ reported that when considered together, ozone concentration and fungal spore exposure are associated with asthma exacerbations.

In addition to its effect on exacerbation of disease, recent studies suggest that ozone might promote development of asthma. A cohort of 3535 children with no history of asthma from schools in southern California was studied for up to 5 years.⁵ During this period, 265 children received a newly recognized diagnosis of asthma. It was observed that participation in outdoor sports (presumably associated with increased minute ventilation) in areas of increased ozone concentration was a risk factor for asthma development relative to similar exercise in areas with low ozone exposures. McDonnell et al¹⁹ prospectively studied a cohort of 3091 adult nonsmokers. Over a 15-year interval, new diagnoses of asthma by a physician occurred in 3.2% of men and 4.3% of women. In the men (but not the women) with newly diagnosed asthma, the 20-year mean 8-hour average for ambient ozone levels was a significant risk factor associated with new asthma (relative risk of 2.09 for a 27-ppb increase in ambient air ozone). These data suggest that long-term exposure to ambient ozone is associated with development of asthma in adult male subjects. In general, ozone exposure is strongly associated with increased asthma morbidity, is

TABLE II. Interactions between pollutant and allergen exposure: Effects of *in vivo* airway challenge to ozone, diesel exhaust particles, and LPS on response to allergen in allergic volunteers

Observed effect of pollutant in human subjects	Ozone	DEP	LPS
Response to recall eosinophilic response to nasal allergen challenge	Increased	Increased	Increased
Immediate-phase response to inhaled allergen (PD ₂₀)	Increased	Unknown	Increased
Effect on development of IgE response to a neoantigen	Unknown	Increased	Unknown
Effect on local (airway) IgE levels	Unknown	Increased	Unknown

DEP, Diesel exhaust particle.

a trigger for asthma exacerbation in summer months, and has recently been associated with new diagnoses of asthma.

As with gaseous pollutants, respirable PM (<10 μm in size) is also associated with episodes of increased asthma exacerbation.²⁰ Increased ambient air particulate levels have been linked to need for asthma medication in a cohort of asthmatic subjects studied in Utah.^{21,22} Hospitalization because of increased asthma severity in Seattle was found to occur in conjunction with increases in airborne PM.²³ Similar observations have been made in other locations as well, including Germany, the Czech Republic, Mexico City, and others.²⁴⁻²⁶ Several studies, too numerous to detail here, also show that occupational exposure to PM components, including metals and biologic agents like endotoxin, contribute to wheezing and asthma exacerbation.² These reports demonstrate the important role that particulates could play in asthma morbidity.

Studies performed in the Utah Valley offer a unique opportunity to link the effect of particulates to the work activity of a local steel mill.^{21,22} That study examined the occurrence of respiratory disease episodes (eg, asthma exacerbation and hospital admission for respiratory complaints) that took place during the year that the mill was closed because of a labor dispute, as well as the years before and after the strike. Respiratory morbidities and the level of particulates were both markedly decreased during the strike year, demonstrating a link between levels of ambient air particulates and occurrence of disease exacerbation in asthma and bronchitis.

Particulates are also a significant problem in indoor environments, with environmental tobacco smoke (ETS) being perhaps the most significant remediable source of indoor PM. Overall particle levels in homes without smokers equals that found in ambient air, whereas levels in homes with smokers are often several fold higher than ambient air levels.¹ Numerous case reports and studies have suggested that ETS is an important factor in asthma exacerbations. A meta-analysis of 37 studies conducted by the California Environmental Protection Agency confirmed the increased risk for asthma and wheezing in children exposed to ETS. Maternal tobacco use is associated with increased wheezing, reported asthma, bronchial reactivity, and total and antigen-specific IgE levels in exposed children.^{1,27} ETS might contribute to the development of allergic disease (including asthma), with a number of studies supporting the idea that ETS enhances

atopy development in susceptible individuals.²⁸⁻³⁰ The link between ETS and asthma exacerbation is even clearer. Other indoor air contaminants likely contribute to asthma exacerbation as well, including biologic agents like endotoxin. Although endotoxin exposure in very early life might protect children from the development of asthma, asthma severity of persons already sensitized to allergens correlates well with endotoxin levels in dust samples recovered from their homes. Increased indoor humidity levels, which would contribute to exposure to indoor biologic agents (allergens, endotoxin, and fungal products) is associated with asthma severity.¹

