Asthma and Persistent Wheeze in the Harvard Six Cities Study*

Frank E. Speizer, M.D., F.C.C.P.†

**TABLE 1**

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTPS</td>
<td>Body temperature and pressure standardized</td>
</tr>
<tr>
<td>FEV1</td>
<td>Forcible expiratory volume in 1 s</td>
</tr>
<tr>
<td>FVC</td>
<td>Forcible vital capacity</td>
</tr>
<tr>
<td>NAAQS</td>
<td>National Ambient Air Quality Standard</td>
</tr>
<tr>
<td>TSP</td>
<td>Total suspended particulates</td>
</tr>
</tbody>
</table>

The understanding of the effects of ambient particulates on respiratory health has undergone substantial change since the introduction of the Clean Air Act in 1970. This report provides a brief perspective on some of the work carried out as part of the Harvard Six Cities Study that has contributed to our understanding of the health effects of ambient pollutants. The study was originally designed to assess the impact of total suspended particulates (TSP) and sulfur dioxide (SO2), among other pollutants, on the health of children and adults. One aspect of the study that became more focused had to do with the components of the particles as related to size in regard to inhalable or respirable elemental characteristics as a means for source apportionment, and wet chemistry to assess acidity. The health impact was measured on children and adults followed for up to 12 years. Most of the data have yet to be analyzed; however, it is clear that in children, respiratory symptoms, but not pulmonary function levels, are related to ambient particulate concentrations, and more specifically appear to be related to the inhalable or respirable fraction, and potentially to the acidity of the particles. Whether these symptomatic changes, which relate both to long-term exposures (annual averages) or short-term exposures (acute changes in symptoms and pulmonary function following episodes of exposure), will have long-term consequences on these children must await further analyses and follow-up as these children accumulate additional exposures as they mature into early adult life. In adults similarly followed for up to 12 years, the data are less clear because of the potential confounding effects of cigarette smoking and other occupational and environmental exposures.

In regard to occupationally or environmentally related asthma, the Harvard Six Cities Study provides some insight into the role of ambient pollutants in the exacerbation of symptoms in these diseases. In general, new onset asthma does not appear to be related to ambient particulate levels. However, exacerbations of symptoms in asthmatic children are associated with levels of exposure. Thus, the data suggest that symptoms of persistent wheeze or a history of asthma does identify a subgroup of the population that appears to be at increased risk at levels of ambient exposure at and below the current ambient standards for particulate exposure. These data should be useful in guiding policy makers in revising the particulate standards in the Clean Air Act, as well as providing an approach to gathering population-based information on the consequence of general environmental exposures and asthma.

**HARVARD SIX CITIES STUDY**

The Harvard Six Cities Study began in 1974. The investigation was designed initially as a prospective epidemiologic study of the effects of ambient sulfur oxides and particulate matter on the respiratory health of children and adults living in six cities in the eastern United States (Watertown, MA, Kingston and Harriman, TN, Steubenville, OH, St. Louis, MO, Portage, WI; and Topeka, KS). After a staggered enrollment of randomly selected adults and children over three years, participants have been followed in each community for 12 years with concurrent air pollution measurements. The objectives of the study have been expanded to incorporate new air pollution measurement technologies, to collect new types of health data, and to assess the health effects of exposure to indoor as well as outdoor ambient pollution.

When the study started, the epidemiologic evidence of the National Ambient Air Quality Standard (NAAQS) was based in large part on work carried out in the 1950s and 1960s in Great Britain, particularly for TSP and SO2. Much of the environmental assessment compared the blackness of British smoke to total mortality, or compared "dirty" to "clean" cities in terms of respiratory symptoms, illness rates, or level of pulmonary function. Since that time the methodology for monitoring ambient (and indoor) exposure has become increasingly sophisticated. Because of this increasing sophistication, we are now able not only to quantify mass of exposure, but also to understand the size and chemistry of the particles, to assess level of penetration in the airways, to evaluate potential chemical interactions, and, from an environmental perspective, to apportion more accurately the source of the pollutants.

