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Acute Effects of Ambient Ozone on Asthmatic, Wheezy, and Healthy Children

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Includes the Commentary of the Institute's Health Review Committee

Research Report Number 82
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HEI Statement

Synopsis of Research Report Number 82

Effects of Ambient Ozone on Healthy, Wheezy, and Asthmatic Children

BACKGROUND

The Clean Air Act of 1970 requires the U.S. Environmental Protection Agency to establish air quality standards that will protect sensitive populations from adverse health effects caused by air pollutants. These populations generally include the young, the elderly, and people with preexisting respiratory or heart disease. One such chronic respiratory disease is asthma, which is characterized by reversible airway obstruction, airway inflammation, and increased responsiveness of the airways to irritant stimuli such as ozone.

Some evidence suggests that ozone-induced airway inflammation is greater in asthmatic adults than in healthy adults. A number of studies also have shown that both healthy and asthmatic children exposed to elevated levels of ozone can experience transient decreases in lung function and increases in respiratory symptoms such as cough or wheeze. Thus, it is reasonable to suspect that children with asthma may be more sensitive to ozone than other children. HEI supported this study by Avol, Peters, and colleagues because it was designed to evaluate the effects of ambient ozone on potentially sensitive population subgroups (asthmatic and wheezy children), and to comprehensively assess ozone exposure and health outcomes.

STUDY DESIGN

Dr. John Peters and colleagues of the University of Southern California School of Medicine compared the lung function, respiratory symptoms, activity levels, and bronchodilator use of 10- to 12-year-old healthy, asthmatic, and wheezy children. They conducted the study in Southern California during mid-spring (when ozone levels were expected to be low) and late summer (when ozone levels were expected to be high). Regional air pollution monitors provided hourly ozone measurements, and small ozone-detecting badges were pinned to the children's clothes in an effort to estimate their personal exposures to ozone. The children measured their lung functions with small spirometers and carried diaries to record their respiratory symptoms, medication use, and outdoor activity levels (the latter for comparison with information from small heart-rate monitors worn across their chests).

The study design had both strengths and limitations. For example, baseline lung function measurements were similar among asthmatic, wheezy, and healthy children. Therefore, it is not certain that the three groups were distinctly different, despite the symptoms and medication needs of the children designated as asthmatic or wheezy. In addition, there were problems with the quality of the data generated by the ozone badges and spirometers and with the children's compliance in performing a complex series of tasks. The use of medication by asthmatic children may also have modified their lung function measurements and masked any effect of ozone.

RESULTS AND IMPLICATIONS

Contrary to the investigators' expectations, ambient ozone levels were generally low (below 100 parts per billion [ppb]) in both study periods, and exceeded 120 ppb on some days in both seasons. Overall, the investigators reported few statistically significant changes in lung function measurements or symptoms during the periods of elevated ozone and, in most instances, the three groups responded similarly. Only one of four lung function measurements (forced vital capacity) showed a statistically significant decrease on days when ozone levels were high, and this occurred only in healthy children in the summer (but not on high-ozone days in the spring). Some indices of lung function unexpectedly showed apparent improvement during periods of high ozone. Asthmatic children increased their use of inhalers during periods of elevated ozone in the spring (but not on high-ozone days in the summer).

The results of this study are difficult to interpret because the patterns of lung function changes associated with ozone exposure were inconsistent, and the results often do not agree with those of other epidemiologic studies of ozone's effects on lung function in healthy and asthmatic children. There are a number of possible explanations for the apparently anomalous findings. The levels of ozone prevailing during the study may have been too low to affect the children. The impact of other pollutants that were not measured, such as environmental tobacco smoke, particulate matter, and allergens, may have affected the children's responses to ozone. In addition, limitations in some of the methods used and certain aspects of the study design resulted in a data set that was inadequate to answer the complex questions being addressed.

This Statement, prepared by the Health Effects Institute and approved by its Board of Directors, is a summary of a research project sponsored by HEI from June 1993 to December 1995. This study was conducted by Dr. John Peters and colleagues of the University of Southern California, Los Angeles, CA. The following Research Report contains both the detailed Investigators' Report and a Commentary on the study prepared by the Institute's Health Review Committee.

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I. STATEMENT Health Effects Institute

This Statement, prepared by the HEI and approved by the Board of Directors, is a nontechnical summary of the Investigators' Report and the Health Review Committee's Commentary.

II. INVESTIGATORS' REPORT

When an HEI-funded study is completed, the investigators submit a final report. The Investigators' Report is first examined by three outside technical reviewers and a biostatistician. The Report and the reviewers' comments are then evaluated by members of the HEI Health Review Committee, who had no role in selecting or managing the project. During the review process, the investigators have an opportunity to exchange comments with the Review Committee and, if necessary, revise the report.

III. COMMENTARY Health Review Committee

The Commentary on the Investigators' Report is prepared by the HEI Health Review Committee and staff. Its purpose is to place the study into a broader scientific context, to point out its strengths and limitations, and to discuss the remaining uncertainties and the implications of the findings for public health.

INVESTIGATORS' REPORT

Acute Effects of Ambient Ozone on Asthmatic, Wheezy, and Healthy Children

Edward L. Avol, William C. Navidi, Edward B. Rappaport, and John M. Peters

ABSTRACT

Southern California children (10 to 12 years old) participated in a two-season study to assess the potential acute respiratory effects of ambient ozone (O_3)*. Asthmatic (n = 49), wheezy (n = 53), and healthy (n = 93) children completed a four-day (Friday through Monday) study protocol, once in spring and again in summer, that included the use of daily activity and symptom diaries, heart rate recording devices, personal O_3 samplers, and maximal effort spirometry several times per day. Data from regional monitoring stations were used to establish ambient hourly O_3 concentrations.

Analyses revealed that the children spent more time outdoors and were more physically active in the spring. Girls spent less time outdoors and were less physically active than boys. Personal O_3 samplers correlated poorly with, and generally gave lower readings than, outdoor ambient monitors. Higher personal O_3 exposures were associated generally with increased inhaler use, more outdoor time, and more physical activity. Children with asthma spent more time outdoors and were more active in the spring on high-O_3 days (measured by personal sampler), and had the most trouble breathing, the most wheezing, and the most inhaler use on these days. Activity pattern data suggested that children with asthma protected themselves by being less physically active outdoors during the summer on high-O_3 days. Wheezy children had the most trouble breathing during the summer on low-O_3 days (measured by personal sampler).

Observed relationships between O_3 and pulmonary function were erratic and difficult to reconcile with existing knowledge about the acute respiratory effects of air pollution. We conclude that although asthmatic and wheezy children behave differently from their healthy peers with regard to symptoms and patterns of activity when challenged by ambient ozone, the nature of these changes remains inconsistent and ill-defined.

INTRODUCTION

As information about the health risks associated with air pollution has become available, attention has focused increasingly on individuals with preexisting respiratory impairment (such as asthma, or a history of wheezing) as subpopulations of possible concern. Previous laboratory studies have identified persons with asthma as being sensitive to air pollution (Linn et al. 1987) and have suggested that such persons may be more sensitive to O_3 exposure than are their healthy peers (Hackney et al. 1989; Kreit et al. 1989). In epidemiologic investigations, children with a history of asthma or wheezing have exhibited increasing rates of bronchitis with increasing levels of air pollution (Dockery et al. 1989).

Children specifically may be at increased risk from air pollution, because their typical activity patterns and exercising ventilation rates predispose them to increased exposure during peak daily outdoor pollution episodes. In addition, the apparent lack of subjectively reported symptoms in exercising children exposed to O_3, observed during laboratory and field studies, raises concerns about the ability of children to undertake appropriate avoidance behaviors during ambient pollution episodes (Avol et al. 1985; McDonnell et al. 1985).

Ozone is a pollutant primarily formed by ambient photochemical processes, with no important indoor sources in nonoccupational settings. It has been noted that children spend more than 85% of their time indoors (Wiley 1991; Jenkins et al. 1992), where O_3 concentrations can be quite

* A list of abbreviations appears at the end of the Investigators' Report.

This Investigators' Report is one part of Health Effects Institute Research Report Number 82, which also includes a Commentary by the Health Review Committee, and an HEI Statement about the research project. Correspondence concerning the Investigators' Report may be addressed to Dr. John Peters who was the Principal Investigator, at University of Southern California, Division of Occupational and Environmental Medicine, School of Medicine, 1540 Alcazar Street, Suite 236, Los Angeles, CA 90033.

Although this document was produced with partial funding by the United States Environmental Protection Agency under Assistance Award R824835 to the Health Effects Institute, it has not been subjected to the Agency's peer and administrative review and therefore may not necessarily reflect the views of the Agency, and no official endorsement by it should be inferred. The contents of this document also have not been reviewed by private party institutions, including those that support the Health Effects Institute; therefore, it may not reflect the views or policies of these parties, and no endorsement by them should be inferred.

low (Stock et al. 1985). Thus attempts to characterize children's exposure to O_3 using data from regional outdoor monitors may lead to significant misclassification.

This investigation sought to assess the relative sensitivities of asthmatic, wheezy, and healthy children to ambient O_3, as well as to evaluate the children's respective location (indoor vs outdoor) and activity patterns during spring and summer ambient O_3 exposure.

METHODS

Three subgroups (asthmatic, wheezy, and healthy volunteers) aged 10 to 12 years participated in each of two seasons of the year (midspring and late summer). Approximately 20 children at a time were studied for periods of four consecutive days, including two weekdays (Friday and Monday) and the intervening weekend. Children from six greater Los Angeles communities participating in a longitudinal study of respiratory health (Peters 1996) were recruited (see Figure 1). Historical ozone levels for these communities have consistently exceeded the former National Ambient Air Quality Standard (0.12 parts per million [ppm] for one hour) during summer photochemical smog episodes (Air Resources Board 1989, 1990).

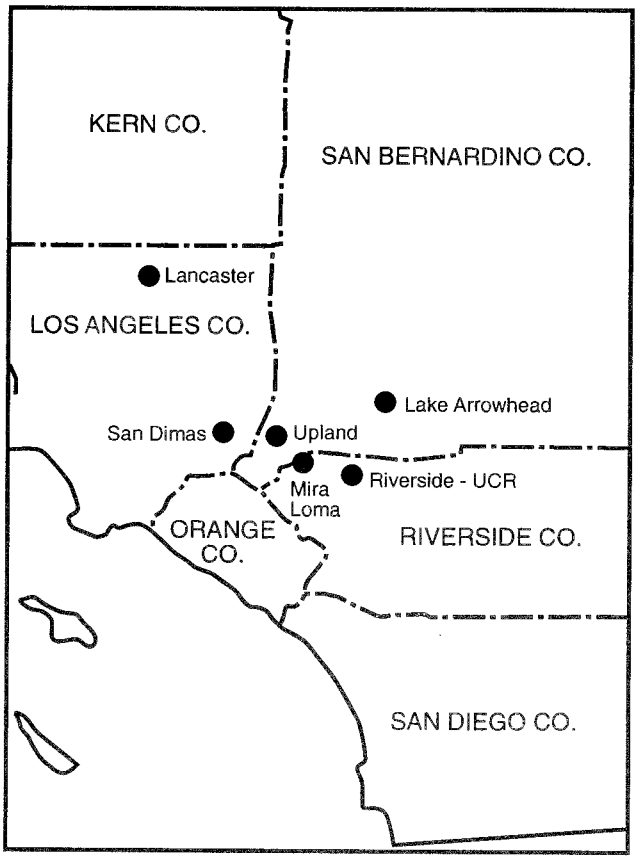

Figure 1. Map of study location.

