Association of Low-Level Ozone and Fine Particles With Respiratory Symptoms in Children With Asthma

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Context Exposure to ozone and particulate matter of 2.5 μm or less ($PM_{2.5}$) in air at levels above current US Environmental Protection Agency (EPA) standards is a risk factor for respiratory symptoms in children with asthma.

Objective To examine simultaneous effects of ozone and $PM_{2.5}$ at levels below EPA standards on daily respiratory symptoms and rescue medication use among children with asthma.

Design, Setting, and Participants Daily respiratory symptoms and medication use were examined prospectively for 271 children younger than 12 years with physician-diagnosed, active asthma residing in southern New England. Exposure to ambient concentrations of ozone and $PM_{2.5}$ from April 1 through September 30, 2001, was assessed using ozone (peak 1-hour and 8-hour) and 24-hour $PM_{2.5}$. Logistic regression analyses using generalized estimating equations were performed separately for maintenance medication users (n=130) and nonusers (n=141). Associations between pollutants (adjusted for temperature, controlling for same- and previous-day levels) and respiratory symptoms and use of rescue medication were evaluated.

Main Outcome Measures Respiratory symptoms and rescue medication use recorded on calendars by subjects' mothers.

Results Mean (SD) levels were 59 (19) ppb (1-hour average) and 51 (16) ppb (8-hour average) for ozone and 13 (8) μg/m^3 for $PM_{2.5}$. In copollutant models, ozone level but not $PM_{2.5}$ was significantly associated with respiratory symptoms and rescue medication use among children using maintenance medication; a 50-ppb increase in 1-hour ozone was associated with increased likelihood of wheeze (by 35%) and chest tightness (by 47%). The highest levels of ozone (1-hour or 8-hour averages) were associated with increased shortness of breath and rescue medication use. No significant, exposure-dependent associations were observed for any outcome by any pollutant among children who did not use maintenance medication.

Conclusion Asthmatic children using maintenance medication are particularly vulnerable to ozone, controlling for exposure to fine particles, at levels below EPA standards.

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CHILDREN WITH ASTHMA ARE particularly vulnerable to the adverse health effects of high levels of air pollution. Studies of children with asthma living in some of the most highly polluted regions of the world conclude that exposure to levels of ozone or particulate matter (especially particles ≤2.5 μm in diameter [$PM_{2.5}$]) regularly in excess of US Environmental Protection Agency (EPA) air quality standards (120 ppb [1-hour average] and 80 ppb [8-hour average] for ozone and 65 μg/m^3 for 24-hour $PM_{2.5}$) significantly enhances the risk of respiratory symptoms, asthma medication use, and reduced lung function.[1-5]

Studies of children with asthma living in regions with levels of pollution within or near compliance with EPA air quality standards suggest that the current standards do not protect these more vulnerable members of the population.[6-10] Asthma severity, as measured by symptoms, medication use, restrictions in activity, or use of medical services, has been shown to be affected by exposure to ozone (1-hour maximum measurement[6-10] or 8-hour average[6-9]), particles 10 μm or smaller (PM_{10}),[6,8] or $PM_{2.5}$ (12-hour total).[6]

Of interest in many recent studies of children with asthma are the simultaneous effects of ozone and particulates on asthma severity.[2,3,8] Simultaneous exposure to high levels of both ozone and

See also p 1915 and Patient Page.

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Table 1. Ozone, Particulate Matter of 2.5 µm or Less ($PM_{2.5}$), and Temperature in Southern New England, April 1 to September 30, 2001

			Percentile				
	Mean (SD)	Range	20th	40th	50th	60th	80th
Ozone, ppb							
1-Hour average	58.6 (19.0)	27.1-125.5	43.2	51.6	55.5	58.9	72.7
8-Hour average	51.3 (15.5)	21.4-99.6	39.1	45.9	50.0	52.1	63.3
$PM_{2.5}$, 24-hour total, µg/m^3	13.1 (7.9)	3.7-44.2	6.9	9.0	10.3	12.1	19.0
Temperature, 24-hour maximum, °C	23.5 (6.0)	4.89-36.2	17.6	23.7	25.0	26.1	28.4

$PM_{2.5}$ (fine particles)[2] or PM_{10} (coarse particles)[3] found in Mexico City, Mexico, contributed to increased respiratory symptoms among children with asthma. In a region of lower pollution, asthma symptoms were associated with both ozone and course particles.[8] In the current study, we examined the simultaneous effects of ozone and fine particles on daily respiratory symptoms and rescue medication use of children with asthma residing in southern New England during spring and summer 2001.

METHODS

Participants

The study participants were 271 children from a cohort of families living in Connecticut and the Springfield area of Massachusetts who were participating in a study of asthma development.[11,12] From 1997 through 1999, 1002 infants born to families with at least 1 child with physician-diagnosed asthma were enrolled in the original birth cohort. Beginning in 2000, eligible asthmatic siblings (1 per cohort family) were identified and invited to participate in a 1-year prospective study of asthma severity. Eligibility criteria were that the child was younger than 12 years at the time of enrollment and had exhibited respiratory symptoms or used asthma medication within the previous 12 months. Included in the current analysis are subjects enrolled for all or part of the 183-day sampling period (April 1 through September 30, 2001), which includes the summertime, high-ozone pollution months in this region. Of 357 children identified as being eligible for inclusion in the current analysis, 56 refused follow-up, 16 were lost to follow-up, and 14 withdrew before April 1, 2001, leaving a total of 271 (76%). The Human Investigation Committee of Yale University, New Haven, Conn, approved this study, and all respondents (mothers of study subjects) gave informed consent before participation.

