The Role of Ozone Exposure in the Epidemiology of Asthma

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Asthma is a clinical condition characterized by intermittent respiratory symptoms, nonspecific airway hyperresponsiveness, and reversible airway obstruction. Although the pathogenesis of asthma is incompletely understood, it is clear that airway inflammation is a paramount feature of the condition. Because inhalation of ozone by normal, healthy subjects causes increased airway responsiveness and inflammation, it is somewhat surprising that most controlled human exposure studies that have involved asthmatic subjects have not shown them to be especially sensitive to ozone. The acute decrement in lung function that is the end point traditionally used to define sensitivity to ozone in these studies may be due more to neuromuscular mechanisms limiting deep inspiration than to bronchoconstriction. The frequency of asthma attacks following ozone exposures may be a more relevant end point. Epidemiologic studies, rather than controlled human exposure studies, are required to determine whether ozone pollution increases the risk of asthma exacerbations. Asthma affects approximately 10 million people in the United States and, thus, the answer to this question is of considerable public health importance. Both the prevalence and severity of asthma appear to be increasing in many countries. Although increased asthma morbidity and mortality are probably of multifactorial etiology, a contributory role of urban air pollution is plausible. The epidemiologic database to support an association between asthma and ozone exposure is limited, but the results of several studies suggest such an association. Some potential approaches to further investigation of the relationship between asthma and ozone, including those that would link controlled human exposures to population-based studies, are considered. — Environ Health Perspect 101(Suppl 4):219–224 (1993).

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Asthma and Ozone

Under the provisions of the Clean Air Act of 1970, the Environmental Protection Agency is required to set a standard for ambient air quality regarding ozone that will protect the health of the general population, including sensitive subgroups such as persons with asthma. Considerable research has been conducted on the health effects of ozone exposure over the past two decades in an effort to provide an adequate scientific foundation for regulation of ozone concentration in ambient air. Despite this research effort, there is still some uncertainty about whether persons with asthma are particularly sensitive to ozone.

Asthma is a clinical condition characterized by intermittent respiratory symptoms (e.g., dyspnea, chest tightness, wheezing, cough), airway hyperresponsiveness to a variety of nonspecific stimuli, and reversible or variable airway obstruction (*1*). Although the pathogenesis of asthma remains incompletely understood, it is clear that the condition is of multifactorial etiology. Currently, airway inflammation (i.e., edema; infiltration by leukocytes, especially eosinophils; epithelial injury) is considered to be the paramount feature of asthma (*2*). Several of the stimuli known to cause increased airway responsiveness, such as viral respiratory tract infections (*3*) and inhaled antigen (*4*), also cause airway inflammation. Recurrent exacerbations of asthma associated with increased airway inflammation may lead to the development of chronic airway obstruction (*5*), and recently published guidelines for the treatment of asthma stress the importance of preventing such exacerbations by the avoidance of exposure to inciting agents and the use of prophylactic antiinflammatory medications (*6–8*). It is clear that airway hyperresponsiveness alone does not define asthma since there are many persons with this physiologic characteristic who do not have symptomatic asthma. Whether such persons are at increased risk of developing asthma with viral respiratory tract infections or exposure to pollutants is not known.

Controlled Human Exposure Studies

The results of multiple controlled human exposure studies have documented that inhalation of ozone causes respiratory symptoms (*9*), acute decrements in pulmonary function (*10–12*), and increased airway responsiveness to nonspecific stimuli such as methacholine or histamine (*13,14*) in a dose-dependent manner in normal, healthy subjects. Most of these studies have focused on short-term exposures (i.e., $\leq$ 2 hr), perhaps because the National Ambient Air Quality Standard (NAAQS) is based on a 1-hr maximum concentration (0.12 ppm). With short-term exposures, concentrations of ozone > 0.12 ppm are usually required to cause significant mean decrements in forced expiratory volume in 1 sec (FEV_1). However, there is considerable interindividual variability in the magnitude of the response, with 10 to 25% of subjects tested at 0.12 ppm developing decrements in FEV_1 of $\geq$ 10% after 1 to 2 hr of exposure (*15*). Longer exposure duration and increased minute ventilation with exercise are required to see significant mean effects at ozone concentrations < 0.12 ppm (*16,17*).