Another way to examine the effect of pollutants on lung health is to assess the effect of exposure to specific sources of pollutants and exacerbations of respiratory disease (Table II). Gauderman et al³¹ studied 1759 ten-year-old children from 12 Southern California cities until the age of 18 years and examined the effect of exposure to a number of products of vehicle fuel combustion (ozone, NO₂, acid vapor, PM_{2.5} (PM <2.5 μm in diameter), PM₁₀ (PM <10 μm in diameter), and elemental carbon) on lung function. Of these, NO₂, acid vapor, PM_{2.5}, and elemental carbon exposure were all significantly correlated to decreased lung function. By using PM_{2.5} as an example, the percentage of children with an FEV₁ of less than 80% of predicted value was 1.6% with exposure to nearly 5 mg/m³ air versus 7.9% with exposure of more than 20 mg/m³. This level of impairment is similar to that found in the children of smoking mothers.

Further evidence of the effect of vehicular traffic in asthma is found in studies of the relationship of proximity to a roadway on health measures. In a study of children aged 5 years or less in Birmingham, United Kingdom,³² those admitted to the hospital with a diagnosis of asthma were more likely to reside in a high-traffic exposure area (>24,000 vehicles per 24 hours at the nearest segment of main road) than either children admitted for nonrespiratory reasons ($P < .02$) or well children ($P < .002$), with traffic exposure (vehicles per 24 hours) correlating well with admission in those living less than 500 m from a road ($P < .006$). Compared with well children, those admitted for respiratory reasons were more likely to live within 200 m of a main road ($P < .02$).

In a German study³³ a group of 7509 schoolchildren were randomly selected to participate in a survey of traffic exposure on asthma and allergy outcomes, with 83% participating. Allergen skin testing, assessment of serum

TABLE III. Interventions reported to decrease the effect of pollutants*

Intervention	Ozone	DEP	LPS	PM
Decreased exposure to motor vehicle exhaust	Decreased ED hospital use by asthmatic subjects	Unknown	Unknown	Decreased ED hospital use by asthmatic subjects
Decreased point source emissions	Unclear	Unclear	Unclear	Decreased ED hospital use by asthmatic subjects, decreased death rates
Inhaled corticosteroids	Decreased response to ozone by allergic asthmatic subjects, no protection in healthy volunteers	Ineffective in one study	Decreased response to LPS by allergic asthmatic subjects, mild protection in healthy volunteers	Unknown
Vitamins C and E	Reports of protection from asthma exacerbation	Unknown	Unknown	Unknown
Non-steroidal anti-inflammatory agents	Protection from immediate decrease in lung function caused by ozone in both asthmatic and healthy volunteers, not a clear effect on allergic inflammation	Unknown	Unknown	Unknown

DEP, Diesel exhaust particle.

*Many items listed as unknown are currently under study, and existing current studies are inconclusive.

IgE levels, and lung function testing were conducted, and traffic exposure was estimated on the basis of traffic counts and an emission model that predicted soot, benzene, and NO₂ exposure. Traffic counts correlated with active asthma, cough, and wheeze and, in children exposed to ETS, a positive skin test response. Pollutant exposure was also linked to cough, wheeze, and asthma. A case-control study in Erie County, NY, in children aged 0 to 14 years (n = 417 and n = 461, respectively) indicated that exposure to high truck volume within a 200-m distance was associated with increased risk for hospitalization because of asthma.³⁴ In US Veterans there is a reported 1.7 relative risk of wheeze associated with living within 50 m of a heavily traveled road compared with the risk among those living more than 400 m from a road.³⁵ Other health outcomes, most notably myocardial infarction, have also been associated with proximity to vehicular traffic.³⁶