Data Collection

Demographic information and medical histories were collected during a home interview with the mother at enrollment. Daily respiratory symptoms (wheeze, persistent cough, chest tightness, shortness of breath) and medication use (maintenance medications, including inhaled or systemic steroids, cromolyn sodium, and leukotriene inhibitors, and rescue medications, including bronchodilators) were recorded on symptom and medication calendars by the child's mother and collected through monthly telephone interviews. Additional information about the previous 12 months was collected at an exit interview (eg, dates the child had been away from the southern New England region during the study year).

Air Quality Assessment

Study subjects resided in a 6691-square mile area in Connecticut and the Springfield area of Massachusetts. All ambient air quality monitoring sites (14 sites for ozone, 10 in Connecticut and 4 in Massachusetts; 4 sites for daily $PM_{2.5}$, 2 in Connecticut and 2 in Massachusetts; 13 temperature sites, 12 in Connecticut and 1 in Massachusetts) were located within a 52.5-mile radius centered at Southington, Conn (14 miles southwest of Hartford). The maximum distance between sites was 105 miles; the minimum distance was 4 miles. The Departments of Environmental Protection (DEPs) of Connecticut and Massachusetts provided measurements for hourly ozone concentrations and temperatures and daily 24-hour $PM_{2.5}$ (total $PM_{2.5}$ accumulated during 24 hours). Since both ozone and fine particle pollutants, as well as meteorological variables, tend to be regional,[13] the maximum daily 1-hour average (mean over 1 hour) and the 8-hour rolling average (mean over previous 8 hours) for ozone, daily $PM_{2.5}$ concentration, and maximum daily temperature were averaged across monitoring sites. Between-site correlation coefficients (Pearson r) were high for the 4 daily $PM_{2.5}$ sites (median r=0.91; range, 0.84-0.95) and the 13 temperature sites (median r=0.97; range, 0.85-0.99). There was more variability among the 14 ozone monitoring sites (median r=0.83; range, 0.50-0.97 for the 1-hour average; and median r=0.81; range, 0.47-0.97 for the 8-hour average). For technical details on ambient air quality monitoring, see the Web sites for the Connecticut DEP[14] and the Massachusetts DEP.[15]

Data Analysis

To examine the effects of ozone and $PM_{2.5}$ on children with different degrees of asthma severity, children were divided into 2 groups: those who used any maintenance medication during the 183-day observation period (n=130) and those who did not (n=141). Use of maintenance medication was used as a proxy for asthma severity to avoid using the outcome measures (respiratory symptoms and rescue medication use) in the assessment of severity. Logistic regression analyses, using generalized estimating equations (PROC GENMOD with AR1 autoregressive structure in SAS statistical software)[16-18] and adjusted for maximum daily temperature, were used to evaluate the association between levels of ozone and $PM_{2.5}$, with presence or absence of specific respiratory symptoms or rescue medication use. Using a repeated-measures technique permitted each subject to serve as his or her own control; therefore, personal variables (eg, race and other sociodemographic factors) that would not change during the study were not included in the models.

Subgroup analysis, which included either 17 160 observations (an average of 132 days of data for 130 users of maintenance medication) or 19 035 observations (135 days for 141 nonusers of maintenance medication), focused directly on the association between exposures and health effects.

Exposure variables were categorized into quintiles, then entered into the model as dummy variables. The reference category for each was the lowest quintile. Both same-day and previous-day levels of ozone and $PM_{2.5}$ were examined. Analyses were performed separately for each severity group and each outcome. In single-pollutant models, a test for linear trend was performed by examining the model when the pollutant was entered as a continuous variable instead of as quintiles. In copollutant models, a test for goodness of fit was performed using the Hosmer-Lemeshow statistic for logistic regression. Significance level for all tests was set at .05.