Seltzer et al. found ozone-induced increases in methacholine responsiveness to be associated with the presence of excess polymorphonuclear cells (PMNs) in bronchoalveolar lavage (BAL) fluid that was collected 3 hr after intermittently exercising healthy subjects were exposed to 0.4 ppm for 2 hr (*14*). A subsequent study by EPA investigators using an identical exposure protocol demonstrated that the increase in PMNs was still present when they collected BAL fluid 18 hr after exposure (*18*). In addition, these investigators also reported significant mean increases in various biochemical end points indicative of an inflammatory response in BAL fluid collected

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after the 2-hr ozone exposure as compared to that collected after sham exposure. More recently, the same team of EPA investigators has reported their findings in BAL fluid obtained 16 hr after 6.6-hr exposure of healthy subjects to 0.1 and/or 0.08 ppm ozone during continuous moderate exercise (*19*). Similar to what has been noted with pulmonary function responses at lower concentrations of ozone, there was considerably greater intersubject variability in the degree of inflammatory response observed at 0.10 and 0.08 ppm as compared to the earlier study using 0.4 ppm. This series of BAL studies, in healthy human subjects coupled with studies using dogs (*20*) and guinea pigs (*21*), have clearly demonstrated the potential for inhaled ozone to cause airway inflammation.

Given the impressive data base on the responses of normal, healthy subjects to controlled exposures to ozone, in terms of both increased airway responsiveness and evidence of inflammation, one would expect asthmatic subjects to be particularly sensitive to ozone. Thus, it is somewhat surprising that most controlled exposure studies that have involved asthmatic subjects have not documented significantly greater mean responses for these subjects.

Several studies in the late 1970s looked at symptomatic and pulmonary function responses of asthmatic subjects to short-term exposures to ozone at concentrations in the range of 0.2 to 0.25 ppm. In a study of 22 asthmatic subjects exposed to 0.2 to 0.25 ppm ozone for 2 hr with intermittent light exercise, Linn et al. found no significant changes in either spirometric indices of pulmonary function or respiratory symptoms (*22*). A similar study by Silverman of 17 asthmatic subjects exposed to 0.25 ppm ozone while at rest also demonstrated no significant mean changes in symptoms and spirometry after exposure (*23*). However, in 6 of the 17 subjects, there was a >10% decrease in FEV_1 after ozone exposure, which suggests the possibility of a more sensitive subgroup. Another study by Linn et al. involved exposures to polluted ambient air in a mobile laboratory in which the mean (± SD) ozone concentration was 0.22 (± 0.09) ppm (*24*). Other pollutant concentrations were low except for total suspended particulate matter, which was 182 (± 42) $\mu g/m^3$. Thirty asthmatic and 34 normal subjects were tested using a protocol identical to that of the previous study by these investigators. The responses of the asthmatic and normal subjects were not generally different. Most subjects exhibited slight decrements in lung function and mild increases in respiratory symptoms. The investigators did note, however, that a possible explanation for their failure to find any difference in response between the groups was that many of their normal subjects had a history of respiratory allergy and "appeared atypically reactive to respiratory insults."

Two more recent studies by Koenig et al. involving exposure of adolescents to lower concentrations of ozone also failed to show a significant difference in response between asthmatic and healthy subjects. The first study compared the responses of 10 asthmatic and 10 healthy adolescent subjects to exposure to filtered air or 0.12 ppm ozone for 1 hr while at rest (*25*). There were no significant pulmonary function changes in either group and no measurable differences between the two groups. A follow-up study involved exposure of 10 asthmatic and 10 healthy adolescents to filtered air, 0.12 and/or 0.18 ppm ozone, for 30 min while at rest, followed by 10 min of moderate exercise (minute ventilation 30–40 $L/min/m^2$) (*26*). Decrements in FEV_1 were in the range of 3 to 6% for both groups and, again, there were no significant differences between the groups.

The latest study to examine the responses of asthmatic subjects to inhaled ozone, by Eschenbacher et al. (*27*), was designed to provide a greater exposure to ozone than was administered in the previous studies. A higher concentration was used (0.4 ppm), exposures were longer (2 hr), moderate exercise (minute ventilation 30 $L/min/m^2$) was performed for sufficiently long periods (15 min of exercise alternating with 15 min of rest), and bronchodilator medications were withheld. Under these conditions, a differential response between asthmatic and nonasthmatic subjects was demonstrated. Mean decrement in FEV_1 across the 2-hr exposure was 24% for asthmatic subjects and 13.2% for healthy controls. The results of this study, which have been criticized because a methacholine challenge test was performed immediately prior to each exposure and because most of the asthmatic subjects developed exercise-induced bronchospasm to the filtered air exposure, challenge the widely held position that persons with asthma are not more sensitive to ozone than normal, healthy persons.