GENETICS OF AIR POLLUTANT RESPONSE

The immediate effect of air pollutants on airway function in both healthy and allergic persons has been extensively reviewed, and a full review can be found elsewhere.^{1,2} However, in considering the genetics of response to pollutants, a brief review of the phenotypes of such responses is warranted. Ozone, NO₂, and PM (or various components of PM, including diesel exhaust particles and endotoxin) have all been shown to induce acute inflammatory responses in the airway and, in allergic persons, acute eosinophilia as well. These pollutants have also been shown to enhance immediate- and late-phase responses to inhaled allergen. Of note, each of these pollutants either acts as an oxidant or induces oxidant responses from the host. Airway or plasma antioxidant

status has been associated with protection from the effect of pollutant exposure. As might be anticipated from these observations, genetic studies to date on the effect of pollutants in asthma have focused on genes thought to play a role in the inflammation or antioxidant protection, with *GST* antioxidant genes having been the best studied in human subjects in the context of air pollution.²

Antioxidants, such as ascorbate and uric acid, are recovered from plasma and airway lining fluids and likely serve to prevent extrinsically generated oxidants from affecting surface tissues. Glutathione is an important antioxidant and is an important component of intracellular antioxidant defense mechanisms. Glutathione-S-transferases (GSTs) are phase II xenobiotic defense pathway components and are central to protection from external or intrinsically generated oxidants. Although glutathione is thought of as an intracellular antioxidant and uric acid and ascorbate are thought of as extracellular antioxidants, total antioxidant capability of an individual almost certainly involves complex interactions between glutathione, uric acid, ascorbate, and other antioxidants, such as tocopherols. At a genetic level, perhaps the best studied antioxidant in the context of protection from environmental oxidants is glutathione. Glutathione-S-transferase M1 (*GSTM1*) is a member of the μ family of GSTs. *GSTM1* has a null allele (*GSTM1*0*), which results in no protein expression, with resultant decreases in antioxidant capability. Approximately 40% of the population is affected by this allele. Another GST of interest is *GSTP1*, in which the single-nucleotide polymorphisms at the 105 position are important.

GST genes play a role in lung growth, as shown in a study of a large cohort of 1954 schoolchildren in Southern California, in which children with the *GSTM1*-null allele or a *GSTP1* val105/val105 genotype have decreased lung function growth over a 4-year period.³⁷

Studies of children in Mexico City have examined the risk for asthma relative to lifetime ozone exposure. These studies indicate that expression of GST proteins is an important determinant of asthma severity. *GSTM1*-null children with asthma have decreased lung function associated with ozone exposure compared with those who are *GSTM1* sufficient. Interestingly, within this group, if one also screens for a second antioxidant, SNP (the Pro187Ser single nucleotide polymorphism for nicotinamide adenine dinucleotide [phosphate] reduced: quinone oxidoreductase [*NQO1*]), those with the Pro/Pro allele genotype for *NQO1* have significantly reduced asthma risk ascribed to ozone exposure compared with *GSTM1*-null children with other *NQO1* genotypes.³⁸ Thus although the *GSTM1*-null state is associated with risk for ozone-induced asthma exacerbation, this risk might be mitigated by other protective genes. These investigators also studied the ability of dietary supplementation of vitamins C and E to protect asthmatic subjects from ozone-induced exacerbation of disease. Overall, there was a significant protective effect observed in the entire group of asthmatic subjects, but this effect was much more apparent in those children with the *GSTM1*-null genotype.³⁹

Diesel exhaust challenge and ETS have been shown to induce production of IgE and, like ozone, act as adjuvants for increased response to allergen. It has recently been reported that the adjuvant effect of diesel exhaust on response to ragweed challenge of the nasal airway is greater in subjects having either the *GSTM1*-null or *GSTP1* I105 wild-type genotypes.^{40,41} Nuclear factor erythroid 2-related factor 2, a regulatory nuclear factor that activates phase II antioxidant pathways (including *GSTM1* expression), has also been found to protect macrophages and epithelial cells from the adverse effects of diesel exhaust particles, demonstrating the role of *GSTM1*-related antioxidants in protection from the effects of diesel exhaust.