Children in five of the six study communities were tested in each sampling week, with the six communities rotated sequentially through the ten consecutive testing weeks in each season. Field staff also were rotated through testing communities, with one of five staff assigned to each community in each testing week.

LUNG FUNCTION TESTING

Pulmonary function was assessed with portable spirometry units (Medi-Facts Remote Spirometry Unit, Creative BioMedics, San Clemente CA). Such units previously have been used to measure pulmonary function in acute and long-term air pollution effects studies (Ware et al. 1981; Hackney et al. 1984; Detels et al. 1987; Stram et al. 1991). The notebook-sized units contained a temperature-corrected pressure transducer interfaced to a computer capable of storing over 100 digitized spirometric loops for subsequent downloading and review.

Recorded spirometric data included forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), peak expiratory flow rate (PEFR), forced expiratory flows with 25%, 50%, and 75% of the volume remaining (FEF_{75}, FEF_{50}, and FEF_{25}, respectively), and the maximum midexpiratory flow (MMEF); FEV_1, FVC, PEFR, and FEF_{75} results are reported here.

Testing was performed in the presence of project staff on the evening before the first study day and on the evening of the fourth study day. During the intervening period, children were asked to perform unsupervised spirometry in their homes at least three times per day: in the morning upon awakening, in the midafternoon or when they returned from school, and in the evening before going to bed. On each occasion, children were to perform three to five maximal effort exhalations to obtain at least three consistent maneuvers (in other words, three FEV_1 measurements within a 5% range and three FVC measurements within a 5% range). (However, regardless of performance consistency, all flow-volume loops were recorded in the computerized data base.)

EXPOSURE ASSESSMENT

Passive samplers (Ogawa Passive Sampler, Ogawa and Co. USA, Pompano Beach, FL) developed by Koutrakis and coworkers (Koutrakis 1990, 1991) were used to monitor individual O_3 exposure. The sampling device consisted of two chemically saturated filters housed in a cylindrical

Teflon holder worn on the child's lapel. Exposed filters were analyzed by ion chromatography to quantify O_3 collection.

A separate concurrent validation effort (Lurmann et al. 1994) identified difficulties in the precise specification of the effective sampling flow rate and face velocity of the passive sampler. From the investigators' perspective, these limitations did not prevent the useful application of the personal sampler to stratify O_3 exposure in this study. However, personal sampler data were grouped into nonoverlapping distributions of "low" and "high" exposure for data analyses (see Results section for additional details).

We used the passive O_3 sampler in conformance with several other investigations (Liu et al. 1993; Brauer and Brook 1995). We instructed the children to remove the sampling vial from its sealed container when they awoke each morning, and to attach the sampler to their shirt or blouse. We asked them to keep the sampler with them at all times during the day, and to return it to the sealable container after nightfall.

Hourly ambient O_3 information from regional monitoring sites also was collected to assess the accuracy of personal exposure classification on the basis of monitoring station data. Ozone levels were monitored continuously at stationary community locations operated by regional regulatory agencies, using commercial ultraviolet photometers conforming to agency operating guidelines. Ambient hourly data then were aggregated to correspond to the time periods of personal sampler use by the subjects.

TIME AND ACTIVITY DIARIES

The children used diary-type questionnaire booklets to document daily temporal and spatial activity patterns. This has been shown to be an effective method of activity documentation in previous field studies (Johnson 1987; Lichtenstein et al. 1989; Schwab et al. 1991; Shamoo et al. 1991; Wiley 1991). The specific format and questions asked were based on previous field investigations and modified by study investigators. Children carried the booklet each study day, and were instructed to document physical activity levels, physical location, and health status at hourly intervals.

HEART RATE AND VENTILATION ASSESSMENT

Heart rates were recorded using a commercially available data-logging cardiac monitor (Polar-Electro Vantage XL, Kempele, Finland) to obtain independent confirmation of diary reports of increased physical activity. Similar units have been used previously to quantify time and activity patterns for individuals in air pollution studies (Linn et al. 1990, 1992; Shamoo et al. 1990; Spier et al. 1992). Children initiated the monitoring at the start of each day's sampling period (at 7 a.m. or upon awakening, whichever was later); monitoring continued until 9 p.m. that evening. Project staff, using factory-provided software, subsequently downloaded data files of minute-by-minute recorded heart rate information to a personal computer.

THE SUBJECT POPULATION

Randomized lists of potential study participants were computer-generated, by study community, on the basis of their concurrent participation in an ongoing air pollution health study (Peters 1996). Each week of the spring sampling period, approximately twenty children were recruited to participate for the following week. During the summer sampling portion of the study, only those who had completed the previous spring study were eligible for study participation. Subjects were paid a small amount for their participation. Criteria for participation in the study included the child's having no physical or activity restrictions, qualification into the subgroups listed, a willingness to participate, and written informed consent of both child and parent (or legal guardian).

STATISTICAL METHODS AND DATA ANALYSIS

We calculated means and standard deviations for each of the measurement endpoints to provide a summary overview of the collected data set. For categorical variables (symptoms and medication), we performed logistic regressions to obtain parameter estimates, consider potential interactions, and assess the statistical significance of identified response variables. For continuous variables under investigation (lung function; air monitoring; and physical, temporal, and spatial activity pattern data), a linear model procedure was used to assess the relative importance of observed responses. In this model, we included a separate intercept for each child, thereby avoiding issues of within-subject correlation.

Collected O_3 data were stratified by three independent criteria for analysis. First, we divided the collected data into subsets of "high" and "low" ambient O_3, on the basis of peak one-hour monitoring station values on the day (and in the community) of study being above or below 100 ppb; this was denoted the station O_3 dichotomous approach. We defined "high" and "low" values for the daily integrated personal sampler data as values above and below 40 ppb; this was denoted the personal O_3 dichotomous approach. Finally, we selected two nonoverlapping extremes of the personal sampler data distribution by monotonically ordering the samples and defining exposure (Brauer and Brook 1995) so that the lowest value in the "high" exposure sub-

group was at least 35% higher than the highest value in the "low" exposure subgroup; this was denoted the personal O_3 35% rule. Analytical results using the personal O_3 dichotomous or 35% rule approaches did not vary dramatically; thus O_3 data are reported as measured by station peak data or by personal sampler (using the 35% rule).

The time interval for analysis of outdoor activity patterns was restricted to the period 11 a.m. to 6 p.m. (Pacific Daylight Time, or PDT) each day. This approach considered the hours of highest ozone exposure levels in each community, assessed children's activity patterns when they were outside after school, and minimized the number of missing hours of subjects' activity data for off-peak ozone exposure levels (mornings and evenings).

We assessed the relation between total time spent outdoors and O_3 exposure using a linear regression. The model allowed for subject-specific baselines, and separate slopes for asthmatic, wheezy, and healthy children. We performed spring and summer analyses separately, to control for confounding with season. We performed similar analyses using total time physically active as the outcome variable, and using the previously described approaches to define O_3 exposure.

To study pulmonary function, we defined the variable ΔFEV_1 to be the difference between evening and morning FEV_1 (evening FEV_1 minus morning FEV_1). By this convention, negative values represent loss of function (dysfunction), and positive values reflect a gain of function (improvement). The evening measurement was defined as the first consistent testing occurring after 5 p.m., and the morning measurement was defined as the first consistent testing occurring before 11 a.m. Values for changes in other lung function indices (FVC, PEFR, MMEF, and FEF_{75}) were defined in a similar manner.

We studied the relations between pulmonary function and O_3 exposure with a linear regression. We performed these analyses in the same manner as those previously described for the study of activity patterns, except that season was not considered as a confounder. Separate models were used to fit O_3 exposure by hourly ambient and by personal sampler measurements.

We used logistic regression to study the relation between O_3 exposure and the incidence of reported symptoms (e.g., trouble breathing, wheezing) and the incidence of taking oral medication and using inhalers. Covariates in the analyses included gender, health status, and all interactions between health status and peak hourly O_3 levels. Gender specification was found to be not significant, and a final model was fit without it. We used similar approaches to study the relations between O_3 exposure and the incidence of reported symptom of wheeze, O_3 and the incidence of taking oral medication, and O_3 and the incidence of using inhalers. The unit of analysis was the subject-day. This method has one disadvantage, in that days within subject may be correlated. The effect of ignoring these correlations should be to underestimate standard errors, thus overestimating statistical significance. In principle, these correlations could be eliminated by assigning subject-specific baselines, as we did for the analyses of time-activity and pulmonary function. We chose not to do this in this situation, because subjects who never reported symptoms, or who reported symptoms every day, would yield no information with such an approach.

RESULTS

SUBJECT PARTICIPATION

The spring sampling study was completed by 210 children (53 asthmatic, 54 wheezy, and 103 healthy children). Of these, 195 individuals completed the summer study protocol (49 asthmatic, 53 wheezy, and 93 healthy children). Of the 15 children who failed to complete both phases of the protocol, eight had moved away from the study area between the spring and summer sampling times, and seven refused continued participation in the study.

Summary baseline data for the three groups are presented in Table 1. The ages, heights, and weights of the three groups were nearly identical. The asthmatic group contained significantly more males, and exposure to passive smoking was less common among healthy children. Baseline pulmonary function results were nearly the same, with healthy children having slightly higher values for all measures of pulmonary function except FVC.

DATA COMPLETION RATES

Collection rates for each of the five data sets are presented by subject group in Table 2. We observed no dramatic differences in capture rates between subgroups. Regional (ambient) O_3 data were successfully collected for 98% to 100% of all study days and for 98% to 100% of study hours of interest (11 a.m. to 6 p.m., PDT). Personal O_3 samplers provided data for 85% to 88% of all study days. Diary, spirometry, and heart rate information involved more individual child participation and was more difficult to collect. Acceptable lung function data were available for at least one testing time each study day for 96% to 98% of all subject days. However, the requirement for acceptable lung function data at both morning and evening test periods in each study day reduced the collection rate to 79% in the spring and 66% in the summer. Lung function data were

Table 1. Summary of Subjects' Characteristics

Variable	Asthmatic	Wheezy	Healthy
Number of subjects	53	54	103
Age (years)	11.3 ± 0.5[a]	11.2 ± 1	11.3 ± 0.5
Females (% of group)	33	52	56
Height (cm)	145 ± 6	144 ± 7	146 ± 7
Weight (kg)	39.8 ± 8.7	39.2 ± 8.7	39.3 ± 9.0
Smokers in home (%)	19	20	13
FVC (L)	2.97 ± 0.50	2.91 ± 0.45	2.94 ± 0.41
FEV_1 (L)	2.36 ± 0.40	2.36 ± 0.38	2.41 ± 0.34
PEFR (L/sec)	5.64 ± 1.14	5.82 ± 1.19	5.97 ± 1.16
MMEF (L/sec)	2.69 ± 0.78	2.79 ± 0.69	2.96 ± 0.66
FEF_{75} (L/sec)	1.44 ± 0.48	1.54 ± 0.47	1.60 ± 0.51

[a] Data given in this form are means ± SD.