Given the paucity of data on the response of asthmatic subjects from controlled studies that have been conducted with adequate exposure, it is relevant to review the limited data on the response of atopic subjects without clinical asthma. Holtzman et al. exposed nine atopic subjects (i.e., with a personal history of allergic rhinitis or childhood asthma and at least two positive responses to a battery of seven skin-prick tests with common aeroallergens) and seven nonatopic subjects to 0.6 ppm ozone or filtered air for 2 hr while at rest (*13*). Airway responsiveness to histamine was measured before and after each exposure and was increased in most of the subjects following ozone exposure. Although the authors concluded that the response to ozone was not affected by atopic status, the increase in histamine responsiveness was greater in the atopic subjects than the nonatopic subjects. This difference did not achieve statistical significance due to the small sample size and variability of response among the atopic subjects.

A similar study by McDonnell et al. at the EPA involving 26 nonasthmatic subjects with allergic rhinitis exposed to 0.18 ppm ozone or filtered air also failed to demonstrate a markedly different response to ozone as compared to previously tested nonatopic subjects (*28*). Because McDonnell and coworkers had anticipated that the magnitude of the response to ozone would be associated with baseline airway responsiveness, they speculated that both the size of their sample and the range of airway responsiveness in their subjects may have been too small to detect this relationship.

A recently completed study by Aris et al. (*29*) was designed to determine whether exposure to nitric acid fog would enhance the effects of ozone on pulmonary function in healthy subjects. It generated results contrary to those reported by McDonnell and coworkers. The Aris study protocol involved screening prospective subjects for ozone sensitivity based on a 10% decline in FEV_1 across a 3-hr exposure during moderate exercise (minute ventilation 40 L/min) to 0.2 ppm. Ten subjects selected in this manner demonstrated greater responsiveness to methacholine than 10 prospective subjects excluded from the full study protocol because of their lack of sensitivity to ozone. The study by Aris and coworkers provided a broader range of both baseline airway responsiveness and responses to ozone than did the McDonnell study.

The Aris study results are supported by a recent study by Linn et al. in which 8 of 12 subjects (responders), selected because of their sensitivity to ozone (as measured by decrements in FEV_1), demonstrated hyperresponsiveness to methacholine (*30*). These two recent studies, coupled with the Eschenbacher study involving subjects with asthma, suggest that persons with nonspecific airway hyperresponsiveness, whether clinically asthmatic or healthy, may be a subgroup that has an enhanced sensitivity to

ozone. Because asymptomatic, nonspecific airway hyperresponsiveness is common, the issue of whether such persons are at increased risk for ozone-induced pulmonary toxicity is of obvious importance to the design of adequately protective regulatory strategies.

The acute decrement in FEV_1 in response to ozone inhalation is thought to be due more to chest discomfort and/or neuromuscular mechanisms limiting deep inspiration than to bronchoconstriction (*31*), and it may be that asthmatic subjects are not especially sensitive to ozone for this end point. The frequency of asthma attacks following ozone exposure may be a more relevant end point to monitor. Epidemiologic studies, rather than controlled human exposure studies, are required to answer the question of whether ozone pollution increases the risk of asthma exacerbations.

Epidemiologic Studies

Asthma affects approximately 10 million people in the United States (*32*). Both the prevalence and severity of asthma appear to be increasing (*33*), despite improved understanding of the pathophysiology of the disease and the availability of effective drugs for its management.

Asthma mortality in the United States declined from 1968 to 1978; it has been steadily increasing since 1979 (*34*). The annual number of asthma deaths has increased over 30% since 1980 (*35*). The asthma mortality rate has increased more rapidly for females than for males and for older persons than for young. Because asthma hospitalization and mortality rates are considerably higher for African-Americans than for Whites, it has been argued that the urban poor's decreased access to and utilization of health care are the primary factors responsible for the increase in asthma mortality. A provocative study by Weiss and Wagener confirmed that the asthma mortality is higher in African Americans than Whites, that this gap is widening, and that New York City and Chicago had the highest rates of asthma deaths (*36*).