In a Southern California study children with the *GSTM1*-null genotype and born to mothers who smoked during pregnancy also have increased occurrence of early-onset asthma, persistent asthma, exercise-induced wheeze, need for rescue medication use, and ED visits for asthma compared with children with protective *GST* alleles or born to nonsmoking mothers.⁴² A German study from a cohort of 3504 children revealed that exposure to ETS was associated with a markedly increased risk of asthma and asthma symptoms in *GSTM1*-null individuals.⁴³ *GSTM1*- and *GSTT1*-insufficient children exposed to *in utero* ETS were also found to have decreased lung function. Taken together, these studies suggest that specific SNPs of *GST* genes modulate the response of asthmatic subjects to a variety of oxidizing air pollutants.

INTERVENTIONS (TABLE III)

Public health approaches to decrease air pollutants have been shown to have a measurable effect on health

outcomes. One example of this occurred in concert with the 1996 Olympic Games held in Atlanta. Coincident with attempts by the local government to decrease ozone generation caused by vehicle exhaust, there was not only a decrease in summer ozone levels but also a significant decrease in asthma morbidity noted during this time.⁴⁴ Likewise, in Dublin, Ireland, a ban on bituminous coal sales was implemented on September 1, 1990, to improve air quality.⁴⁵ In the 72 months after the ban, there was a 70% decrease in black smoke concentrations, a 5.7% decrease in nontrauma death rates, a 15.5% decrease in respiratory death rates, and a 10.3% decrease in cardiovascular death rates when compared with the 72 months preceding the ban.

In addition to societal interventions, specific nutritional and pharmacologic intervention might prove useful. Antioxidants might prove to be very useful in preventing adverse effects of environmental agents in asthma and lung disease. Although not all studies agree, there are a number of reports that suggest that antioxidants, such as ascorbate and tocopherol, might be useful in preventing ozone-induced lung responses.⁴⁶⁻⁵⁰ Exposure to pollutants is linked to loss of antioxidants from the airway,^{51,52} and asthmatic subjects have been reported to have decreased baseline airway fluid antioxidant levels.⁵³ Samet et al⁵⁴ found that combination therapy with ascorbate and tocopherol prevented ozone-induced decreases in lung function in healthy volunteers who had preceded supplementation with an antioxidant-depleted diet. Trenga et al⁵⁵ found that vitamin E and C pretreatment blunted acute bronchospastic response to sulfur dioxide (SO₂) challenge in persons who had been exposed to ozone (using the SO₂ as a replacement for methacholine). Studies cited previously in this review^{39,50,56,57} suggest that genetic factors might determine which asthmatic subjects are better candidates for antioxidant supplement therapy because those with *GSTM1* deficiency had better benefit from the effect of ozone. Animal studies suggest that the thiol-based antioxidants N-acetylcysteine and buccillamine decrease the adjuvant effects of diesel exhaust particles.⁵⁸

Corticosteroids have also been shown to blunt the effect of pollutants on airway inflammation in allergic asthmatic subjects. The effect of SO₂ and NO₂ on allergen-induced bronchial inflammation and NO₂-induced nasal eosinophilic inflammation in the airway is blunted by fluticasone.⁵⁹ In allergic asthmatic subjects budesonide has been shown to inhibit ozone-induced neutrophil influx but has no effect on immediate changes in lung function.⁶⁰ Corticosteroids have not been found to have any protective effect against ozone in healthy volunteers.^{60,61}

Corticosteroids have also been examined in the context of diesel exhaust particle and endotoxin challenge. Topical fluticasone has little effect on diesel exhaust particle-induced production of IgE or T_H2 cytokines, although equivalent doses did (as expected) inhibit antigen-specific IgE and T_H2 inflammatory responses after ragweed allergen challenge in allergic subjects.⁶² In healthy volunteers treatment with corticosteroids before

inhalation challenge with endotoxin-rich grain dust extracts offers only mild protection from the typical inflammatory and bronchoconstrictive responses in healthy volunteers.⁶³ Our group reported that allergic patients with mild asthma treated with inhaled fluticasone for 2 weeks before challenge with 5 µg of nebulized endotoxin had decreased expression of CD14 on airway monocytes and macrophages immediately before challenge and a significant inhibition of endotoxin-induced neutrophil influx.⁶⁴

COX inhibitors have also been studied in both allergic asthmatic and healthy volunteers exposed to ozone. These drugs have been found to decrease immediate effects of ozone on lung function, with little effect on inflammation.¹ Leukotriene modifiers have not been studied for their potential antipollutant effects.