Table 2. Data Collection Capture Rates by Data Type and Health Status[a]

	Spring Data[b]				Summer Data[c]			
	All	Asthmatic	Wheezy	Healthy	All	Asthmatic	Wheezy	Healthy
Spirometry								
Any data[d]	98	99	100	97	96	95	95	97
a.m. and p.m.[e]	79	77	78	80	66	65	66	66
Diary								
Any data	94	93	97	92	92	89	93	93
11 a.m.–6 p.m.[f]	76	78	80	74	75	71	74	77
Personal Sampler[g]								
Any data	85	84	92	81	88	83	87	91
Station Monitor[h]								
Any data	100	99	99	99	98	97	96	99
Heart Rate								
Any data	84	91	81	82	81	79	78	83
11 a.m.–6 p.m.	55	59	50	55	50	48	50	51

[a] All values are expressed as percentages.

[b] Spring data were obtained from 210 subjects × 4 study days, or 840 possible reporting days.

[c] Summer data were obtained from 195 subjects × 4 study days, or 780 possible reporting days.

[d] Any data refer to the existence of any valid data on any possible seasonal reporting days.

[e] a.m. and p.m. refer to valid morning and evening spirometric test data.

[f] 11 a.m.–6 p.m. refers to the existence of valid data during these testing hours.

[g] Personal sampler O_3 data are reported as integrated data for the cumulative hours that the sampler was worn, based on the individual subjects' daily diaries.

[h] Station monitor O_3 data are reported as integrated data for the cumulative hours that the personal sampler was worn, based on the individual subjects' daily diaries.

most likely to be missing on Sunday or Monday (the third or fourth day of the study cycle), whereas personal ozone sampler and diary activity information were most likely to be missing on Monday.

Data capture rates for heart rate information during the 11 a.m. to 6 p.m. daytime interval were lower than for any other type of data. Heart rate data were available for some part of 81% to 85% of all study subject days, but for only 50% to 55% of all study subject days between 11 a.m. and 6 p.m. This resulted from social pressures (resistance to wearing the unit in the presence of peers), practical limitations (removal of the unit for swimming, soccer, football, baseball, bathing, or taking showers), and improper watch operation (misuse or mechanical failure).

EXPOSURE ASSESSMENT

Ozone concentrations reported by regional monitoring stations, across all subject study days, are illustrated in Figure 2. Levels exceeding the former National Ambient Air Quality Standard of 0.12 ppm (120 ppb) for one hour occurred during both the spring and summer study periods. Personal O_3 sampling results are depicted in Figure 3 (and include editing to invoke a lower limit of detection of 5 ppb and to invalidate extreme outliers). Figure 4 compares personal O_3 exposure data to fixed-site station data, adjusted for comparable time periods of exposure. Personal O_3 sampling measurements were almost always lower than integrated ambient hourly data, and measurement correlation was poor (n = 1336 pairs, r = 0.28).

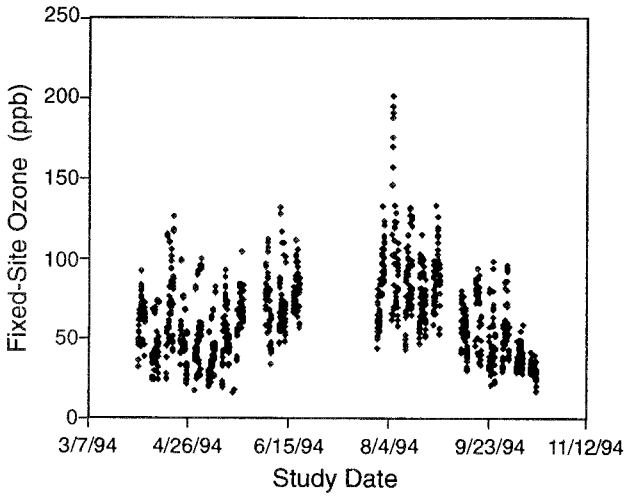

Figure 2. Monitoring station hourly O_3 distribution across study periods.

VALIDATION OF DIARY ACTIVITY LEVELS BY HEART RATE RECORDING

Heart rate data were surprisingly consistent across subject groups at any given activity level (Table 3). Heart rates

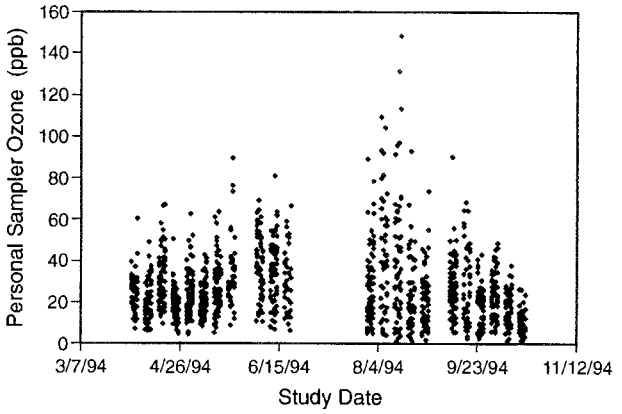

Figure 3. Personal sampler O_3 data vs study date.

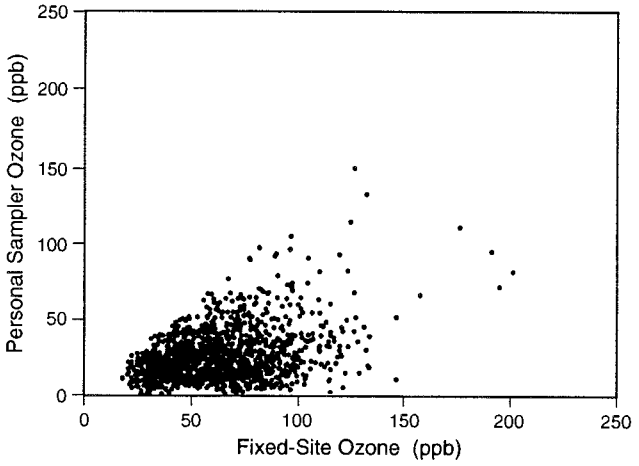

Figure 4. Personal sampler O_3 data vs monitoring station O_3 data for all communities.

Table 3. Activity Levels and Heart Rates[a] by Health Status

Activity Level	Asthmatic	Wheezy	Healthy
0	99 ± 0.3	99 ± 0.3	98 ± 0.2
1	103 ± 0.5	103 ± 0.4	101 ± 0.3
2	111 ± 0.8	108 ± 0.7	108 ± 0.6
3	117 ± 1.1	112 ± 1.0	111 ± 0.8

[a] Heart rates are expressed in bpm as means ± SE.

monotonically increased with increasing level of reported exertion, from about 99 beats per minute (bpm) at activity level "0" (representing "no" time spent very physically active), to about 115 bpm, representing "all" of a given hour spent very physically active. This independent and objective assessment of physical activity helped to strengthen investigator confidence in the general accuracy of subject-completed activity diaries.

SYMPTOMS, MEDICATION USE, OUTDOOR TIME, AND PHYSICAL ACTIVITY

The relations of symptoms, medication use, outdoor time, and physical activity by subject group, season, and O_3 level are summarized in Table 4. Predictably, more children with asthma had trouble breathing, wheezed, and used medications than did wheezy or healthy children. Children with asthma had the most trouble breathing and most wheezing during spring season high-O_3 days (with O_3 measured by either station peak or personal sampler). Among wheezy children, more reported having trouble breathing on low-O_3 days in summer. Slightly more symptoms and medication use were reported during the spring season, but the results were not statistically significant (and are not shown here). More asthmatic and wheezy children reported being active and spending time outdoors than did healthy children, even on high-O_3 days in the spring. More wheezy children

Table 4. Frequency[a] of Reported Symptoms, Medication Use, and Activity by Subject Group, Season, and Ozone Level

Endpoint	All Days Endpoint Reported	Station O_3 (dichotomized)[b]				Personal O_3 (35% Rule)[c]			
		Spring		Summer		Spring		Summer	
		Low O_3	High O_3	Low O_3	High O_3	Low O3	High O_3	Low O_3	High O_3
Trouble breathing									
Asthmatic	19.8	18.9	27.1	18.3	15.2	16.7	27.6	13.3	13.6
Wheezy	7.7	6.6	8.2	14.4	2.2	8.6	5.8	12.3	2.0
Healthy	4.9	4.6	8.1	5.5	2.7	8.6	6.9	3.1	5.7
Wheezing									
Asthmatic	22.5	31.5	21.2	17.1	15.2	16.7	37.9	4.4	22.7
Wheezy	10.4	11.8	4.1	15.5	8.6	14.3	5.8	10.5	12.2
Healthy	5.5	3.9	9.8	7.9	3.2	10.0	5.9	2.1	4.6
Oral Medication									
Asthmatic	11.6	12.3	16.1	3.9	12.2	18.5	11.4	7.1	16.7
Wheezy	6.0	8.2	5.8	4.6	5.1	0.0	2.8	4.8	0.0
Healthy	6.3	6.8	4.3	6.2	7.5	4.9	5.7	4.8	2.9
Inhalers									
Asthmatic	23.2	24.6	30.4	25.0	12.2	18.5	37.1	28.6	8.3
Wheezy	3.6	2.7	5.8	6.2	0.0	4.5	0.0	2.4	3.4
Healthy	0.8	1.5	0.0	0.0	1.0	0.0	1.9	0.0	0.0
Outdoor activity									
Asthmatic	66.0	71.6	72.2	63.9	56.5	48.9	87.8	50.9	69.7
Wheezy	66.6	59.6	70.6	66.7	71.4	47.4	73.7	59.1	77.5
Healthy	61.4	66.5	68.3	60.6	50.3	54.3	80.2	48.3	62.1
Physical activity									
Asthmatic	57.2	67.1	59.7	56.9	42.0	59.6	75.7	40.0	54.5
Wheezy	68.7	67.3	73.5	70.2	65.7	57.9	77.2	60.6	85.0
Healthy	55.8	61.1	64.4	49.2	48.4	55.3	71.6	46.7	45.4

[a] Days in which each subject group reported a specific endpoint shown as a percentage of all subject study days.

[b] Fixed-site data above and below 100 ppb.

[c] Personal sampler lows of 15.6 ppb or less and highs of 32.4 ppb or more.

reported being physically active than did their peers throughout the study, especially during the summer and on high-O_3 summer days.