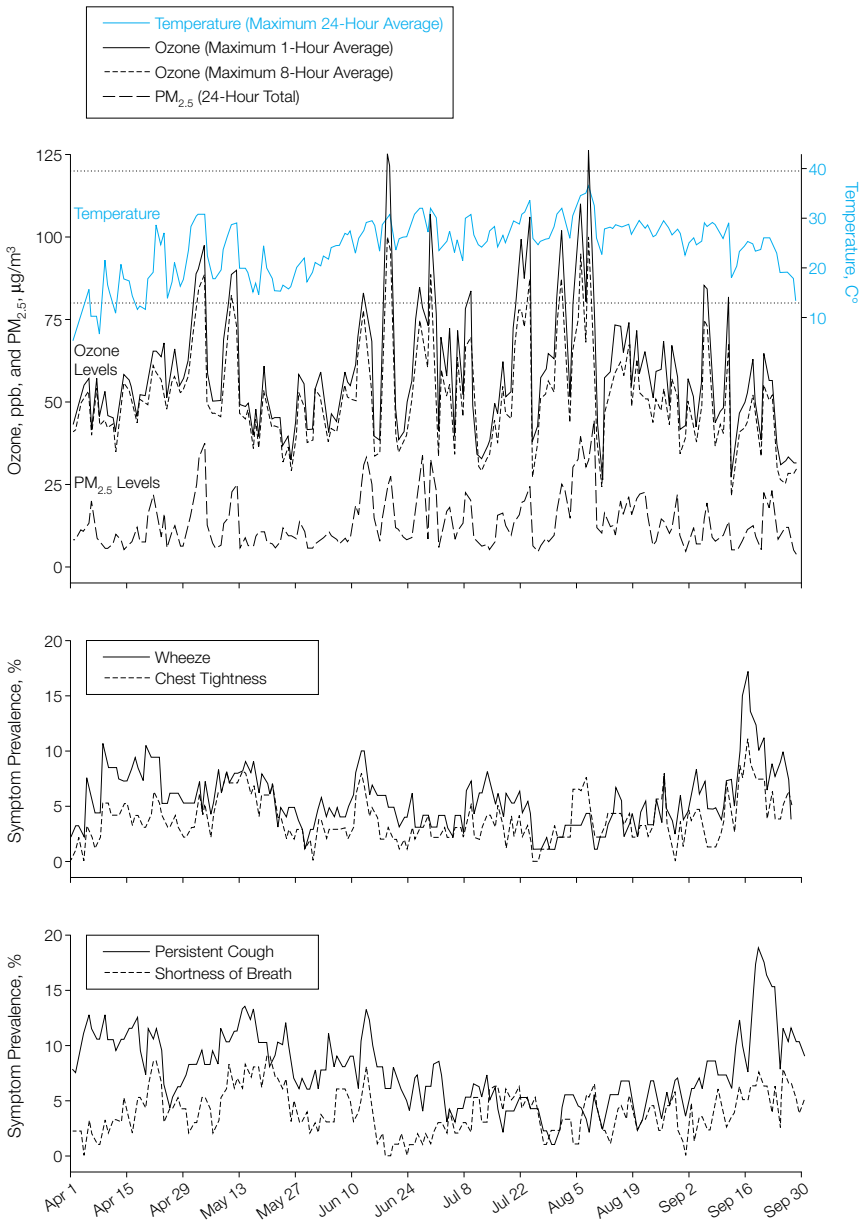
RESULTS

Descriptive Statistics

Levels of ozone, $PM_{2.5}$, and temperature from April through September 2001 are summarized in TABLE 1 and the FIGURE. The EPA 1-hour standard (120 ppb) was exceeded on 3 days, and the 8-hour ozone standard (80 ppb) was exceeded on 10 days of the 183 days of observation. There were no days when the level of $PM_{2.5}$ exceeded the EPA 24-hour standard of 65 $\mu g/m^3$. There was a strong correlation between ozone and fine particles ($PM_{2.5}$ vs 1-hour average ozone $r=0.77$ vs 8-hour average $r=0.74$) (TABLE 2).

There were no significant differences between the users (n=130) of maintenance medication and nonusers (n=141) for mean (SD) age of study subjects (age on April 1, 2001, for users, 8.8 [2.0] years [range, 2.4-12.7 years]; age of nonusers, 8.3 [2.2] years [range, 2.0-12.6 years]; *t* test $P=.71$) or mean days of participation (mean participation for users, 132 [48] days [range, 3-183 days]; mean participation for nonusers, 135 [51] days [range, 5-183 days]; *t* test $P=.50$). Sex and ethnicity did not differ by medication use. Nearly two thirds of each group were male (users, 64.6%; nonusers, 64.5%; χ^2 test $P=.99$), and most children in each group were white, with smaller numbers of black and Hispanic children (users, 80.0%, 8.5%, and 11.5%, respectively; nonusers, 70.9%, 11.4%, and 17.7%, respectively; χ^2 test $P=.22$). Compared with nonusers of maintenance medication, users had significantly more days of all respiratory symptoms and rescue medication use: 50% of

Figure. Daily Levels of Ozone (Both 1-Hour Average and 8-Hour Average), Particulate Matter of 2.5 µm or Less ($PM_{2.5}$), and Daily Maximum Temperature, With Daily Prevalence of Respiratory Symptoms for Users of Asthma Maintenance Medication (n=130) for Southern New England, April 1 through September 30, 2001



Dotted lines at 80 ppb and 120 ppb indicate Environmental Protection Agency standards for 8-hour average and 1-hour average ozone, respectively. Note that daily exposure levels shown here are the result of averaging over regional monitoring sites (14 ozone, 4 $PM_{2.5}$, and 13 temperature sites).

this group experienced approximately 1 week of persistent cough or wheeze, had 2 to 3 days of chest tightness or shortness of breath, and used rescue medication for nearly 3 weeks during the 26-week study period. At least half of all nonusers experienced no symptoms and did not use rescue medication during this same period (TABLE 3). Daily prevalence of symptoms for users of maintenance medication is shown in the Figure. With the exception of somewhat higher rates of symptoms in the early spring and late summer when the temperatures tended to be lowest, there was overall conformity of reporting all 4 symptoms across the observation period.

Single-Pollutant Models for Users of Maintenance Medication

Ozone (1-Hour Average). An ozone concentration of 51.6 ppb or higher (the top 3 quintiles of the distribution of the maximum 1-hour average) on the same day as the reported symptom was the only exposure variable associated with an increased likelihood of wheeze (by 16%, 16%, and 22%, respectively) (TABLE 4, model 1). A 4% increase in bronchodilator use was also associated with same-day levels of ozone (51.6-58.8 ppb) (Table 4, model 1). Previous-day levels of maximum 1-hour average ozone were associated with increased likelihoods of persistent cough (16% increase for levels ≥72.7 ppb), chest tightness (by 21%, 30%, and 37% for levels ≥51.6 ppb), and shortness of breath (by 22% and 30% for levels ≥58.9 ppb) (Table 4, Model 2). The effects of previous-day levels on chest tightness and shortness of breath were significant in an exposure-dependent way: for each 50-ppb increase in previous-day, 1-hour ozone levels, the likelihood of these symptoms increased by 26% (odds ratio [OR], 1.26; 95% confidence interval [CI], 1.0-1.48) and 22% (OR, 1.22; 95% CI, 1.02-1.45), respectively.