Decreased access to or availability of appropriate health care for asthma is not likely to be the sole explanation for increasing asthma morbidity and mortality in the United States, because these rates also are increasing in other Western countries, such as Canada, France, Denmark, and Germany, with more equitable health care delivery systems (*37*). In the United Kingdom, asthma mortality rates have risen more rapidly than in the United States (*38*). At the peak of an epidemic of asthma deaths in New Zealand in the 1970s, the mortality rate for asthma was 10 times higher than that in the United States (*33*).

Other proposed explanations for the observed increases in asthma morbidity and mortality include the following: *a*) the 1979 change in the *International Classification of Diseases* (ICD) coding of asthmatic bronchitis as asthma rather than bronchitis, *b*) a shift in physician diagnosis away from bronchitis to asthma, *c*) an improved ability of physicians to diagnose asthma through greater availability and use of pulmonary function tests, *d*) increased toxicity due to asthma medications, and *e*) a true increase in the prevalence and/or severity of asthma (*33*). Which of these explanations is playing an important role is unclear, but it is likely that the rise in asthma mortality is of multifactorial origin.

The results of the Weiss and Wagener study indicate that the change in ICD coding is not the only factor at work since the increase in asthma death started in 1978, before the latest version of the ICD was introduced, and continued unabated through 1987 (*36*). The observation by Weiss and Wagener that there were geographic areas with exceptionally high asthma mortality (New York City; Cook County, Illinois; Maricopa County, Arizona; Fresno County, California) also suggests that improved physician diagnosis of asthma is unlikely to have caused the increases in asthma morbidity and mortality. A companion study by Gergen and Weiss found that among children 0 to 17 years old, there was a 4.5% annual increase in asthma hospitalization from 1979 to 1987 (*39*). The authors found that while much of the increase in hospitalizations for asthma could be explained by a shift in diagnostic coding from bronchitis to asthma, other factors such as environmental pollution may be playing a role.

Although consideration must be given to other possible explanations for the increase in asthma mortality, the weight of the evidence favors a true increase in asthma prevalence. Asthma prevalence data from the United States (*40*), the United Kingdom (*41*), and New Zealand (*42*) are remarkably consistent in documenting an increase. For example, a study by Gergen and coworkers using serial National Health and Nutrition Examination Survey (NHANES) data showed that the prevalence of ever having asthma increased from 4.8 to 7.6% among children 6 to 11 years old from the early to the late 1970s (*40*). While it has been postulated that this rise in asthma prevalence is due to an increase in environmental allergens, an increase in nonallergenic environmental pollution is just as plausible. Weiss has reported a seasonal pattern of asthma mortality, with deaths in patients 5 to 35 years old peaking in June through August, that is consistent with an ozone effect (*43*).

The epidemiologic data base supporting the concept that air pollution can cause exacerbations of asthma is reasonably convincing, but the evidence linking ozone to asthma attacks is limited. In 1961, Schoettlin and Landau reported the results of a study of a panel of 137 asthmatic subjects in Pasadena, California, that showed there were significantly more attacks on days with a maximum 1-hr oxidant concentration greater than 0.2 ppm than on days with lower levels of oxidant pollution (*44*). A later study by Whittemore and Korn examined the relationship between daily asthma attack occurrence and 24-hr average pollutant concentrations and meteorologic conditions using 16 panels of asthmatic subjects residing in six Los Angeles communities (*45*). An innovative statistical approach involving a separate multiple logistic model for each subject's asthma attack probability was employed, and variables representing previous attack history, day of week, and time since the start of the study were included in the regressions. The dominant predictor of attacks was the presence of an attack on the preceding day; but oxidant concentration, particulate concentration, and cool temperature also were positively associated with asthma attacks. Based on their data, the authors calculated that a 0.1-ppm increase in the 24-hr average oxidant concentration would lead to an increase in asthma attack probability of approximately 15%. Potential problems with this study include covariation between air pollutants, high panelist dropout rate, and lack of generalizability to all persons with asthma because relatively severe asthmatic subjects were used on the panels.