Spatial and activity pattern results are illustrated in Figures 5, 6, and 7. Overall, children with asthma did not differ from their peers with respect to time spent outdoors (Figure 5) or time spent being active (Figure 6). However, during the summer on high-O_3 days, asthmatic children spent more outdoor time being physically inactive than did either wheezy or healthy children (0.78 hours, compared to 0.03 or 0.36 hours, respectively; see Figure 7).

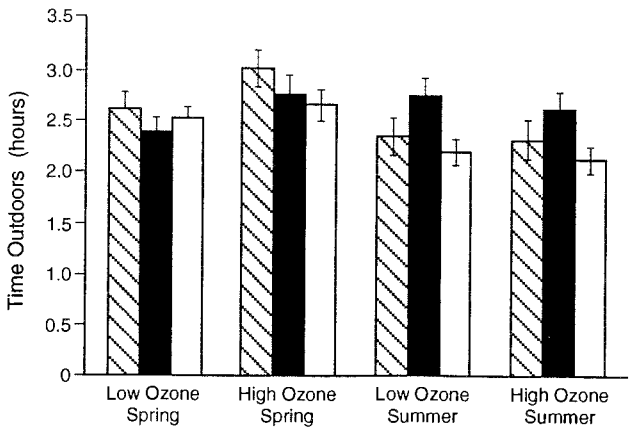

Figure 5. Spatial pattern results, by subject group and O_3 level (means and standard errors) based on monitoring station O_3 data. Bars with diagonal stripes represent asthmatic children, filled bars represent wheezy children, and open bars represent healthy children.

CHANGES IN PULMONARY FUNCTION

Analysis of pulmonary function performance by health subgroup is presented in Figures 8 and 9, by station and by personal sampler O_3 level. Analytical results by both of the ozone exposure metrics (station peak or personal sampler) were largely consistent.

Patterns in the analyses of lung function performance using station peak O_3 were erratic and often in the direction of functional improvement. Changes in peak flow rate, from morning to evening measurement (ΔPEFR), were one of the few consistent indices across subgroups and exposure, always improving regardless of exposure. Only healthy children during high-O_3 exposures in the summer showed statistically significant decrements in lung function, dropping 45 mL in ΔFVC. Although there were some trends in subgroup data toward smaller improvements in function upon high-O_3 exposures (for example, in wheezy children during the spring), no convincing group changes were observed.

The results were not any clearer when personal sampler O_3 data were used instead of station O_3 data in the analysis (Figure 9). Peak flow generally improved without regard to O_3 exposure, yet FVC decreased in healthy subjects during high-O_3 days in the summer.

REGRESSION ANALYSES

Table 5 summarizes the results of seasonal analyses for time spent outdoors or physically active, station peak O_3, and health status. No statistically significant interactions were observed between health status and season. The near-significant effect for peak ambient O_3 during the

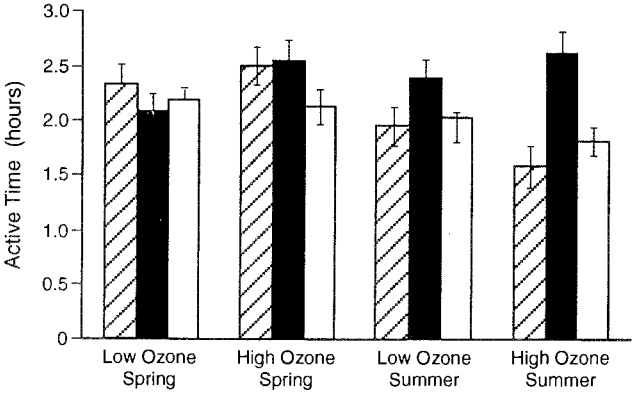

Figure 6. Activity pattern results, by group and O_3 level (means and standard errors) based on monitoring station O_3 data. Bars with diagonal stripes represent asthmatic children, filled bars represent wheezy children, and open bars represent healthy children.

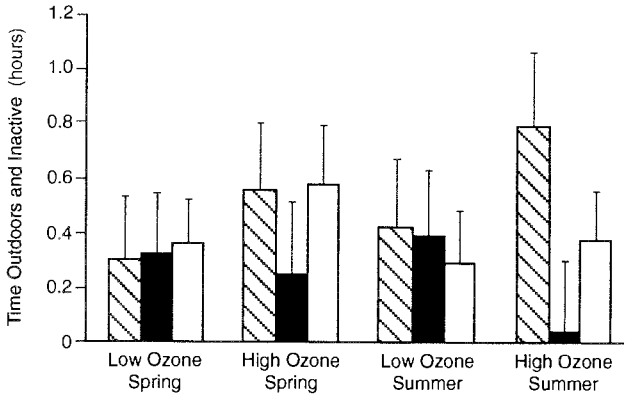

Figure 7. Inactivity results, by group and O_3 level (means and standard errors) based on monitoring station O_3 data. Bars with diagonal stripes represent asthmatic children, filled bars represent wheezy children, and open bars represent healthy children.

spring ($p < 0.057$) suggested that increased ambient O_3 levels were associated with a small amount of increased outdoor time in the spring.

There were differences in both time spent outdoors and physical activity by gender (Table 6). On average, boys spent half an hour longer outside in the spring than girls, and slightly less than half an hour more outside in the summer ($p < 0.04$). Boys also spent almost 40 minutes longer than girls being physically active during spring days ($p < 0.00$).

Neither asthmatic nor wheezy children appeared to vary their time spent outdoors or time spent being physically active in response to peak O_3. Asthmatic and wheezy children spent about the same overall amount of time outdoors,

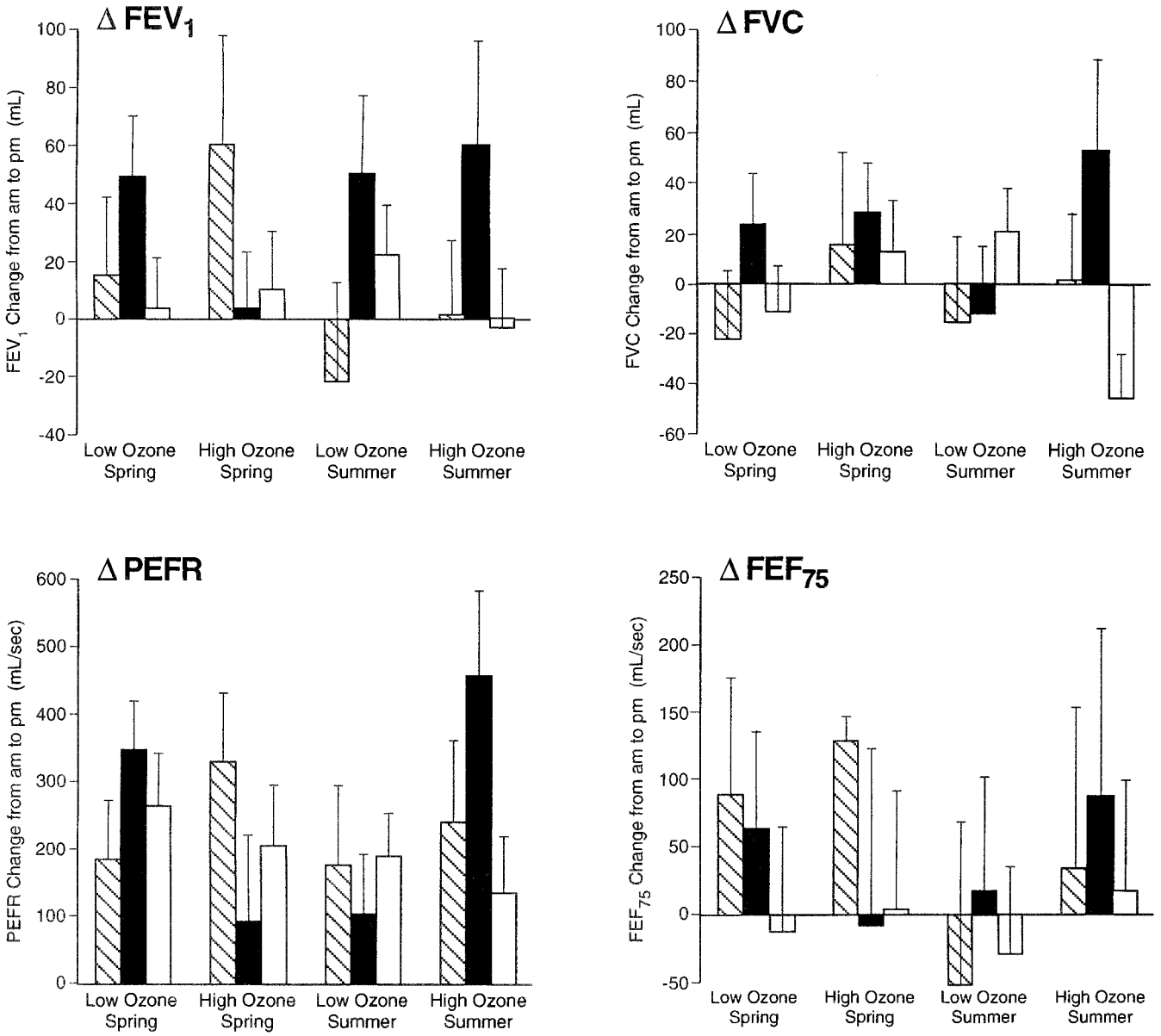

Figure 8. Lung function testing results, based on monitoring station O_3 data. Bars with diagonal stripes represent asthmatic children, filled bars represent wheezy children, and open bars represent healthy children.

and also spent about the same amount of time being physically active. Table 7 depicts the statistical analysis of the gender difference in time spent outdoors and time being physically active.