Ozone (8-Hour Average). An ozone concentration of 63.3 ppb or higher, measured as the maximum 8-hour average on the same day as the reported symptom, was associated with a 30% increase in chest tightness (Table 4, model 3). Previous-day levels of 52.1 ppb or higher were associated with increased chest tightness, persistent cough, and shortness of breath (Table 4, model 4). As was the case with 1-hour ozone levels, the associations with the symptoms of chest tightness and shortness of breath were exposure dependent: a 50-ppb increase in previous-day, 8-hour ozone level increased the likelihood of chest tightness (OR, 1.33; 95% CI, 1.09-1.62) and shortness of breath (OR, 1.30; 95% CI, 1.05-1.61).

$PM_{2.5}$. Increased likelihood of chest tightness was associated with same-day levels of $PM_{2.5}$ from 12.1 to 18.9 $\mu g/m^3$ (Table 4, model 5). Previous-day levels of 19.0 $\mu g/m^3$ or higher were associated with persistent cough, chest tightness, and shortness of breath (Table 4, model 6).

Copollutant Models for Users of Maintenance Medication

In logistic regression models of both ozone and fine particles for children taking maintenance medication, an increased likelihood of respiratory symptoms was associated with levels of ozone on the same day, previous day, or both; and increased bronchodilator use was associated with the highest level of same-day ozone. Neither respiratory symptoms nor bronchodilator use were associated with level of fine particles.

Ozone (1-Hour Average) and $PM_{2.5}$. Increased likelihood of wheeze was associated with same-day levels of 1-hour average ozone of 43.2 ppb or higher in an exposure-dependent manner (TABLE 5). When ozone is entered into this same model as a continuous variable, a 50-ppb increase in same-day ozone increases the likelihood of wheeze

Table 2. Pearson Correlation Coefficients for Same Day and Previous Day Levels of Ozone and Particulate Matter of 2.5 µm or Less ($PM_{2.5}$)

	Ozone					
		8-Hour		$PM_{2.5}$		
	1-Hour (Previous Day)	Same Day	Previous Day	Same Day	Previous Day	Temperature
Ozone, ppb						
1-Hour average	0.56	0.98	0.57	0.77	0.40	0.63
1-Hour average, previous day		0.52	0.98	0.58	0.76	0.46
8-Hour average			0.54	0.74	0.35	0.56
8-Hour average, previous day				0.56	0.74	0.41
$PM_{2.5}$					0.57	0.58
$PM_{2.5}$, previous day						0.44

Table 3. Rates of Respiratory Symptoms and Rescue Medication Use for Study Subjects Stratified by Use of Maintenance Medication (Southern New England, April 1-September 30, 2001)*

	Users (n = 130)		Nonusers (n = 141)	
Variable	Median (IQR)	Range	Median (IQR)	Range
Symptom rates, %†				
Wheeze	2.8 (9.3)	0-40.5	0.0 (0.9)	0-26.8
Persistent cough	4.4 (9.8)	0-100	0.0 (3.5)	0-45.7
Chest tightness	1.2 (4.9)	0-40.5	0.0 (0.0)	0-20.8
Shortness of breath	1.5 (6.0)	0-40.5	0.0 (0.7)	0-21.5
Rescue medication use rate, %	9.4 (27.9)	0-100	0.0 (1.7)	0-71.2

Abbreviation: IQR, interquartile range.
*Subjects were divided into 2 groups: those who did (users) and those who did not (nonusers) use any asthma maintenance medications (including systemic or inhaled steroids, cromolyn sodium, and leukotriene inhibitors).
†Symptom and rescue medication use rates were calculated for each subject by dividing the number of days of symptoms or medication use by days of participation × 100. Rates of symptoms and medication use were significantly different for users and nonusers (Wilcoxon test, $P<.001$).

by 35% (OR, 1.35; 95% CI, 1.11-1.65). None of the exposure variables was associated with an increased likelihood of persistent cough, and only 1-hour average ozone levels between 43.2 and 51.5 ppb were associated with a decreased likelihood of cough (OR, 0.88; 95% CI, 0.78-0.99). The likelihood of chest tightness was significantly increased by same-day (≥58.9 ppb) and previous-day (≥51.6 ppb) levels of ozone in an exposure-dependent way. The likelihood of chest tightness increases by 47% (OR, 1.47; 95% CI, 1.18-1.84) for each 50-ppb increase in same-day levels of ozone,

Table 4. Odds Ratios From 6 Single-Pollutant Logistic Regression Models of Respiratory Symptoms or Rescue Medication Use of Maintenance Medication Users (n = 130) (Southern New England, April 1 to September 30, 2001)*