FUTURE DIRECTIONS

Clearly much remains to be learned by using systems biologic, genomic, and epidemiologic approaches in examining *in vivo*, cellular, and population responses to pollutant stress. Antioxidants and regulators of inflammation are logical targets for investigation. Traditional therapy that decreases chronic allergic inflammation, such as inhaled corticosteroids, also protects allergic asthmatic subjects (but not healthy individuals) against the effect of challenge with air pollutants. Other anti-inflammatory approaches have not been studied but might hold promise for protection of asthmatic subjects from pollutants. Genetic studies will be important to identify persons at greater risk for pollutant-induced exacerbation of lung disease and perhaps identification of specific interventions that might be most appropriate for a given individual.

Public health approaches to decrease exposure to air pollutants can be implemented and are associated with improved health outcomes. Decreased use of fossil fuels is essential to decreasing ambient air pollutant levels. Changes in design of the built environment (city and neighborhood planning) that allows for easier use of mass transit; pedestrian traffic to and from home, work, and school; and use of telecommuting to decrease traffic might all be useful in decreasing pollutant burden and environmentally induced exacerbations of lung disease.

REFERENCES

- Peden DB. Air pollution: indoor and outdoor. In: Adkinson NF Jr, Yunginger JW, Busse WW, Bochner BS, Holgate SK, Simons FE, editors. *Middleton's allergy: principles and practice*. Philadelphia: Mosby; 2003. p. 515-28.
- Bernstein JA, Alexis N, Barnes C, Bernstein IL, Bernstein JA, Nel A, et al. Health effects of air pollution. *J Allergy Clin Immunol* 2004;114:1116-23.
- McConnell R, Berhane K, Gilliland F, Molitor J, Thomas D, Lurmann F, et al. Prospective study of air pollution and bronchitic symptoms in children with asthma. *Am J Respir Crit Care Med* 2003;168:790-7.
- McConnell R, Berhane K, Gilliland F, London SJ, Vora H, Avol E, et al. Air pollution and bronchitic symptoms in Southern California children with asthma. *Environ Health Perspect* 1999;107:757-60.
- McConnell R, Berhane K, Gilliland F, London SJ, Islam T, Gauderman WJ, et al. Asthma in exercising children exposed to ozone: a cohort study. *Lancet* 2002;359:386-91.
- Committee of the Environmental and Occupational Health Assembly of the American Thoracic Society. Health effects of outdoor air pollution. *Am J Respir Crit Care Med* 1996;153:3-50.
- Dijkstra L, Houthuijs D, Brunekreef B, Akkerman I, Boleij JS. Respiratory health effects of the indoor environment in a population of Dutch children. *Am Rev Respir Dis* 1990;142:1172-8.
- Brunekreef B, Houthuijs D, Dijkstra L, Boleij JS. Indoor nitrogen dioxide exposure and children's pulmonary function. *J Air Waste Manage Assoc* 1990;40:1252-6.
- Neas LM, Dockery DW, Ware JH, Spengler JD, Speizer FE, Ferris BG Jr. Association of indoor nitrogen dioxide with respiratory symptoms and pulmonary function in children. *Am J Epidemiol* 1991;134:204-19.
- van Strien RT, Gent JF, Belanger K, Triche E, Bracken MB, Leaderer BP. Exposure to NO₂ and nitrous acid and respiratory symptoms in the first year of life. *Epidemiology* 2004;15:471-8.