Table 8 summarizes results for ΔFEV_1, ΔFVC, and ΔFEF_{75} (the changes in FEV_1, FVC, and FEF_{75} from morning to evening, respectively) and O_3 exposure measured by station-collected peak data and by personal samplers. Regardless of method of O_3 measurement, the lung function results for ΔFEV_1 and ΔFEF_{75} were similar. No significant effects were found, nor was there any evidence that asthmatic or wheezy children responded differently to O_3 than

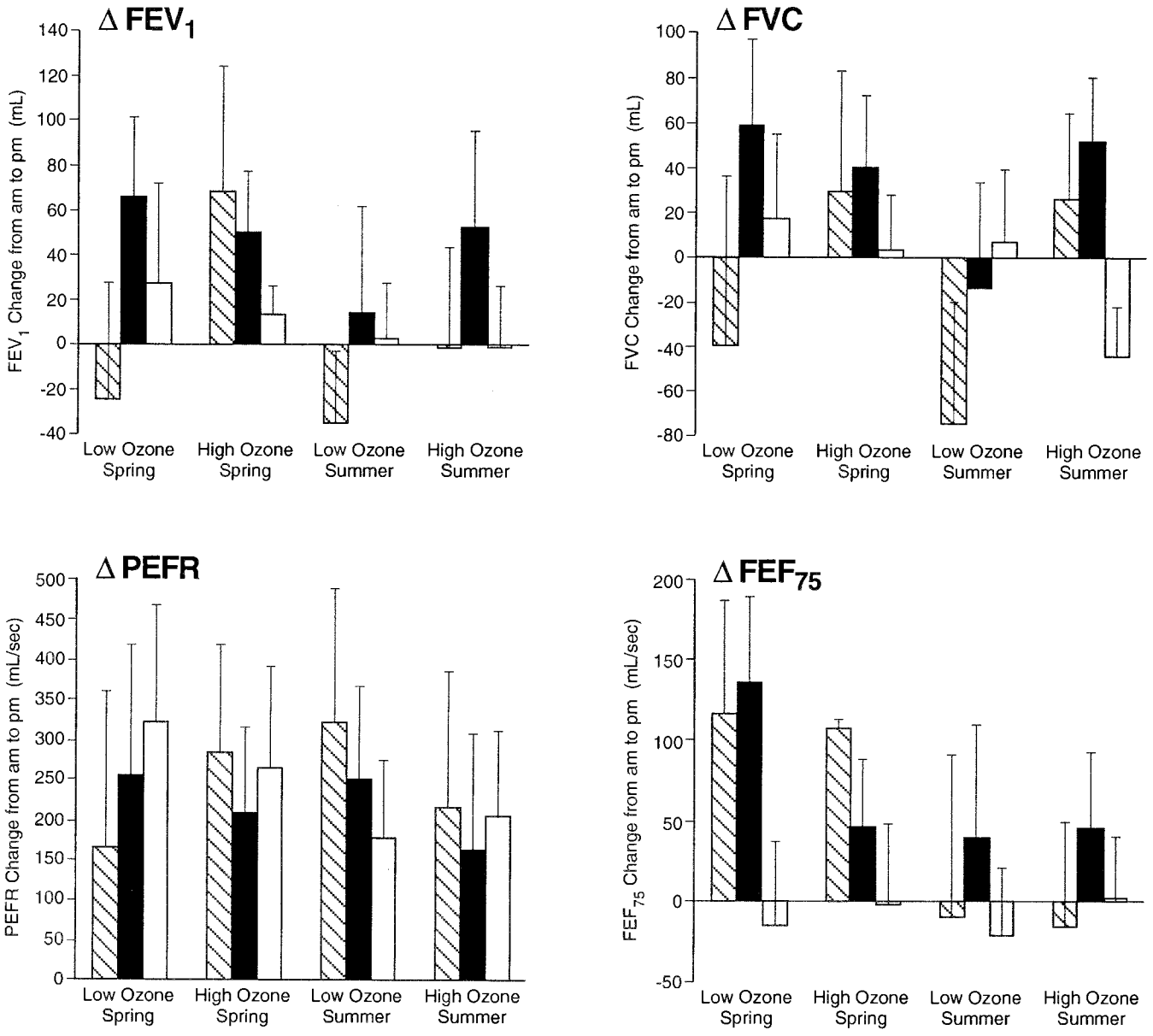

Figure 9. Lung function testing results, based on personal sampler O_3 data. Bars with diagonal stripes represent asthmatic children, filled bars represent wheezy children, and open bars represent healthy children.

did healthy children. For ΔFVC, we observed an effect of O_3, as measured by personal sampler, in the direction of dysfunction. Results near statistical significance ($p \approx 0.06$ to 0.07) were observed for interactions between health status and ΔFVC and between O_3 measured by personal sampler and ΔFVC, but the observed changes were in the direction of functional improvement. This suggested that increased O_3 levels were associated with increased dysfunction in healthy children, but not in asthmatic or wheezy children.

DIARY-BASED RESULTS FOR SYMPTOMS AND MEDICATION

Subjective symptoms (such as wheeze and having trouble breathing) and medication use (pills or inhalers) were recorded in the hourly diaries completed by study subjects and analyzed by investigators. Observed responses were, for the most part, predictable in nature. Asthmatic and wheezy children reported significantly more trouble breathing and more wheezing than did their healthy peers.

Table 6. Relationship Between Time Outdoors or Physically Active Time and Gender[a]

	n	Time Outdoors (hours)	Physically Active Time (hours)
Spring			
Males	100	2.83 ± 1.18	2.52 ± 1.27
Females	95	2.22 ± 0.97	1.87 ± 1.61
Summer			
Males	81	2.46 ± 1.16	1.97 ± 1.31
Females	86	2.10 ± 1.17	1.80 ± 1.37

[a] Time is expressed as mean ± SD; unit of analysis is the subject.

Table 5. Relationship Between Time Outdoors or Physically Active Time and Peak Ambient Ozone[a]

	Time Outdoors		Physically Active Time	
	β	*p* Value	β	*p* Value
Spring Only				
Peak O_3	0.009	0.057	0.003	0.495
Interactions				
O_3 × asthmatic	0.012	0.117	0.007	0.363
O_3 × wheezy	−0.010	0.190	−0.007	0.313
Summer Only				
Peak O_3	0.001	0.867	0.001	0.806
Interactions				
O_3 × asthmatic	0.003	0.614	0.001	0.845
O_3 × wheezy	−0.002	0.760	−0.003	0.562

[a] Units of time are hours, units of O_3 are ppb, and unit of analysis is the subject. Baseline is a healthy male with peak O_3 of 0 ppb. β is a regression coefficient.

Table 7. Statistical Analysis of the Difference Between Males and Females for Time Spent Outdoors and Physically Active Time[a]

	Time Qutdoors			Physically Active Time		
	Difference (hours)	p Value	95% CI	Difference (hours)	p Value	95% CI
Spring	0.61 ± 0.16	0.00	0.31, 0.92	0.65 ± 0.17	0.00	0.30, 0.99
Summer	0.36 ± 0.18	0.04	0.01, 0.72	0.17 ± 0.21	0.42	−0.24, 0.58

[a] Difference is shown as mean ± SE. Unit of time is hours. Unit of analysis is the subject.

No significant differences in pill use (oral medication) were reported, but asthmatic and wheezy children used inhalers considerably more than did healthy individuals.

To examine whether O_3 levels influenced health status, we compared asthmatic and wheezy children to healthy children at three differing ambient O_3 levels: 30 ppb, 75

Table 8. Relationship Between Changes in Pulmonary Function Measures and O_3 Concentration by Source of O_3 Data[a]

	ΔFEV_1		ΔFVC		ΔFEF_{75}	
Effect	β	*p* Value	β	*p* Value	β	*p* Value
Using station peak O_3 data[b]						
Peak O_3	−0.291	0.367	−0.366	0.250	0.162	0.753
Interactions						
O_3 × Asthmatic	0.731	0.198	0.548	0.328	0.635	0.484
O_3 × Wheezy	0.105	0.847	0.479	0.374	−0.236	0.787
Using personal sampler data						
Personal O_3	−1.019	0.191	−1.474	0.052	−0.962	0.441
Interactions						
O_3 × Asthmatic	1.831	0.199	2.666	0.055	1.831	0.423
O_3 × Wheezy	2.007	0.123	2.273	0.072	1.104	0.596

[a] Change in a pulmonary function measure is calculated by subtracting morning data from evening data for each measure; a negative value indicates change toward dysfunction. Unit of analysis is the subject. β is a regression coefficient.

[b] Ambient regional monitoring data.

Table 9. Relative Risks for Reported Symptoms and Medication Use for Increasing Peak Ozone Levels[a]

	Asthmatic		Wheezy	
Variance	Odds Ratio	95% CI	Odds Ratio	95% CI
Trouble breathing				
At 30 ppb O_3	4.76	2.13, 10.66	4.03	1.67, 9.72
At 75 ppb O_3	4.80	3.13, 7.36	1.49	0.88, 2.53
At 120 ppb O_3	4.85	2.46, 9.56	0.55	0.20, 1.57
Wheezing				
At 30 ppb O_3	7.52	3.54, 15.96	3.54	1.56, 7.99
At 75 ppb O_3	5.01	3.35, 7.48	1.96	1.24, 3.09
At 120 ppb O_3	3.34	1.70, 6.57	1.08	0.46, 2.53
Oral medication				
At 30 ppb O_3	1.07	0.35, 3.23	0.69	0.20, 2.39
At 75 ppb O_3	1.87	1.04, 3.37	0.93	0.48, 1.81
At 120 ppb O_3	3.26	1.21, 8.82	1.27	0.38, 4.19
Inhaler use				
At 30 ppb O_3	9.90	2.34, 41.86	—	—
At 75 ppb O_3	8.12	3.87, 17.06	—	—
At 120 ppb O_3	6.66	1.86, 23.85	—	—

[a] Ozone levels are ambient regional monitoring data. Baseline is a healthy study subject, except for inhaler use analyses, which use wheezy study subjects as the baseline. Unit of analysis is the subject day.

ppb, and 120 ppb (see Table 9). For children with asthma, there were increased risks of having trouble breathing and using oral medication at the three selected O_3 concentrations, and a suggestion of an increasing dose-response relationship for oral medication. Children with asthma were likely to report significant wheezing at all three O_3 levels, but wheezing seemed most troublesome at lower O_3 levels (inhaler use by asthmatic children also followed this inverse response). Wheezy children also had the most difficulty at lower, as opposed to higher, O_3 exposure. For wheezy children, breathing difficulty seemed to decrease as O_3 levels increased.

When the effect of O_3 exposure was assessed by personal sampler exposure (the 35% rule), asthmatic children's risks were high but essentially unchanged for having trouble breathing and using oral medication in low or high O_3 exposures (see Table 10). Increased risks for wheezing and use of inhalers were observed at higher O_3 levels. The relative risks for having trouble breathing and for wheezing decreased for wheezy children as O_3 levels increased; risks were unchanged for using oral medication.

DISCUSSION

DATA CAPTURE

Given the complexity of this project and the age of the study population, we expected and received imperfect compliance. The primary reasons for the failure of all data sets to achieve 100% data capture included the voluntary compliance of the children studied, difficulty in use of instrumentation, inappropriate situations for equipment use, instrument failure, and incorrect use of equipment by the individual child.

Children were sometimes reluctant to complete portions of the testing protocol (using the heart rate monitors, completing the activity and symptom diaries, or performing the lung function testing). They occasionally forgot about the routine use of the passive sampler, the diary, or lung function testing, or were away from home without access to the instrumentation. They were sometimes unable to use the assigned equipment because of instrument failure or inappropriate sampling conditions (such as contact sports). Telephone reminders by the field staff and special visits to the child's home only partially addressed these problems. The compliance rates achieved here likely reflect the attention span of the age group studied (10- to 12-year-old children) and the complexity of the sampling effort (hourly completion of written diaries, daily use of the heart rate monitor, daily use of a passive O_3 sampler, and at least twice-daily maximal effort spirometry).