	Odds Ratio (95% Confidence Interval)				
Pollutant	Wheeze	Persistent Cough	Chest Tightness	Shortness of Breath	Bronchodilator Use
Ozone, ppb					
Model 1 (same day, 1 hour)					
<43.2	1.00	1.00	1.00	1.00	1.00
43.2-51.5	1.04 (0.89-1.21)	0.88 (0.79-0.99)	1.11 (0.91-1.36)	0.95 (0.74-1.20)	1.00 (0.96-1.05)
51.6-58.8	1.16 (1.00-1.35)	0.97 (0.87-1.08)	1.01 (0.83-1.23)	0.96 (0.79-1.15)	1.04 (1.00-1.09)
58.9-72.6	1.16 (1.00-1.35)	0.92 (0.81-1.05)	1.16 (0.97-1.39)	1.06 (0.87-1.28)	1.02 (0.98-1.07)
≥72.7	1.22 (0.97-1.53)	0.99 (0.80-1.22)	1.31 (0.97-1.77)	1.24 (0.94-1.64)	1.05 (0.97-1.13)
Linear trend *P* value	.90	.69	.75	.80	.30
Model 2 (previous day, 1 hour)					
<43.2	1.00	1.00	1.00	1.00	1.00
43.2-51.5	1.00 (0.86-1.17)	1.09 (0.99-1.20)	1.08 (0.86-1.37)	1.14 (0.92-1.40)	1.02 (0.98-1.06)
51.6-58.8	0.93 (0.82-1.06)	1.08 (0.95-1.16)	1.21 (1.02-1.44)	1.10 (0.93-1.31)	1.00 (0.96-1.03)
58.9-72.6	1.00 (0.88-1.14)	1.08 (0.98-1.20)	1.30 (1.10-1.55)	1.22 (1.03-1.44)	1.01 (0.97-1.06)
≥72.7	1.11 (0.94-1.30)	1.16 (1.04-1.29)	1.37 (1.11-1.71)	1.30 (1.04-1.63)	1.03 (0.98-1.08)
Linear trend *P* value	.47	.06	.005	.03	.53
Model 3 (same day, 8 hour)					
<39.1	1.00	1.00	1.00	1.00	1.00
39.1-45.8	1.10 (0.94-1.30)	0.93 (0.82-1.07)	1.15 (0.92-1.44)	1.03 (0.82-1.30)	1.02 (0.98-1.06)
45.9-52.0	1.05 (0.90-1.22)	0.94 (0.84-1.06)	1.07 (0.87-1.31)	0.94 (0.77-1.14)	1.03 (0.99-1.08)
52.1-63.2	1.06 (0.92-1.23)	0.94 (0.82-1.07)	1.04 (0.86-1.27)	1.02 (0.85-1.23)	1.01 (0.96-1.06)
≥63.3	1.11 (0.90-1.37)	0.97 (0.79-1.19)	1.30 (1.00-1.68)	1.23 (0.94-1.60)	1.06 (0.99-1.13)
Linear trend *P* value	.63	.67	.99	.73	.13
Model 4 (previous day, 8 hour)					
<39.1	1.00	1.00	1.00	1.00	1.00
39.1-45.8	0.95 (0.83-1.08)	1.04 (0.93-1.16)	1.06 (0.89-1.26)	1.11 (0.93-1.32)	1.01 (0.98-1.06)
45.9-52.0	0.99 (0.85-1.15)	1.02 (0.92-1.14)	1.05 (0.84-1.32)	1.09 (0.87-1.37)	0.99 (0.95-1.03)
52.1-63.2	0.98 (0.85-1.12)	1.08 (0.96-1.20)	1.24 (1.02-1.49)	1.19 (0.99-1.44)	1.01 (0.97-1.06)
≥63.3	1.09 (0.93-1.27)	1.11 (1.00-1.24)	1.32 (1.07-1.62)	1.27 (1.05-1.63)	1.03 (0.97-1.08)
Linear trend *P* value	.38	.07	.004	.02	.64
$PM_{2.5}$, $\mu g/m^3$					
Model 5 (same day)					
<6.9	1.00	1.00	1.00	1.00	1.00
6.9-8.9	0.95 (0.83-1.10)	0.95 (0.87-1.04)	1.01 (0.86-1.19)	1.01 (0.87-1.17)	1.04 (0.99-1.09)
9.0-12.0	1.04 (0.89-1.20)	0.96 (0.87-1.06)	1.06 (0.89-1.26)	1.03 (0.87-1.22)	1.02 (0.96-1.08)
12.1-18.9	1.05 (0.92-1.20)	1.00 (0.91-1.09)	1.24 (1.06-1.45)	1.07 (0.91-1.25)	1.04 (0.99-1.09)
≥19.0	0.93 (0.78-1.11)	0.95 (0.83-1.09)	1.05 (0.84-1.33)	1.03 (0.83-1.28)	1.02 (0.97-1.08)
Linear trend *P* value	.89	.51	.12	.22	.18
Model 6 (previous day)					
<6.9	1.00	1.00	1.00	1.00	1.00
6.9-8.9	1.06 (0.95-1.20)	1.04 (0.94-1.14)	1.03 (0.87-1.23)	1.00 (0.84-1.19)	0.98 (0.94-1.03)
9.0-12.0	1.09 (0.94-1.28)	1.05 (0.94-1.17)	1.04 (0.85-1.27)	1.09 (0.90-1.31)	0.99 (0.95-1.03)
12.1-18.9	1.03 (0.89-1.19)	1.03 (0.94-1.14)	1.00 (0.84-1.19)	1.09 (0.90-1.31)	0.97 (0.94-1.01)
≥19.0	1.14 (0.97-1.34)	1.12 (1.02-1.24)	1.21 (1.00-1.46)	1.26 (1.02-1.54)	0.99 (0.95-1.04)
Linear trend *P* value	.48	.78	.16	.14	.57

Abbreviation: $PM_{2.5}$, particulate matter of 2.5 μm or less.
*Separate logistic regression analyses were performed for each outcome measure and each pollutant on the same day or previous day. Models for ozone (1-hour maximum or 8-hour average) were adjusted for maximum daily temperature. Logistic regressions were performed using generalized estimating equations and specifying a 1-day lagged autoregressive structure for the correlation matrix. Linear trend *P* values are from logistic regression models with each pollutant entered as a continuous variable.

and by 42% (OR, 1.42; 95% CI, 1.14-1.78) for each 50-ppb increase in previous-day levels. Shortness of breath and ozone were similarly associated; likelihood of the symptom was increased by same-day levels of 72.7 ppb or higher and previous-day levels from 58.9 to 72.6 ppb (by 32%). Increased likelihood of bronchodilator use was associated with same-day levels of 72.7 ppb or higher (Table 5).