**STUDY DESIGN**

Enrollment in the study began in September 1974, with two communities enrolled each year for three years. Similar procedures were followed in each community. Approximately 2,000 adults, aged 25 to 74 years, were randomly selected and invited to a central location, where they were interviewed with a standardized respiratory symptom questionnaire that included a detailed residential and occupational history as well as a detailed smoking history.

---

*From the Department of Environmental Health, Harvard School of Public Health, and the Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston
†Representing the Harvard Six Cities Study research group. Dr. Speizer is funded in part by NIEHS Research Grant No. ES01108, EPA Cooperative Agreement No. CR-816071, and Contract RP-1001 from Electrical Power Research Institute.

Reprint requests: Dr. Speizer, Department of Environmental Health, Harvard School of Public Health, 665 Huntington Avenue, Boston 02115
Height was measured in stocking feet and spirometry was performed with water-sealed spirometers with the subject in a sitting position without a nose clip. All values were converted to BTPS. Subjects unwilling or unable to come to the central location were seen in their homes. Follow-up examinations were performed 3, 6, and 12 years after the initial examination. Vital status was determined annually for all subjects.

The sampling scheme in children was considerably more complex. In each city, depending on its demography, either all the children, children from a selected geographic area within the city, or children from a random sample of schools in the district were included. The children in each city were enrolled in the same sequence as the adults (ie, two cities per year). Children in first and second grade were invited to enroll in the study through a questionnaire sent home to the parents. In one city, Portage, first through fourth grade children were enrolled. In subsequent years, new first grade children were enrolled until approximately 1,500 children in each city were in the cohort. These children were followed annually until they moved out of the school district or graduated from high school. The parent completed the standardized respiratory symptom questionnaire, until grade 9, at which time the questionnaire was completed by the child. Personal smoking history was obtained from the child directly starting at age 9 at the time of the annual spirometry testing.

In 1982 we began to establish a second cohort of approximately 1,000 in each city of second through fifth grade children who were similarly enrolled and followed for three annual cycles with respiratory symptom questionnaires and two annual measures of pulmonary function. In each city, approximately 300 households of children from this cohort were enrolled for indoor measurements of particles and NO	extsubscript{2} for four weeks during the school year. The child's parent also completed a daily symptom diary for approximately nine months.

A unique part of this study has been the detailed assessment of ambient and indoor exposure measurements that have provided an integrated measure of exposure for the participants in the study. These measurements have been state-of-the-art measures that have met U.S. Environmental Protection Agency quality assurance schemes and have often led in applying advanced laboratory techniques to the field to monitor the environments of interest in this study.

Ambient measurements included hourly measures of SO	extsubscript{2}, NO	extsubscript{2}, ozone, and 24-h measures of TSP, PM10 (particulate matter less than 10 \(\mu m\)), and PM2.5. Particulate fractions were subject to elemental chemical analyses by x-ray fluorescence. The analyses were then used to define relative source contributions. More recently, new techniques have been developed to measure hydrogen ion concentration (ie, acidity) of both particulate and gas phase pollution samples. It is this latter development that has led to some new studies on the health effects of the precursors of acid rain; this will be discussed later.

Air Pollution in the Six Cities

At the time the six cities were originally chosen, two of the cities had annual averages for TSP and/or SO	extsubscript{2} above the NAAQS for annual average. Two were well below the standards, and two were in the midrange (Fig 1). However, it was soon recognized that not all particulate mass loading could be considered equal. With the introduction of dichotomous sampler techniques one could begin to partition the mass of particulate previously considered as TSP.