FIXED-SITE O_3 DATA AND PERSONAL O_3 EXPOSURE

In this study, O_3 data collected at community fixed-site stations consistently over-estimated exposures relative to values reported by personal O_3 samplers. Several explanations are readily available to account for the observed weak

Table 10. Relative Risks for Reported Symptoms and Medication Use for Low and High Ozone Levels[a]

	Asthmatic		Wheezy	
Variance	Odds Ratio	95% CI	Odds Ratio	95% CI
Trouble breathing				
Low ozone	5.06	2.83, 9.06	2.70	1.44, 5.05
High ozone	5.35	3.13, 9.15	1.69	0.90, 3.19
Wheezing				
Low ozone	3.68	2.13, 6.35	2.18	1.21, 3.91
High ozone	6.14	3.72, 10.13	1.88	1.05, 3.36
Oral medication				
Low ozone	1.98	0.97, 4.04	0.77	0.32, 1.85
High ozone	2.03	0.99, 4.17	0.66	0.26, 1.67
Inhaler use				
Low ozone	6.27	2.67, 14.71	—	—
High ozone	7.74	3.14, 19.04	—	—

[a] Ozone levels are from personal samplers: Low ozone includes 24-hour averages less than 15.6 ppb; high ozone includes 24-hour averages greater than 32.4 ppb. Baseline is a healthy study subject, except for inhaler use analyses, which use wheezy study subjects as the baseline. Unit of analysis is the subject day.

relationship. First, ambient sampling performed at regional stations conforms to rigid sampling protocols; measurements are made in spatially unencumbered areas several meters above the ground. The personal exposure measurements in this study were collected at a height of about one meter above the ground (on children's lapels), close to potential localized O_3 sinks (such as automotive exhaust, foliage or garden canopies, and building surfaces). Under these conditions, one might reasonably expect that measurements of reactive species such as O_3 would be lower at "people" level.

In addition, previously identified technical shortfalls in personal sampler performance (regarding variable effective sampling rate and effective face velocity [Lurmann et al. 1994]) may have limited the ability of the sampler to accurately measure true O_3 concentrations. Sampling artifacts, such as starvation at the sampler filter face or an overestimate of effective sampling rate, would tend to underpredict actual O_3 concentrations.

Perhaps most important, the spatial activity patterns reported by study subjects suggested that a significant amount of time was spent indoors, rather than in the ambient environment sampled by the fixed-site station monitor. In the absence of any appreciable indoor source of O_3, time spent indoors would significantly reduce the indicated personal O_3 exposure. The lack of agreement between the personal O_3 sampler and community station data therefore truly may reflect real differences in actual O_3 exposure. In principle, personal sampler O_3 data ought to provide better exposure classification information for health risk assessment than do fixed-site data.

SYMPTOMS, MEDICATION USE, AND ACTIVITY

The results of this study do not point to any consistent or clear role of O_3 in producing changes in reported symptoms or medication use. Children with asthma predictably reported more respiratory distress (difficulty breathing, and wheezing) and took more medication (pills and inhalers) than their wheezy or healthy peers. In addition, asthmatic children had more respiratory distress on high-O_3 spring days than on any other days. However, asthmatic and wheezy children also reported more outdoor activity time and more physically active outdoor time than did their healthy peers. The observation that children with asthma reported more time spent outdoors physically inactive on high-O_3 summer days than the other children suggests a form of personal protective behavior that should be more fully examined. Reduced levels of physical activity would reduce ventilation rates. This would deliver a lower pollutant dose to subjects' lungs, presumably resulting in a diminished effect.

The apparently disparate observations of increased symptoms and medication use on high-O_3 spring days, but not high-O_3 summer days, may be explicable in terms of seasonal reactivity (Hackney et al. 1989) or development of some adaptation to the acute effects of O_3 (Horvath et al. 1981; Linn et al. 1982). Children may have been more sensitive to O_3 exposure in the spring, having had only sporadic prior exposure to O_3 in the previous several months. Following several months of elevated ambient O_3 levels, children may have attained some tolerance for (or adaptation to) elevated O_3 exposures.

For wheezy children, symptom and medication findings were often paradoxical, suggesting that this group may be more broadly defined clinically and that it behaved differently from the healthy and asthmatic subgroups. The symptom "trouble breathing" evoked rates from the wheezy group similar to those in the healthy category, whereas the symptom "wheezing" obtained response rates similar to those for children with asthma. Relative risks for these symptoms bore an inverse relationship with increasing O_3 level (as was the case for wheezing, but not trouble breathing, in asthmatic children). On the basis of observed responses, some subject confusion as to the specific meaning of "trouble breathing" may have occurred (because healthy children would not typically be expected to report trouble breathing at rates similar to those for wheezy children).

CHANGES IN PULMONARY FUNCTION

The diurnal changes (morning to evening) in measures of pulmonary function did not appear to follow any pattern by season, by O_3 level, or by health group. Statistically significant improvements as well as decrements in lung function performance were observed. The general tendency for improvement could have resulted from natural diurnal patterns, learning effects, or both. For most measures of pulmonary function, few changes were significant; however, for PEFR, all groups showed increases with most being statistically significant. This is plausibly attributable to a learning phenomenon. We speculate that the decreases in FVC in the healthy group may have resulted from discomfort in taking a deep breath on smoggy days. One potential explanation as to why this discomfort apparently was not perceived by the asthmatic and wheezy groups has to do with their typical breathing difficulties, which somewhat define their health status. Occasional difficulty during breathing may be common enough for asthmatic and wheezy groups that small changes in discomfort go unnoticed.

The use of inhalers could have modified observable pulmonary responses to air pollutants and obscured changes in pulmonary function that otherwise might have been measurable. On almost one-fourth of the study days, children with asthma reported using inhalers, and the relative risks for asthmatic children for both wheezing and inhaler use increased with increasing personal O_3 exposure. Inhaler use among wheezy children was considerably lower, and almost nonexistent in the healthy children.

The failure to detect clear evidence of acute pulmonary effects in these three groups may be due to the fact that O_3 levels were not sufficiently elevated during the period of study. In controlled chamber research at levels in the 80 ppb range, acute effects can be demonstrated in healthy subjects exercising continuously for six or more hours (Horstmann et al. 1990). Ozone reached these levels during the period of our study, but the children in this study, on average, did not spend this amount of time outdoors nor did they spend the time exercising at the high levels reported in the chamber investigations.

This study did not consider exposure to other pollutants, such as particulate matter or nitrogen oxides, which also have seasonal patterns of exposure. Seasonal exposure to bioaerosols also may have been a confounding factor, as the Southern California region is host to a wide variety of flora with extended growing and blooming seasons.

CONCLUSIONS

We studied asthmatic, wheezy, and healthy children during periods of varying ozone levels in spring and late summer to assess subjects' comparative differences with regard to symptoms; lung function performance; and patterns of physical, temporal, and spatial activity. From the collected data, we conclude: (1) personal sampler O_3 concentrations correlated poorly with and were generally lower than O_3 levels measured at fixed-site stations using commercial photometers; (2) the accuracy of subjective diary reports of physical exertion levels was validated by objective heart rate recording; (3) higher personal sampler O_3 values were associated with increased inhaler use, more outdoor time, and more physical activity; (4) subjects spent more time outdoors and were more physically active in the spring than in the summer; (5) girls spent less time outdoors and were less physically active than boys; (6) asthmatic children had the most trouble breathing, the most wheezing, and the most inhaler use on high-O_3 days in the spring, and also spent more time outdoors and were more active on those days; (7) asthmatic children protected themselves by being less physically active on high-O_3 days in summer; (8) wheezy children had the most trouble breathing and wheezed more during low-O_3 days in summer, were more active, and spent more time outdoors than healthy children; and (9) changes in lung function performance were difficult to reconcile with existing knowledge about the acute respiratory effects of air pollution.

This study provides support for the claims that both asthmatic and wheezy children differ from healthy children and that asthmatic children differ from their wheezy peers. Pursuit of the reasons for these differences, and improved understanding of the seemingly conflicting findings among wheezy children, may prove to be areas of fruitful future investigation.

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ABBREVIATIONS

bpm	beats per minute
CI	confidence interval
FEF_{75}	forced expiratory flow with 25% of the volume remaining
ΔFEF_{75}	change in FEF_{75} from morning to evening
FEF_{50}	forced expiratory flow with 50% of the volume remaining
FEF_{25}	forced expiratory flow with 75% of the volume remaining
FEV_1	forced expiratory volume in one second
ΔFEV_1	change in FEV_1 from morning to evening
FVC	forced vital capacity
Δ FVC	change in FVC from morning to evening
MMEF	maximum midexpiratory flow
O_3	ozone
PDT	Pacific Daylight Time

PEFR	peak expiratory flow rate	ppb	parts per billion
Δ PEFR	change in PEFR from morning to evening	ppm	parts per million

INTRODUCTION

Clinical and epidemiologic studies have shown that some people experience transient decrements in lung function and an inflammatory response in the nose and lungs when they are exposed for short periods of time to ozone (reviewed by Lippmann 1993; U.S. United States Environmental Protection Agency 1996). In contrast, limited data have been gathered about the effects of long-term ozone exposure on the human respiratory system (U.S. United States Environmental Protection Agency 1996). To address this lack of information, HEI issued a Request for Applications (RFA) in 1991 entitled, *Epidemiologic Studies of the Health Effects of Long-Term Ozone Exposure.* The RFA especially sought applications to explore whether ozone exacerbates preexisting respiratory diseases such as asthma. Six studies were funded under this RFA. The results of three studies have been published (Loomis et al. 1996; Borja-Aburto et al. 1997; Künzli et al. 1996, 1997a,b; Künzli and Tager 1997; Kinney et al. 1998; Tager et al. 1998a,b) or are in press (Nikiforov et al. 1998).

Dr. John Peters and colleagues of the University of Southern California (USC) School of Medicine, submitted a proposal to assess the relative sensitivities of asthmatic, wheezy, and healthy children to ambient levels of ozone, and to evaluate the time they spent outdoors and their activity patterns during seasonal periods of elevated ozone levels in Southern California.[†] The investigators hypothesized that asthmatic and wheezy children may be at greater risk of adverse respiratory effects caused by air pollution than their more healthy peers. HEI funded Peters and colleagues to study a cohort of approximately 200 children who were selected from a larger cohort that was part of a ten-year prospective study (led by Dr. Peters) sponsored by the California Air Resources Board (CARB). The latter study, entitled *Epidemiologic Investigation to Identify Chronic Health Effects of Ambient Air Pollutants in Southern California*, will be referred to in this document as the USC/CARB Air Pollution Study. The following Commentary on the Investigators' Report is intended to inform HEI sponsors and the public by highlighting both the strengths and limitations of the study, and by placing the Investigators' Report into scientific and regulatory perspective.