Ozone (8-Hour Average) and $PM_{2.5}$. For 8-hour average ozone levels, the likelihood of chest tightness was increased by same-day (OR, 1.64; 95% CI, 1.23-2.17) and previous-day (OR, 1.45; 95% CI, 1.10-1.92) levels of 63.3 ppb or higher. Shortness of breath was similarly associated; likelihood of the symptom was increased by same-day (OR, 1.45; 95% CI, 1.10-1.91) and previous-day (OR, 1.31; 95% CI, 1.00-1.71) levels of 63.3 ppb or higher. As seen for the highest 1-hour ozone level, increased bronchodilator use was associated with same-day levels of 63.3 ppb or higher for 8-hour ozone measurements (OR, 1.09; 95% CI, 1.02-1.17).

Nonusers of Maintenance Medication

Single-Pollutant Models. Similar analyses for nonusers of maintenance medication revealed no significant associations among the top 3 concentration quintiles for the exposure variables and respiratory symptoms or bronchodilator use. For example, chest tightness was not significantly associated with same-day, 1-hour ozone levels of 72.7 ppb or higher (OR, 0.92; 95% CI, 0.68-1.25), same-day, 8-hour ozone levels of 63.3 ppb or higher (OR, 1.17; 95% CI, 0.72-1.92), or previous-day, 8-hour ozone levels of 63.3 ppb or higher (OR, 0.99; 95% CI, 0.74-1.35). The only significant association was an increased likelihood of wheeze (OR, 1.20; 95% CI, 1.00-1.43) in the presence of previous-day, 8-hour average ozone between 39.1 and 45.8 ppb (the second quintile).

Copollutant Models. For the children who were not users of asthma maintenance medication, neither fine particles nor 1-hour average ozone levels were associated with increased likelihoods of respiratory symptoms in copollutant models. Increased bronchodilator use was associated with previous-day fine particle concentrations between 9.0 and 12.0 $\mu g/m^3$ in the model with 1-hour ozone levels (TABLE 6) and with these same levels in the model with 8-hour ozone (OR, 1.30; 95% CI, 1.02-1.65). An increase in the likelihood of wheeze was associated with

Table 5. Odds Ratios From the Copollutant Logistic Regression Model for Same-Day and Previous-Day Levels of Ozone (1-Hour Average) and Particulate Matter of 2.5 µm or Less ($PM_{2.5}$) Related to Each Respiratory Symptom or Rescue Medication Use of Maintenance Medication Users (n = 130) (Southern New England, April 1 to September 30, 2001)*

	Odds Ratio (95% Confidence Interval)				
Pollutant	Wheeze	Persistent Cough	Chest Tightness	Shortness of Breath	Bronchodilator Use
Same-day, 1-hour ozone, ppb					
<43.2	1.00	1.00	1.00	1.00	1.00
43.2-51.5	1.05 (0.90-1.23)	0.88 (0.78-0.99)	1.10 (0.88-1.38)	0.97 (0.75-1.26)	1.00 (0.96-1.05)
51.6-58.8	1.18 (1.00-1.38)	0.99 (0.88-1.11)	1.05 (0.83-1.32)	0.98 (0.79-1.21)	1.04 (0.99-1.08)
58.9-72.6	1.25 (1.05-1.50)	0.95 (0.81-1.12)	1.32 (1.04-1.67)	1.23 (0.95-1.59)	1.02 (0.97-1.03)
≥72.7	1.47 (1.13-1.90)	1.12 (0.89-1.41)	1.83 (1.30-2.57)	1.57 (1.13-2.19)	1.08 (1.01-1.16)
Previous-day 1-hour ozone, ppb					
<43.2	1.00	1.00	1.00	1.00	1.00
43.2-51.5	1.00 (0.86-1.17)	1.04 (0.94-1.14)	1.14 (0.89-1.46)	1.16 (0.93-1.45)	1.03 (0.98-1.07)
51.6-58.8	0.97 (0.85-1.11)	1.07 (0.95-1.21)	1.25 (1.01-1.55)	1.10 (0.89-1.34)	1.02 (0.97-1.06)
58.9-72.6	1.02 (0.88-1.25)	1.07 (0.93-1.24)	1.46 (1.13-1.88)	1.32 (1.04-1.66)	1.03 (0.96-1.10)
≥72.7	1.13 (0.90-1.42)	1.15 (0.99-1.35)	1.53 (1.15-2.05)	1.22 (0.94-1.58)	1.05 (0.97-1.15)
Same-day $PM_{2.5}$, $\mu g/m^3$					
<6.9	1.00	1.00	1.00	1.00	1.00
6.9-8.9	0.89 (0.75-1.29)	0.95 (0.84-1.06)	0.90 (0.74-1.09)	0.95 (0.80-1.12)	1.03 (0.98-1.08)
9.0-12.0	1.02 (0.87-1.19)	0.97 (0.86-1.10)	0.97 (0.79-1.18)	1.00 (0.82-1.21)	1.01 (0.96-1.07)
12.1-18.9	0.94 (0.77-1.15)	0.97 (0.84-1.11)	0.97 (0.76-1.25)	0.90 (0.73-1.12)	1.02 (0.95-1.08)
≥19.0	0.83 (0.65-1.06)	0.89 (0.74-1.07)	0.76 (0.54-1.05)	0.87 (0.65-1.17)	0.99 (0.91-1.07)
Previous-day $PM_{2.5}$, $\mu g/m^3$					
<6.9	1.00	1.00	1.00	1.00	1.00
6.9-8.9	1.03 (0.89-1.18)	0.99 (0.89-1.11)	0.89 (0.72-1.10)	0.96 (0.78-1.18)	0.99 (0.94-1.04)
9.0-12.0	1.05 (0.88-1.24)	0.98 (0.86-1.10)	0.90 (0.70-1.16)	1.00 (0.81-1.25)	0.97 (0.93-1.02)
12.1-18.9	0.98 (0.82-1.17)	0.95 (0.83-1.10)	0.81 (0.63-1.03)	0.96 (0.74-1.24)	0.96 (0.91-1.02)
≥19.0	1.05 (0.85-1.29)	1.00 (0.88-1.15)	0.91 (0.71-1.17)	1.20 (0.94-1.52)	0.97 (0.89-1.04)
Goodness-of-fit test *P* value	.68†	.01	.30†	.07†	.007