- McConnell R, Berhane K, Gilliland F, Molitor J, Thomas D, Lurmann F, et al. Prospective study of air pollution and bronchitic symptoms in children with asthma. *Am J Respir Crit Care Med* 2003;168:790-7.
- Chauhan AJ, Inskip HM, Linaker CH, Smith S, Schreiber J, Johnston SL, et al. Personal exposure to nitrogen dioxide (NO₂) and the severity of virus-induced asthma in children. *Lancet* 2003;361:1939-44.
- White MC, Etzel RA, Wilcox WD, Lloyd C. Exacerbations of childhood asthma and ozone pollution in Atlanta. *Environ Res* 1994;65:56-68.
- Romieu I, Meneses F, Sienra-Monge JJ, Huerta J, Ruiz VS, White MC, et al. Effects of urban air pollutants on emergency visits for childhood asthma in Mexico City. *Am J Epidemiol* 1995;141:546-53.
- Romieu I, Meneses F, Ruiz S, Sienra JJ, Huerta J, White MC, et al. Effects of air pollution on the respiratory health of asthmatic children living in Mexico City. *Am J Respir Crit Care Med* 1996;154:300-7.
- Romieu I, Meneses F, Ruiz S, Huerta J, Sienra JJ, White M, et al. Effects of intermittent ozone exposure on peak expiratory flow and respiratory symptoms among asthmatic children in Mexico City. *Arch Environ Health* 1997;52:368-76.
- Gent JF, Triche EW, Holford TR, Belanger K, Bracken MB, Beckett WS, et al. Association of low-level ozone and fine particles with respiratory symptoms in children with asthma. *JAMA* 2003;290:1859-67.
- Delfino RJ, Coate BD, Zeiger RS, Seltzer JM, Street DH, Koutarakis P. Daily asthma severity in relation to personal ozone exposure and outdoor fungal spores. *Am J Respir Crit Care Med* 1996;154:633-41.
- McDonnell WF, Abbey DE, Nishino N, Lebowitz MD. Long-term ambient ozone concentration and the incidence of asthma in nonsmoking adults: the AHSOG Study. *Environ Res* 1999;80:110-21.
- Pope CA III. Epidemiology of fine particulate air pollution and human health: biologic mechanisms and who's at risk? *Environ Health Perspect* 2000;108(suppl 4):713-23.
- Pope CA III. Respiratory hospital admissions associated with PM₁₀ pollution in Utah, Salt Lake, and Cache Valleys. *Arch Environ Health* 1991;46:90-7.
- Pope CA III. Respiratory disease associated with community air pollution and a steel mill, Utah Valley. *Am J Public Health* 1989;79:623-8.
- Schwartz J, Slater D, Larson TV, Pierson WE, Koenig JQ. Particulate air pollution and hospital emergency room visits for asthma in Seattle. *Am Rev Respir Dis* 1993;147:826-31.
- Peters A, Dockery DW, Heinrich J, Wichmann HE. Short-term effects of particulate air pollution on respiratory morbidity in asthmatic children. *Eur Respir J* 1997;10:872-9.
- Peters A, Wichmann HE, Tuch T, Heinrich J, Heyder J. Respiratory effects are associated with the number of ultrafine particles. *Am J Respir Crit Care Med* 1997;155:1376-83.
- Peters A, Goldstein IF, Beyer U, Franke K, Heinrich J, Dockery DW, et al. Acute health effects of exposure to high levels of air pollution in eastern Europe. *Am J Epidemiol* 1996;144:570-81.
- Dijkstra L, Houthuijs D, Brunekreef B, Akkerman I, Boleij JS. Respiratory health effects of the indoor environment in a population of Dutch children. *Am Rev Respir Dis* 1990;142:1172-8.