SCIENTIFIC BACKGROUND

Asthma is one of the most common chronic and potentially disabling respiratory disease in children and adults. It displays familial aggregation and undoubtedly has a genetic basis in many cases, although the genes involved have not been definitively identified. Asthma is characterized by reversible airway obstruction, airway inflammation, and increased airway responsiveness (a heightened tendency of the airways to constrict in response to irritant stimuli, viral infections, or chemical injuries). In recent years, asthma prevalence has increased worldwide (Buist and Vollmer 1990; Balmes 1996a; Woolcock and Peat 1997), especially in children (Gergen et al. 1988; Burr et al. 1989; Weiss et al. 1993); its cause is not clear however. Although air pollutants such as ozone may exacerbate asthma (discussed by Koren and Utell 1997), ambient air pollution is not believed to be a causal factor in the development of the disease (Austin et al. 1994; Woolcock et al. 1995). Instead, exposure to increased levels of indoor allergens and a changing response of the immune system to viral infections have been proposed as possible causal factors in the increased prevalence of childhood asthma (Woolcock et al. 1995; Peat et al. 1996).

In the 1980s, the observational studies of several investigators demonstrated that when healthy and asthmatic children are exposed to elevated levels of ambient ozone, they experience short-term decrements in pulmonary function and increased symptoms such as cough and wheeze (Lippmann et al. 1983; Lioy et al. 1985; Spektor et al. 1988, 1991; Kinney et al. 1989). Table 1 summarizes the results of more recent epidemiologic studies in the United States, Mexico, and Europe that provide further evidence of ozone's effects on this study population. (The abbreviations used in Table 1 and throughout in this Commentary are defined in the accompanying sidebar.)

Early evidence indicated that the transient ozone-induced decrements in lung function are similar in healthy and asthmatic people (Linn et al. 1978; Silverman 1979; Koenig et al. 1985, 1987, 1988; Balmes et al. 1997). However, two indices of airway inflammation in lung fluids (increases in soluble protein and in polymorphonuclear

[†] Dr. Peters' two-year study, *Acute Effects of Ambient Ozone on Asthmatic, Wheezy, and Healthy Children*, began in June 1993 with total expenditures of $727,036. The Investigators' Report from Peters and colleagues was received for review in December 1995. A revised report, received in June 1997, was accepted for publication in August 1997. During the review process, the HEI Review Committee and the investigators had the opportunity to exchange comments and to clarify issues in both the Investigators' Report and the Review Committee's Commentary.

leukocytes) have been reported to be higher in asthmatic adults exposed to ozone than in healthy adults (Scanell et al. 1996; Balmes et al. 1997). Clinical studies also suggest that people with asthma may experience increased airway responsiveness to inhaled allergens after exposure to ozone (Molfino et al. 1991; Jörres et al. 1996). Thus, it is reasonable to suspect that people with asthma could be more sensitive to ozone than healthy people. Evidence for ozone's exacerbation of asthma is suggested by epidemiologic studies that associate elevated levels of ambient ozone with increased asthma attacks and increased hospital admissions and emergency room visits for asthma and other respiratory diseases (discussed by Balmes 1996b).

JUSTIFICATION FOR THE STUDY

HEI chose to fund this study because it addressed the important goal of evaluating the effects of ambient ozone on potentially sensitive population subgroups, asthmatic

FVC (Forced Vital Capacity) — the total volume of air expelled from the lungs following maximal inspiration

FEV_1 (Forced Expiratory Volume in One Second) — the volume exhaled during the first second of a forced expiration following maximal inspiration

$FEF_{25\%-75\%}$ (Forced Midexpiratory Flow) — the mean rate of airflow between the volumes representing 25% and 75% of the FVC

$FEF_{75\%}$ — the instantaneous flow at the point representing 75% of the FVC

PEFR (Peak Expiratory Flow Rate) — the maximal achievable expiratory flow rate

PM_{10} — Particulate matter with an aerodynamic diameter 10 μm or smaller

MMEF — maximum midexpiratory flow rate

Table 1. Recent Epidemiologic Studies of Ozone's Effects on Healthy, Asthmatic, and Wheezy Children

	Effect of Elevated Levels of Ambient Ozone[a]			
Study Population	Lung Function	Symptoms	Medication Use	Reference
Healthy Children	↓ PEFR[b]	NC (Cough)	NA	Neas et al. 1995
	↓ FEV_1 ± PEFR	ND	NA	Kinney et al. 1996
	↓ PEFR	ND	NA	Braun-Fahrländer et al. 1994
	↓ FEV_1, FVC	ND	NA	Ulmer et al. 1997
	↓ FEV_1, FVC	NC Cough, phlegm production, wheeze	NA	Stern et al. 1994
	↓ PEFR	↑ Cough, wheeze	NA	Krzyzanowski et al. 1992
Asthmatic Children	↓ PEFR	↑ Cough, phlegm production, wheeze	↑	Thurston et al. 1997
	ND	↑ Cough, wheeze, sputum production, shortness of breath	↑	Delfino et al. 1996
	NC PEFR	↑ Cough, phlegm production, wheeze, difficulty breathing	The children did not use medication regularly	Romieu et al. 1996
	↓ PEFR	↑ Runny or stuffed nose, sore throat	↑	Gielen et al. 1997
	NC PEFR	↑ Shortness of breath	NC	Ostro et al. 1995
Wheezy Children	ND	↑ Wheeze	ND	Buchdahl et al. 1996

[a] NC = no change; NA = not applicable; ND = not done; ± = variable change.

[b] PEFR normally shows a diurnal improvement; therefore, ↓ = a lesser improvement than normal.

and wheezing children. The Institute's Health Research Committee also noted the strength of the investigator team, and their comprehensive approach to assessing ozone exposure and health outcomes. In addition, the association of the project with the USC/CARB Air Pollution Study provided an extensive database of potential subjects, and afforded the opportunity to compare the effects of short-term exposure to ozone observed in this study with the results of long-term exposure seen in the larger study.

OBJECTIVES AND SPECIFIC AIMS

The major objective of the study was to compare the relative sensitivities of healthy, asthmatic, and wheezy children to ambient levels of ozone. There were four original specific aims:

1. Determine whether the lung function measures of asthmatic or wheezy children show greater seasonal variation (spring versus summer) than those of healthy children. (In Southern California, ambient ozone levels are typically higher in summer than spring).
2. Determine whether acute changes in lung function and personal exposure to ozone follow a dose-response relationship in healthy, asthmatic, and wheezy children.
3. If a dose-response relationship exists, determine whether it is greater for asthmatic or wheezy children than for healthy children.
4. Determine whether children with asthma or wheeze behave differently than their more healthy peers with respect to time spent outdoors or time spent exercising.

The investigators achieved some of their original aims; however, as discussed below, issues associated with the study design and the relatively low levels of ambient ozone during the study period prevented them from fully achieving their goals.

TECHNICAL EVALUATION

STUDY DESIGN AND METHODS

Subjects

The subjects were selected from a subset of 900 children drawn from the USC/CARB Air Pollution Study population of approximately 3,600 10- to 12-year-old children. They all resided in six communities in the South Coast Air Basin of California where ambient ozone levels have consistently exceeded the National Ambient Air Quality Standard during summertime smog episodes. (At the time of this study, the standard was 0.12 parts per million [ppm], a level that was not to be exceeded for more than one hour once per year.) Asthmatic children were identified by responses to a standardized respiratory history questionnaire (completed by their parents) that addressed doctor-diagnosed asthma, medication use, and asthma-related symptoms. Wheezy children were identified by a negative response to the questions on asthma and a positive response to wheeze-oriented questions. Healthy children were defined as those whose parents did not report positive responses to either the asthma- or wheeze-related questions. Only children who participated in the spring of 1994 were asked to participate in the summer.

Table 1 in the Investigators' Report indicates that the three groups responded similarly to five tests of pulmonary function (FVC, FEV_1, PEFR, FEF_{75}, and MMEF). Although measurements tended toward a gradient between those diagnosed with asthma and healthy children, with generally greater variation among asthmatic children than among their healthier peers, it is not certain that the groups were distinctly different with respect to their pulmonary function.

Protocol

The children were studied on four consecutive days (Friday through Monday) in the spring and in the following summer. Testing involved four components: (1) spirometry, (2) ozone exposure assessment, (3) diary recording of physical activity levels, symptoms, and medication use, and (4) heart rate monitoring. Based on earlier surveys of ozone levels (California Air Resources Board 1989, 1990), Peters and coworkers anticipated low ambient ozone levels from April through June and high ozone levels from August through October. However, ozone levels were generally low in both study periods (between 10 and 100 parts per billion [ppb]), whether measured by regional monitors (which have a self-contained analytical system that measures and records pollutant concentrations) or by passive personal samplers (which collect a pollutant over a specified time period and levels are analyzed later). Contrary to expectations, the investigators found periods of elevated ozone in both seasons (above 120 ppb). Therefore, they could not compare their subjects' responses between low- and high-ozone seasons, and instead reported responses on low- and high-ozone days in each season.

Spirometry

The investigators obtained lung function measurements (FEV_1, FVC, PEFR, and FEF_{75}) from hand-held spirometers assigned to each child. The children performed spirometry in the presence of project staff on the evening prior to the first study day and on the evening of the fourth study day; the intervening spirometry was unsupervised. The investi-

gators asked the children to perform spirometry maneuvers at least three times a day: at 7 a.m. or upon waking in the morning, in the midafternoon or when they returned home from school, and in the evening before their bedtime. They were instructed to perform 3 to 5 maximal efforts at each time to obtain at least three successive consistent maneuvers. The spirometric data were stored electronically and downloaded after the four-day testing period.

Because ozone's effects on lung function were a major focus in this study, it was crucial for these measurements to be accurate. Avol, Peters, and colleagues encountered a technical problem with the spirometers at the beginning of their study. (The units were occasionally unable to identify the point at which there was no further flow of air. This made it impossible to identify the end of a subject's exhalation.) Interim reports from the investigators to HEI indicated that spirometer modifications by the manufacturer reduced, but did not fully prevent, this problem. Therefore, the accuracy of the spirometry data is uncertain.

It is not clear how reliably the children performed spirometry when they were unsupervised. Also, noncompliance may have reduced the sample sizes available for data analysis. For example, in Table 2 of their report, the investigators indicate that they obtained acceptable morning and evening spirometry data on only 79% and 66% of study days in spring and summer, respectively. As the authors point out, instrument failure and difficulty in using the spirometer could have contributed to missing or unusable data.

Some other factors need to be considered regarding the reported changes in lung function.

- Normal circadian variation in bronchomotor tone causes spirometric values to rise from early morning levels, peak in the early afternoon, and then decline toward evening. These naturally occurring changes are likely to affect, and may possibly mask or override, small effects of air pollution, especially at the low ambient ozone levels the children were exposed to during much of this study.
- Medication use could have modified the responses of asthmatic and wheezy children to ambient ozone, especially for the evening measurement. The investigators provided no information on the time elapsed between medication use and lung function measurements.
- The investigators defined evening spirometry as the first acceptable measurement made after 5 p.m. Evidence from controlled laboratory studies indicates that some tests of lung function begin to normalize within 30 minutes after exposure to ozone ceases (Weinmann et al. 1995). Therefore, acute functional changes associated with ambient ozone exposure may have begun to reverse in the interval between the children's return to their homes (where there were no significant sources of ozone) and their spirometric measurements.