*Separate analyses were performed for each outcome measure. All models include same-day and previous-day levels of ozone and $PM_{2.5}$ controlling for same-day maximum temperature. Logistic regressions were performed using generalized estimating equations and specifying a 1-day lagged autoregressive structure for the correlation matrix. The Hosmer-Lemeshow goodness-of-fit statistic for logistic regression was calculated for each model.
†*P*>.05 indicates that a model is a reasonable fit for the data.

8-hour ozone, but only for concentrations between 39.1 and 45.8 ppb on the same day (OR, 1.33; 95% CI, 1.00-1.77) or the previous day (OR, 1.31; 95% CI, 1.05-1.63) and between 52.1 and 63.2 ppb for same-day levels (OR, 1.35; 95% CI, 1.00-1.81).

COMMENT

In models controlling for ambient fine particle concentration and typically at levels below EPA air quality standards, daily ambient ozone was found to be significantly associated with increased risk of respiratory symptoms and increased use of rescue medication among children with asthma severe enough to require maintenance medication. Study strengths include frequent telephone follow-up to collect information on daily calendar-recorded symptoms and medication use; absence of reporting bias between symptoms and regionally collected ambient air quality data; the use of both the maximum 1-hour average (sensitive to spikes in concentration) and 8-hour average (a measure of short-term, cumulative exposure) to assess daily ambient ozone levels; use of $PM_{2.5}$ levels measured daily; and examination of the simultaneous effects of ozone and $PM_{2.5}$ at levels near or below current EPA ambient standards. Our results contribute to the limited literature examining the simultaneous effects of ozone and suspended particles on daily respiratory symptoms for a sensitive subpopulation in models adjusted for daily temperature.

One potential limitation of the study is that ambient ozone and particle concentrations were represented as means over regional sites. For the 14 ozone sites on any particular day, the mean (SD) ratio of maximum to minimum reading was 1.70 (0.50), which is similar to the mean ratio of upper to lower limit of each quintile of the summer ozone distribution of 1.38 (0.30) from our study. This suggests that the analysis using quintiles of the ozone distribution captures the variability that exists in the study region. Variability among $PM_{2.5}$ sites was less, but a potential limitation is that there were only 4 sites with daily measurements. However, a comparison between readings from these 4 sites and readings from the 10 sites with $PM_{2.5}$ readings every 3 days revealed good agreement. For the 61 days all sites had in common, the 10-site mean (SD) was 13.8 (8.2) compared with 12.8 (7.7) $\mu g/m^3$ for the 4 sites, and the Pearson correlation was 0.97.

Another potential limitation is the lack of personal variables (eg, race) in the regression models. However, by taking advantage of the repeated measurements we had for each subject, we were able

Table 6. Odds Ratios From the Copollutant Logistic Regression Model for Same-Day and Previous-Day Levels of Ozone (1-Hour Average) and Particulate Matter of 2.5 µm or Less ($PM_{2.5}$) Related to Respiratory Symptoms and Rescue Medication Use of Maintenance Medication Nonusers (n = 141) (Southern New England, April 1 to September 30, 2001)*