Holguin et al. applied the approach of Whittemore and Korn to a study they conducted in Houston to estimate the probability of an asthma attack as a function of maximum hourly ozone concentration (*46*). The daily maximum ozone concentrations ranged from 0.02 to 0.27 ppm during the 6-month period of study from May to October. A greater effect of ozone on asthma attack probability was found in this study as compared to the previous Los Angeles-area study. Assuming the baseline probability of an attack was 10%, an increase in the 1-hr maximum ozone concentration of 0.1 ppm was calculated to

increase the attack probability to 16%, a 60% increase or four times the effect predicted by Whittemore and Korn.

An important study of the relationship between hospital admissions and levels of various pollutants (including ozone), the Ontario Air Pollution Study, has been reported in a series of publications by Bates and Sizto (*47–49*). The study involves all 79 hospitals in a region of southern Ontario that admit acute cases and pollutant data from 17 sampling stations in a monitoring network that covers the region. Hospital admissions for respiratory disease have consistently been associated with daily levels of ozone, sulfates, and temperature during summer months throughout a period of study more than 10 years. Admissions for a group of nonrespiratory conditions showed no such association. The major problem with this study is the inability to isolate the effect of a specific pollutant. Bates and Sizto have summarized the evidence for and against the role of ozone (*49*). It is the only one of the pollutants studied that has been shown to be an irritant at the ambient concentrations measured in southern Ontario. When the region was divided into subregions and each sampling station was associated with a group of adjacent hospitals, respiratory admissions on high ozone (0.08 to 0.2 ppm) days were approximately 7% greater than admissions on low ozone (0.01 to 0.06 ppm) days, if only the same days of the week in the same season in the same year are compared. Ozone concentration also showed a stronger association with admissions for asthma than did the levels of other pollutants and temperature. However, in June of 1983 when ozone levels were unusually high, there was no increase in hospital admissions for respiratory disease. Further, sulfate concentration had a higher correlation coefficient with admissions for all respiratory diseases than did ozone concentration. Because of the ambiguities in their data analysis, Bates and Sizto have concluded that neither ozone nor sulfate alone was responsible for the observed association with acute respiratory admissions. They have speculated that ozone may increase airway responsiveness and thus render individuals more susceptible to other pollutants and/or allergens. There are animal data to support such an effect (*50–52*).

The results of a recently reported controlled human exposure study supported the animal toxicologic evidence that ozone exposure may enhance sensitization to inhaled antigens (*53*). A group of investigators from Toronto exposed seven asthmatic subjects with specific sensitization to either ragweed or grass to 0.12 ppm ozone for 1 hr while at rest. As expected for these conditions of ozone exposure, there were no acute changes in FEV_1 or methacholine responsiveness. This level of exposure did cause, however, a significant shift to the left in the dose–response relationship during inhalation challenge testing with the specific antigens to which the subjects were sensitized. Although the Toronto investigators could only speculate about biological mechanisms responsible for this finding, it is possible that ozone-induced airway inflammation leading to increased epithelial permeability allows increased penetration of antigen to submucosal mast cells. The investigators did note that the public health implications of the study are great; thus, the current NAAQS for ozone is probably not adequately protective of the health of persons with asthma. A major caveat to such an interpretation of this study's results is that the number of subjects who completed the complicated protocol is small ($n = 7$).

Research Needs

The two major questions that need to be answered concerning the relationship of asthma and ozone are the following: Does chronic exposure to high ambient concentrations of ozone contribute to the development of new-onset asthma? Does ozone pollution contribute to exacerbation of preexisting asthma? These questions cannot be answered fully by further controlled human exposure studies alone. Rather, population-based approaches will be required.

The epidemiologic database to support an association between asthma and ozone exposure is limited, but the results of several studies suggest that high ambient concentrations can precipitate asthma attacks. As noted above, ozone is likely to be an inducer of increased nonspecific airway responsiveness and airway inflammation that renders persons with asthma more likely to develop bronchoconstriction upon subsequent exposure to substances such as allergens and sulfur dioxide. If ozone inhalation causes airway inflammation in persons susceptible to asthma (e.g., persons with asymptomatic airway hyperresponsiveness and/or atopy) that is sufficient to cause asthmatic symptoms, then ozone can cause new-onset asthma. Further controlled human exposure and epidemiologic studies are necessary to determine both the degree of ozone sensitivity of persons with asthma and the probability that exposure to ambient ozone is contributing significantly to the rise in asthma morbidity and mortality.