28. Gergen PJ. Environmental tobacco smoke as a risk factor for respiratory disease in children. *Respir Physiol* 2001;128:39-46.
29. Gergen PJ, Fowler JA, Maurer KR, Davis WW, Overpeck MD. The burden of environmental tobacco smoke exposure on the respiratory health of children 2 months through 5 years of age in the United States: Third National Health and Nutrition Examination Survey, 1988 to 1994. *Pediatrics* 1998;101(2):E8.
30. Gergen PJ, Weiss KB. The increasing problem of asthma in the United States. *Am Rev Respir Dis* 1992;146:823-4.
31. Gauderman WJ, Avol E, Gilliland F, Vora H, Thomas D, Berhane K, et al. The effect of air pollution on lung development from 10 to 18 years of age. *N Engl J Med* 2004;351:1057-67.
32. Edwards J, Walters S, Griffiths RK. Hospital admissions for asthma in preschool children: relationship to major roads in Birmingham, United Kingdom. *Arch Environ Health* 1994;49:223-7.
33. Nicolai T, Carr D, Weiland SK, Duhme H, von Ehrenstein O, Wagner C, et al. Urban traffic and pollutant exposure related to respiratory outcomes and atopy in a large sample of children. *Eur Respir J* 2003;21:956-63.
34. Lin S, Munsie JP, Hwang SA, Fitzgerald E, Cayo MR. Childhood asthma hospitalization and residential exposure to state route traffic. *Environ Res* 2002;88:73-81.
35. Garshick E, Laden F, Hart JE, Caron A. Residence near a major road and respiratory symptoms in U.S. Veterans. *Epidemiology* 2003;14:728-36.
36. Peters A, von Klot S, Heier M, Trentinaglia I, Hormann A, Wichmann HE, et al. Exposure to traffic and the onset of myocardial infarction. *N Engl J Med* 2004;351:1721-30.
37. Gilliland FD, Gauderman WJ, Vora H, Rappaport E, Dubeau L. Effects of glutathione-S-transferase M1, T1, and P1 on childhood lung function growth. *Am J Respir Crit Care Med* 2002;166:710-6.
38. David GL, Romieu I, Sienra-Monge JJ, Collins WJ, Ramirez-Aguilar M, del Rio-Navarro BE, et al. Nicotinamide adenine dinucleotide (phosphate) reduced:quinone oxidoreductase and glutathione S-transferase M1 polymorphisms and childhood asthma. *Am J Respir Crit Care Med* 2003;168:1199-204.
39. Romieu I, Sienra-Monge JJ, Ramirez-Aguilar M, Moreno-Macias H, Reyes-Ruiz NI, Estela del Rio-Navarro B, 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;59:8-10.
40. Bastain TM, Gilliland FD, Li YF, Saxon A, Diaz-Sanchez D. Intra-individual reproducibility of nasal allergic responses to diesel exhaust particles indicates a susceptible phenotype. *Clin Immunol* 2003;109:130-6.
41. Gilliland FD, Li YF, Saxon A, Diaz-Sanchez D. Effect of glutathione-S-transferase M1 and P1 genotypes on xenobiotic enhancement of allergic responses: randomised, placebo-controlled crossover study. *Lancet* 2004;363:119-25.
42. Gilliland FD, Li YF, Dubeau L, Berhane K, Avol E, McConnell R, et al. Effects of glutathione S-transferase M1, maternal smoking during pregnancy, and environmental tobacco smoke on asthma and wheezing in children. *Am J Respir Crit Care Med* 2002;166:457-63.
43. Kabesch M, Hoeffler C, Carr D, Leupold W, Weiland SK, von Mutius E. Glutathione S transferase deficiency and passive smoking increase childhood asthma. *Thorax* 2004;59:569-73.
44. Friedman MS, Powell KE, Hutwagner L, Graham LM, Teague WG. Impact of changes in transportation and commuting behaviors during the 1996 Summer Olympic Games in Atlanta on air quality and childhood asthma. *JAMA* 2001;285:897-905.
45. Clancy L, Goodman P, Sinclair H, Dockery DW. Effect of air-pollution control on death rates in Dublin, Ireland: an intervention study. *Lancet* 2002;360:1210-4.