Although some reduction in total particulate load occurred from 1975 to 1980, by using the partitioned data from each city, a slightly different perspective was obtained on the nature and relative range of exposure occurring in each city. Figure 2 shows the distribution of fine particles—particles that are less than 2.5 \(\mu m\) in aerodynamic diameter—across the cities. Steubenville remains that most polluted city and Portage and Topeka remain the cleanest. However, the pollution in Kingston now exceeds that in St. Louis and Watertown. We will come back to the point of using these more physiologically relevant measures of exposure later.

In the last five years, methods to measure acidity (H\textsuperscript{+}) were developed, and we have collected daily acid measurements in each community for approximately a one-year period.\textsuperscript{1} In each city, days with elevated H\textsuperscript{+} concentrations were more frequent in summer than in winter. In Kingston and in Steubenville, summertime peak 24-h measurements exceeded 100 nmol/m\textsuperscript{3} (approximately 5 mg/m\textsuperscript{3} of sulfuric acid) on more than 10% of days.
RESULTS RELEVANT TO ENVIRONMENTALLY RELATED ASTHMA

The Harvard Six Cities Study affords an opportunity to explore questions related to asthma and chronic wheeze. With 13,850 school children followed from age 6 to 18, 8,840 adults aged 25 to 74 followed for up to 12 years, and another 6,300 children aged 7 to 11 whose ambient environment has been measured almost their entire lives by a single group of investigators, we have had the opportunity to explore the relationship between environment exposures and the natural history of the asthma/wheeze complex.

Most clinicians would agree on what is a classic case of asthma in a relatively young person. However, in mild disease or in very young children (<2 years), there is no uniformly acceptable set of criteria for establishing the diagnosis of asthma. For purpose of the Six Cities Study, we have used two arbitrary categories of responses to questions to identify potential asthmatic subjects or subjects with persistent wheeze. For the diagnosis of asthma, we have used the question: Has a doctor ever said you (your child) had asthma? If yes, is it still present, not present except in the last year, or only in the past (more than 1 year ago)? The diagnosis of persistent wheeze required a positive response to: Does your (your child's) chest ever sound wheezy or whistling (I) apart from colds, or (2) most days or nights? (It must be noted that these were the definitions used in the Six Cities Study from 1974. In the more recent developed acid aerosol study, to be discussed subsequently, these definitions have been expanded to provide more details on both the diagnosis of asthma and the characteristics of the wheeze syndromes.)

There were 8,131 children seen during the 1980-1981 school year in the six cities. To reduce potential confounding by age and race, we selected only white children aged 10 to 12 years old. Among the 5,422 children meeting these criteria, asthma reporting varied between 3.2% and 5.9% across the cities. Persistent wheeze was reported in a similar pattern across cities, with a range of values of 6.6% to 11.6%. There was no association between any of the pollution measurements and asthma or persistent wheeze. We therefore stratified the sample according to whether or not the

FIGURE 2. Annual levels of fine particles (<2.5 μm) by city.

FIGURE 3. Prevalence of bronchitis in the last year stratified by presence or absence of asthma/wheeze, by level of annual respirable particulates (PM15). (Reproduced by permission from ref 8.)

FIGURE 4. Level of pulmonary function in children, stratified by presence or absence of asthma/wheeze by level of annual respirable particulates (PM15). (Reproduced by permission from ref 8.)
child had asthma or persistent wheeze to test the hypothesis that this symptom complex identified a more susceptible group. Figure 3 shows the prevalence of bronchitis in the previous year, stratified by the presence or absence of persistent wheeze or asthma by annual PM15 level. The trends across the gradient of pollution levels are significant for both groups (overall ratio of relative odds, 1.7). Thus, the asthma or persistent wheeze group, which makes up only slightly more than 10.5% of the total population, accounts for 42% of all bronchitis episodes.

Similar analyses carried out for level of pulmonary function showed essentially no relation to particulate level expressed as PM15 (Fig 4). Children with a history of asthma or persistent wheeze had lower levels of FEV1, than asymptomatic children. However, there did not appear to be any association with level of exposure.