One way to link controlled human exposure studies with epidemiologic studies that plays on the strength of each type of study would be to characterize the acute responses of a panel of asthmatic subjects in the laboratory and then to follow this panel over time. The simplest method of characterizing asthmatic subjects' sensitivity to ozone would be to measure the decrement in FEV_1 over a 2- to 4-hr exposure to a sufficiently high concentration of ozone that would cause a considerable percentage of the subjects to have decrements $\geq$10% (e.g., 0.2–0.4 ppm). However, increased airway responsiveness to methacholine and/or evidence of inflammation on BAL after such an exposure could also be used as markers of ozone sensitivity. Whether acute responses to high ambient levels of ozone administered in a chamber have any predictive value with regard to real-life responses (both acute and chronic) is an important but unanswered question.

What outcome variables should be measured in this panel study? Both respiratory symptoms and serial peak expiratory flow rates can be recorded with relative ease in diaries. Periodic spirometry and methacholine responsiveness, while more difficult to measure, also could be obtained. Serial BAL would be the most direct method of assessing the degree of ozone-induced injury or inflammation in the panel members, but it also would be the most invasive and cumbersome to perform.

Following a panel of asthmatic subjects is fraught with methodologic difficulties. In addition to problems in exposure assessment due to varying patterns and intensity of activity, there will also be problems with exercise-induced bronchospasm independent of ozone exposure and variable medication use. Current progress in personal ozone dosimetry should continue to the point where individual doses can be measured rather than calculated. Time and activity monitoring techniques are improving to the point where level of exercise can be recorded with reasonable accuracy, and perhaps any independent effect of exercise can be controlled for during analysis. Confounding due to variable medication use among panel members perhaps can be minimized by measuring outcome variables, including medication use, during seasons with low ozone exposure and using each subject as his or her own control in the analysis. Although panel studies of the responses of asthmatic subjects to a pollutant may appear difficult to conduct, a

recent study of the effects of atmospheric acidity on a panel of subjects with asthma in Denver provides a successful model (*54*).

Another approach to the question of whether persons with asthma are more susceptible to adverse health effects from ozone exposure would be to follow the Bates and Sizto model of monitoring the rates of emergency room and hospital admissions for exacerbations of asthma in conjunction with regional air quality. Recently, this approach has been applied quite successfully to the study of the effect of particulate pollution on populations residing in several Utah valleys (*55,56*). Pope showed that hospital admissions for respiratory illnesses among both children and adults correlated with changes in PM_{10} concentrations (*55*). However, the success of the Pope study largely depended on the somewhat changeable air quality of the Utah Valley. Most of the particulate pollution came from one source, a steel mill that was shut down intermittently for economic reasons; and concentrations of other pollutants, including ozone, were generally low. The major limitation with further application of the hospital admission versus air quality study model to the epidemiology of ozone-related health effects is the identification of regions where ozone concentrations are high in the absence of elevated concentrations of other pollutants and in the absence of extremes of temperature and humidity.

Comparative studies of rates of hospital admissions or emergency room visits for asthma in different cities with different levels of ozone pollution may provide useful information on dose–response. Recent data indicate that while there is no association between asthma attacks and the relatively low ambient ozone concentrations in Vancouver (*57*), there is a positive association between emergency room visits for asthma and the higher summer ambient ozone concentrations in Atlanta (MC White, unpublished data). When planning studies linking ambient air monitoring data with rates of hospital admission or emergency room visits for asthma, it is important to consider that the ozone concentrations for the several days prior to the admission or visit may be more relevant than the concentration on the day of the attack. Another concern in this type of study is potential misclassification of asthma as acute bronchitis, especially when dealing with children.

It may not be necessary to collect data linking rates of asthma to ambient ozone concentrations in a prospective fashion. Considerable environmental monitoring data already exist; these measurements could be correlated with hospital records from multiple hospitals across a given geographic area, such as the Los Angeles basin, or with NHANES data across several geographic areas with varying levels of ozone pollution.

The issue of whether persons with asthma are more susceptible to ozone-induced respiratory tract injury is of epidemiologic interest because asthma is a common condition that appears to be increasing in terms of both prevalence and severity. Given that many of the over 10 million Americans with asthma live in ozone nonattainment areas, a well-defined association between ozone and either new-onset asthma or exacerbation of preexistent disease would be of great importance to public health.

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