46. Gilliland FD, Berhane KT, Li YF, Gauderman WJ, McConnell R, Peters J. Children's lung function and antioxidant vitamin, fruit, juice, and vegetable intake. *Am J Epidemiol* 2003;158:576-84.
47. Hatch GE. Asthma, inhaled oxidants, and dietary antioxidants. *Am J Clin Nutr* 1995;61(suppl):625S-30S.
48. Kalayci O, Besler T, Kilinc K, Sekerel BE, Saraclar Y. Serum levels of antioxidant vitamins (alpha tocopherol, beta carotene, and ascorbic acid) in children with bronchial asthma. *Turk J Pediatr* 2000;42:17-21.
49. Rahman I, Morrison D, Donaldson K, MacNee W. Systemic oxidative stress in asthma, COPD, and smokers. *Am J Respir Crit Care Med* 1996;154:1055-60.
50. Romieu I, Trenga C. Diet and obstructive lung diseases. *Epidemiol Rev* 2001;23:268-87.
51. Kelly FJ, Mudway I, Blomberg A, Frew A, Sandstrom T. Altered lung antioxidant status in patients with mild asthma. *Lancet* 1999;354:482-3.
52. Mudway IS, Blomberg A, Frew AJ, Holgate ST, Sandstrom T, Kelly FJ. Antioxidant consumption and repletion kinetics in nasal lavage fluid following exposure of healthy human volunteers to ozone. *Eur Respir J* 1999;13:1429-38.
53. Kongerud J, Crissman K, Hatch G, Alexis N. Ascorbic acid is decreased in induced sputum of mild asthmatics. *Inhal Toxicol* 2003;15:101-9.
54. Samet JM, Hatch GE, Horstman D, Steck-Scott S, Arab L, Bromberg PA, et al. Effect of antioxidant supplementation on ozone-induced lung injury in human subjects. *Am J Respir Crit Care Med* 2001;164:819-25.
55. Trenga CA, Koenig JQ, Williams PV. Dietary antioxidants and ozone-induced bronchial hyperresponsiveness in adults with asthma. *Arch Environ Health* 2001;56:242-9.
56. Romieu I, Meneses F, Ramirez M, Ruiz S, Perez PR, Sienra JJ, et al. Antioxidant supplementation and respiratory functions among workers exposed to high levels of ozone. *Am J Respir Crit Care Med* 1998;158:226-32.
57. Romieu I, Sienra-Monge JJ, Ramirez-Aguilar M, Tellez-Rojo MM, Moreno-Macias H, Reyes-Ruiz NI, et al. Antioxidant supplementation and lung functions among children with asthma exposed to high levels of air pollutants. *Am J Respir Crit Care Med* 2002;166:703-9.
58. Whitekus MJ, Li N, Zhang M, Wang M, Horwitz MA, Nelson SK, et al. Thiol antioxidants inhibit the adjuvant effects of aerosolized diesel exhaust particles in a murine model for ovalbumin sensitization. *J Immunol* 2002;168:2560-7.
59. Davies RJ, Rusznak C, Calderon MA, Wang JH, Abdelaziz MM, Devalia JL. Allergen-irritant interaction and the role of corticosteroids. *Allergy* 1997;52(suppl):59-65.
60. Vagaggini B, Taccola M, Conti I, Carnevali S, Cianchetti S, Bartoli ML, et al. Budesonide reduces neutrophilic but not functional airway response to ozone in mild asthmatics. *Am J Respir Crit Care Med* 2001;164:2172-6.
61. Nightingale JA, Rogers DF, Fan CK, Barnes PJ. No effect of inhaled budesonide on the response to inhaled ozone in normal subjects. *Am J Respir Crit Care Med* 2000;161:479-86.
62. Diaz-Sanchez D, Tsien A, Fleming J, Saxon A. Effect of topical fluticasone propionate on the mucosal allergic response induced by ragweed allergen and diesel exhaust particle challenge. *Clin Immunol* 1999;90:313-22.
63. Trapp JF, Watt JL, Frees KL, Quinn TJ, Nonnenmann MW, Schwartz DA. The effect of glucocorticoids on grain dust-induced airway disease. *Chest* 1998;113:505-13.
64. Alexis NE, Peden DB. Blunting airway eosinophilic inflammation results in a decreased airway neutrophil response to inhaled LPS in patients with atopic asthma: a role for CD14. *J Allergy Clin Immunol* 2001;108:577-80.