These findings suggest that although the prevalence of asthma/persistent wheeze in children does not appear to be directly related to general environmental exposure levels, exacerbations of respiratory symptoms in children with asthma or persistent wheeze are directly associated with level of particulate exposure. These particulate exposures readily occur, and thus a substantial number of children appear to be at excess risk of experiencing exacerbations of symptoms.

Increased frequency of persistent wheeze was reported in adults from the six cities who reported occupational exposures to dust and fumes. Korn et al, using a detailed occupational history questionnaire, found an excess percentage of attributable risk of chronic cough, phlegm, persistent wheeze, breathlessness, and lung function impairment (FEV1/FVC below 60%) in 23.5% to 35.5% of subjects exposed to dust in their work environment.* Similar but lower levels of attributable risk were found for exposure to gas or fumes at work. Specifically, there was an exposure-response relation between years of dust exposure and the relative odds of increased persistent wheeze even after controlling for age, gender, current and lifetime smoking, and city of residence (Fig 5). For exposure to gas or fumes, the effect of duration of exposure did not appear to be cumulative. However, for both dust and gas or fumes, current exposure was associated with a higher relative odds ratio than was past exposure only.

These findings indicate that even crudely defined assessment of occupational dust exposure in a general environmental setting can identify symptoms consistent with occupational asthma. As would be expected in a general population sample survey, no specific occupational dust was

![Figure 5](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21621/)
reported frequently enough to allow the nature of the dust exposure associated with the symptoms of persistent wheeze to be identified. Another point of importance perhaps better studied in this general environmental setting was that we were able to determine by multiple logistic regression that the interaction between this crudely defined dust and cigarette smoking was additive rather than multiplicative. This appears to be consistent with much of the literature that attempts to find general chronic respiratory symptoms in the work setting in association with cigarette smoking.

**Conclusion and Recommendations**

Although there are significant limitations in using data collected in a general population setting for studying specific exposures believed to be associated with asthma, there are clear advantages from having such population-based data. The estimates of prevalence are likely to be more accurately representative of the population or region than would be obtained from more selected groups. Since the definitions of asthma are dependent on what a physician has told the patient or the patient's family rather than reflecting any direct physiologic measure of airways responsiveness, the spectrum of disease may be more representative of what is actually occurring in the community. As in many studies, approximately twice the number of children were found to have persistent wheeze symptoms as the number who carried the diagnosis of asthma. Whether the difference in the two groups represents real differences in disease processes or merely reflects different levels of severity along a spectrum of disease is unknown and is an important research question requiring further investigation.

From the standpoint of general air pollution, in contrast to specific occupational dust exposure, children do not show a gradient of asthma/persistent wheeze across exposure gradients. However, symptoms do appear to be worse in asthmatics and in children with a history of persistent wheeze. One important question is whether these children, because of increased symptom burden, are more likely to have increased morbidity from either ongoing general environmental exposures or specific personal (smoking) or occupational (dusts) exposures occurring later in life.

Our adult data, on symptoms related to nonspecific measures of dust exposure, bring into focus one of the questions raised at this symposium. Without defining occupational asthma, the data suggest that cumulative exposure is associated with an increased risk of developing "asthma-like" symptoms. We need to know if this cumulative effect results from increased numbers of workers being at risk for longer periods of time, or if exposure in earlier years resulted in more workers being at risk. Unfortunately, this question cannot be explored fully in general population samples as described here.

Finally, we found that a relatively simple set of questions asked in a standardized fashion identified a subgroup of the population that appears to be at excess risk of other environmental insults. In contrast to the more classic studies of moderate to severe asthmatics, in whom the acute phenomena of the disease process may not be separable from the effects of environmental insults, subjects identified by these simple questionnaire techniques from general population samples may provide insight into the more subtle but potentially more pervasive effects of only modestly elevated levels of environmental insults. The long-term consequences of such exposures are unknown at present and represent a challenge for future population-based environmental research.

**References**