Ozone Exposure Assessment

The investigators used two measures of ozone exposure in their study. Data from regional monitors provided hourly ambient ozone concentrations. However, ozone is highly reactive and its concentration at different locations can vary greatly; for this reason, regional monitors may not accurately estimate the ozone levels where exposure occurs. The investigators attempted to improve the accuracy of their exposure estimates by using a passive sampler to obtain data on the children's personal exposures to ozone. The children were instructed to pin the ozone sampler to their shirt or blouse, wear it all day, and return it to a sealable container at night.

The passive sampler used in this study was designed with two filters coated with sodium nitrite and held in a small plastic cylinder (Koutrakis et al. 1993, 1994). As air passed over the filters (referred to as the "collection rate"), the ozone in the air impacted the filter and converted the sodium nitrite to sodium nitrate; the amount of nitrate formed was analyzed later in a laboratory. When their study began, the investigators were aware of a technical problem with the passive ozone samplers. In a validation study, Lurmann and coworkers (1994) had reported that the collection rate (and therefore the ozone concentrations reported) varied with the velocity of air flowing over the opening of the sampler. The air velocity over the sampler can be influenced by the physical position of the wearers, where they place the sampler on their clothes, and how active they are. Another problem with the passive samplers was the potential sampler-to-sampler variability. For example, based on their comparison of ozone levels measured by two samplers worn next to each other by a group of volunteers, Brauer and Brook (1995) concluded that estimates of ambient ozone levels by the samplers can differ by 35% because of random variation. They concluded that "only differences greater than 35% could, with certainty, be considered true differences in exposure." Avol and colleagues invoked a "35% rule" to separate the data from the personal ozone sampler into categories of high or low ozone levels. This meant that the lowest value in the high-exposure category was at least 35% higher than the highest value in the low-exposure category.

The use of a personal sampler that had not been validated on active subjects in natural settings (Liu et al. 1997) was a limitation in the study design. Avol, Peters, and coworkers originally planned to perform validation studies during the USC/CARB Air Pollution Study. Instead, for that study, they developed a Timed Exposure Diffusion Sampler, which provided a controlled-flow sampling environment. Placing the passive sampler in this device avoided problems with a variable collection rate. However, this sampler also needs to be validated in the field.

Measurement of Activity Levels and Heart Rates

The children recorded their physical activity levels, location, and health status (presence of symptoms and use of medication) in diaries at hourly intervals. Avol, Peters, and colleagues validated the degree of physical activity recorded in the diary by having the children wear a small heart rate monitor across their chest from 7 a.m. to 9 p.m. The monitor provided information about heart rate and time of day at the preset interval of "every minute" for each study day. This information was expected to improve the estimates of the children's activity levels, but noncompliance led to missing data, which was a problem in this phase of the study. The investigators obtained complete heart rate data on only 50% to 55% of study days, and complete diary data on 75% of study days (see Table 2 in the Investigators' Report).

Summary

The strengths of the study design were: (1) the opportunity to assess a range of exposures across seasons, (2) the assessment of lung function throughout the day for several days, and (3) the availability of confirmatory or complementary data for three study components (ozone levels from personal ozone samplers and regional ozone monitors; health outcomes from spirometry and symptom reports; and physical activity levels from daily diaries and heart rate monitors). The study, however, was compromised by several factors: a lack of distinct differences in baseline lung function among the three study groups, days with similarly low and high ozone levels in two seasons expected to have distinctly different levels; significant amounts of missing data caused by the children's lack of compliance with the study protocol; the quality of the data generated by the spirometers and ozone samplers; and the lack of information on the effect of medication on diurnal changes in lung function. In addition, the investigators did not consider the effects of possible copollutants such as particulate matter, environmental tobacco smoke, or allergens.

STATISTICAL ANALYSIS

To provide an overview of the data set, the investigators calculated means and standard deviations for each of the measurement endpoints. They used logistic regressions to study the relations between ozone exposure and each physical response (trouble breathing, wheeze, and use of oral medication or inhalers). In the latter analyses, multiple measurements were used as independent observations. This analytic approach would tend to produce estimates of standard error that are too small. Other techniques, such as the Generalized Estimating Equation, could have dealt with this data set more appropriately.

Peters and colleagues also employed a general linear model to analyze the relations among lung function, ozone levels, and activity patterns. They suggested that by including a separate intercept for each subject, within-subject correlations were avoided; however, this technique may not totally eliminate this problem if there were differences in slopes across subjects. The relations between ozone exposure and total time spent outdoors, ozone and total time spent physically active, and ozone and pulmonary function were determined by linear regression. Different models were used to relate pulmonary function measurements with ozone levels on the basis of whether the ozone level was measured by regional monitor or by passive sampler. Again, the statistical approaches to the analyses of pulmonary function responses to ozone did not account for the correlated nature of the data (at least three measurements of each response [FEV_1, FVC, PEFR, FEF_{75}] for four days), which can produce biased estimates of the variance. Time-series models or the Generalized Estimating Equation would have been more effective methods for these analyses.

The unit of analysis was either the subject-day or the subject. By using completed subject-days as the unit of analysis, the investigators maximized the amount of data they collected. For example, a subject could be counted up to four times in each analysis, once for each day of measurement. As the authors state, a disadvantage of this unit of analysis is that the measurements taken on the same subject, even on different days, may be correlated. Ignoring these correlations could underestimate standard errors, and thereby overestimate statistical significance. This effect could make the confidence intervals in Tables 6, 8, and 9 too narrow. Using the subject as the unit of analysis eliminates these correlations.

A further difficulty in this study arises from problems with multiple testing. The investigators performed a large number of statistical analyses, but they did not adjust for multiple testing. Without those adjustments, it is difficult to determine the reliability of the data, and some of the results may be spurious.

As noted above, the children's noncompliance with the study protocol resulted in incomplete spirometric, heart rate, and diary data. Missing data can introduce bias if they are missing from only certain data sets, which is of particular concern if data about ozone exposure or subject susceptibility is systematically missing. The investigators suggest that the missing data are not of concern because their absence was widespread throughout several analyses. However, an alternative interpretation is that the large amounts of missing data should stimulate widespread concern over the validity of the study results. Because of noncompliance, the results may not relate to the entire study population; instead, they may reflect the responses of a unique subset of children who completed most or all of the study protocol.

RESULTS AND INTERPRETATIONS

Exposure Assessment

Peters and coworkers reported that ozone levels measured by the passive samplers and adjusted for comparable time periods of exposure were consistently lower than the hourly measurements provided by the regional monitors, and that the correlation between measurements by the two methods was poor. The investigators reasonably suggest that this can be explained by three factors. First, the regional monitors are located in clear areas several meters above the ground. In contrast, the personal samplers were located on the children's clothes, approximately one meter above the ground, and sampling could have been reduced by ozone reacting with clothing, nearby surfaces, foliage, and automotive exhaust. Second, the children in this study spent much of their time in their homes, where there were no significant sources of ozone. Third, the variable air velocity over the samplers probably affected the collection rate and led to inaccurate ozone measurements.

In summary, although the investigators attempted to reduce exposure misclassification by measuring the children's personal exposures to ozone, this aspect of the study was not successful, largely due to the passive ozone sampler not being ready for use in the field.

Health Endpoints

Avol, Peters, and colleagues reported few consistent or statistically significant responses to elevated levels of ozone; and, overall, the healthy, asthmatic, and wheezy children responded similarly. These responses were independent of whether ozone levels were determined by regional monitors or by passive samplers.

Children's spirometric responses were generally inconsistent and at odds with results from other studies. For example, Avol and colleagues reported no significant ozone-induced changes in FEV_1 or $FEF_{75\%}$. As indicated in Table 1 of this Commentary and reviewed by the U.S. Environmental Protection Agency (1996), a number of investigators have found decrements in FEV_1 in healthy exercising children exposed to elevated ambient levels of ozone. It is conceivable that the levels of ambient ozone encountered in this study, the subjects' reported physical activity levels, and the duration of those reported elevations of physical activity may not have resulted in a sufficient exposure dose to cause an observable effect. In the present study, the investigators also found that, in some instances, changes in response to ozone tended toward functional improvement. Furthermore, in each study group and regardless of their exposure to ozone, the improvement in PEFR from morning to evening was surprising. Several investigators have reported that the diurnal improvement in PEFR in healthy and asthmatic children decreases when ambient ozone levels are elevated (again see Table 1). One of the few statistically significant responses was the decrease observed in FVC from morning to evening in healthy children during high-ozone periods in the summer. This finding agrees with the results of other investigators (see Table 1); however, the FVC of asthmatic and wheezy children did not decline at this time, nor did any group's FVC decline during high-ozone periods in the spring.

Another finding that emerged from this study is that asthmatic children increased their use of inhalers on high ozone days in the spring. The investigators suggested that subjects may have been more sensitive to ozone exposure in the spring. However, springtime also produces profuse pollen blooms; therefore, in addition to a direct effect of ozone, increased inhaler use may have been caused by ozone-induced enhanced bronchial responsiveness to allergens, as suggested by the controlled chamber studies by Molfino and coworkers (1991) and by Jörres and colleagues (1996). An anomalous finding was the increased frequency of inhaler use by asthmatic children during periods of low ozone in the summer rather than during periods of high ozone.

The lack of clear effects of ozone on health endpoints in this study may have been due to random variations in the pulmonary function tests among the children because ozone levels were generally too low to affect them. However, as discussed above, limitations in some of the methods and in certain aspects of the study design also may have contributed to the overall lack of consistent responses and differences among the three study groups.

IMPLICATIONS FOR FUTURE RESEARCH

Future epidemiologic studies of ozone's effects on unsupervised children should include:

- a pilot study to determine the probability that the children will perform the protocol tasks reliably; and on the basis of that assessment, select sample sizes that will provide adequate amounts of data for analyses;
- determination of the time between medication use and lung function measurements;
- estimates of the effects of copollutants; and
- validation of the ozone assessment methods before they are used in the field.

Two strengths of this study that should be incorporated into future studies are: first, the effort to validate the physical exertion levels reported by the children in their diaries by monitoring their heart rates, and second, asking the children to record their activities hourly over several days in their diaries.

CONCLUSIONS

Avol, Peters, and colleagues had the commendable goal of combining intensive monitoring of ozone levels, lung function, symptoms, activity levels, and medication use to evaluate the effect of ozone on healthy, asthmatic, and wheezy children. The investigators found few statistically significant effects of ozone on these outcomes. Moreover, there were few notable differences in response to elevated levels of ozone among the three groups; and in some instances, elevated levels of ambient ozone were associated with functional improvement.

These results are difficult to interpret, because they are inconsistent, and do not always agree with the findings of other epidemiologic studies of ozone's effect on lung function in healthy and asthmatic children. It is possible that the levels of ozone encountered during the study period were generally too low to affect the children. Other pollutants that were not considered, such as environmental tobacco smoke, particulate matter, or allergens, may have confounded the results. In addition, limitations in some of the methods and certain aspects of the study design may have produced a data set that was inadequate to answer the complex questions being addressed.

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