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The epidemiology and genetics of asthma risk associated with air pollution

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

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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 nutriceutical 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
NO_2: Nitrogen dioxide
PM: Particulate matter
SO_2: 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.

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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.

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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 (NO_2), 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).

NO_2 is an important component of indoor and outdoor ambient air pollution, and oxides of nitrogen (NOx, including NO_2) are precursors for production of ambient air ozone.[6] Increased levels of NO_2 in domestic buildings are associated with respiratory symptoms (cough, wheeze, phlegm, and report of bronchitis) in children.[7-9] In 2004, van Strien et al[10] 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 NO_2 measurements were made in the home, and symptoms were monitored, revealing that infants exposed to more than 17.4 ppb NO_2 had significantly increased risk for respiratory disease compared with those experiencing low-level (<5.1 ppb) NO_2 exposure. This finding is consistent with a 2003 report by McConnell et al[11] showing that outdoor NO_2 exposure is associated with bronchitic symptoms in asthmatic children in Southern California. Chauhan et al[12] observed that increased indoor NO_2 exposure was associated with increased severity of viral-induced exacerbation of asthma. Together, these studies and others show that NO_2 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 al[13] reported increased ED visits by school-children 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 al[17] 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 al[18] 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 al[19] 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