	Odds Ratio (95% Confidence Interval)				
Pollutant	Wheeze	Persistent Cough	Chest Tightness	Shortness of Breath	Bronchodilator Use
Same-day 1-hour ozone, ppb					
<39.1	1.00	1.00	1.00	1.00	1.00
39.1-45.8	1.22 (0.96-1.54)	1.05 (0.95-1.19)	1.37 (0.85-2.23)	1.35 (0.97-1.87)	1.18 (1.00-1.40)
45.9-52.0	1.22 (0.94-1.59)	1.06 (0.90-1.25)	1.42 (0.80-2.55)	1.36 (0.93-2.00)	1.18 (0.97-1.44)
52.1-63.2	1.15 (0.86-1.56)	1.02 (0.86-1.22)	1.58 (0.88-2.84)	1.24 (0.84-1.84)	1.19 (0.95-1.49)
≥63.3	0.92 (0.64-1.33)	0.98 (0.78-1.23)	1.83 (0.80-4.23)	1.25 (0.70-2.24)	0.98 (0.76-1.27)
Previous-day 1-hour ozone, ppb					
<39.1	1.00	1.00	1.00	1.00	1.00
39.1-45.8	1.21 (0.95-1.52)	1.08 (0.96-1.22)	1.06 (0.73-1.52)	1.15 (0.87-1.53)	1.00 (0.81-1.22)
45.9-52.0	1.05 (0.84-1.31)	0.97 (0.83-1.12)	0.80 (0.46-1.38)	1.14 (0.81-1.60)	0.91 (0.73-1.15)
52.1-63.2	1.02 (0.79-1.32)	1.04 (0.90-1.20)	0.72 (0.40-1.31)	1.21 (0.80-1.83)	0.99 (0.81-1.20)
≥63.3	1.00 (0.69-1.45)	0.94 (0.77-1.14)	0.79 (0.39-1.57)	0.66 (0.43-1.00)	0.83 (0.63-1.10)
Same-day $PM_{2.5}$, $\mu g/m^3$					
<6.9	1.00	1.00	1.00	1.00	1.00
6.9-8.9	0.92 (0.72-1.17)	0.96 (0.83-1.12)	0.84 (0.54-1.31)	0.61 (0.39-0.95)	0.95 (0.78-1.15)
9.0-12.0	1.08 (0.85-1.36)	1.02 (0.89-1.18)	1.09 (0.74-1.61)	1.13 (0.85-1.50)	0.95 (0.78-1.16)
12.1-18.9	0.94 (0.73-1.22)	0.93 (0.78-1.12)	0.78 (0.47-1.30)	0.72 (0.42-1.23)	0.85 (0.69-1.06)
≥19.0	1.15 (0.75-1.75)	1.07 (0.85-1.34)	0.71 (0.36-1.39)	1.17 (0.72-1.90)	0.99 (0.76-1.30)
Previous day $PM_{2.5}$, $\mu g/m^3$					
<6.9	1.00	1.00	1.00	1.00	1.00
6.9-8.9	1.01 (0.78-1.31)	1.07 (0.94-1.22)	1.44 (0.90-2.30)	0.99 (0.75-1.30)	1.05 (0.85-1.34)
9.0-12.0	1.15 (0.88-1.51)	1.13 (0.97-1.32)	1.50 (0.97-2.33)	1.30 (0.88-1.91)	1.28 (1.01-1.62)
12.1-18.9	1.08 (0.78-1.51)	1.03 (0.87-1.22)	1.56 (0.91-2.66)	0.84 (0.57-1.24)	1.05 (0.80-1.37)
≥19.0	1.18 (0.71-1.97)	1.14 (0.88-1.46)	1.76 (0.83-3.73)	1.48 (0.94-2.34)	1.19 (0.83-1.71)
Goodness-of-fit test *P* value	.69†	.003	.08†	.36†	<.001

*Separate analyses were performed for each outcome measure. All models include same-day and previous-day levels of ozone and $PM_{2.5}$ controlling for same-day maximum temperature. Logistic regressions were performed using generalized estimating equations and specifying a 1-day lagged autoregressive structure for the correlation matrix.The Hosmer-Lemeshow goodness-of-fit statistic for logistic regression was calculated for each model.
†*P*>.05 indicates that a model is a reasonable fit for the data.

to use each subject as his or her own control. The sample of 271 children contributed 36 195 person-days of observations to the analyses. Our within-subjects analytic approach permitted a strong test of the associations between ambient air pollution and health outcomes, and personal variables, since they would not vary within subjects, could be excluded from the models.

In this study, we did not consider medical care utilization as an outcome. Since this was not a clinic-based study, we did not have access to records to confirm medical visit dates. However, medical records are not necessarily more objective than reports of symptoms and medication use, since a number of factors unrelated to symptom severity also influence utilization. Symptoms and medication use vary from day to day and may be a more sensitive indicator of the effects of daily changes in air pollution on respiratory health, since not all symptoms result in a physician visit.

In our copollutant models, ozone but not fine particles significantly predicted increased risk of respiratory symptoms and rescue medication use among children using asthma maintenance medication. We found an immediate (same-day) effect of ozone on wheeze (with the 1-hour ozone metric), chest tightness, and shortness of breath (with both the 1-hour and 8-hour ozone metrics). We also found that previous-day levels of ozone (both metrics) were significantly associated with increased risk of chest tightness and shortness of breath. Goodness-of-fit tests for copollutant models suggest that the models with significant findings (wheeze, chest tightness, and shortness of breath) are reasonably good fits to the data. There were no systematic patterns to the lack of fit for models for persistent cough and bronchodilator use. However, because of repeated measurements, observations were not independent in any of the models, which may affect the interpretation of the Hosmer-Lemeshow statistic. It is possible that the more frequently reported events of persistent cough and bronchodilator use may be associated with ambient air pollution in combination with other factors (eg, activity level) not included in the current study.

Effects of 1-hour ozone among children using asthma maintenance medication, especially the association of same-day ozone with wheeze and previous-day ozone with chest tightness, appear to be more exposure dependent than the effects of small particles. In copollutant models for wheeze and chest tightness, a 50-ppb increase in same-day, 1-hour ozone level increased the likelihood of wheeze by 35% and chest tightness by 47%. However, since particles and ozone were positively correlated, it is difficult to separate their effects in the copollutant models. In the single-pollutant model for chest tightness, a 50-ppb increase in previous-day levels of 1-hour ozone resulted in a 26% increase in the likelihood of having the symptom. When same-day levels of 1-hour ozone were added to the model, the likelihood of this symptom went up to 32%. In the copollutant model, a 50-ppb increase in previous-day, 1-hour ozone level increased the likelihood of chest tightness by 42%. Levels of $PM_{2.5}$ happened to be relatively low and never exceeded EPA standards for the duration of the study period, which likely contributed to the lack of significant particle effects observed in the copollutant models. For our region, an examination of the association between symptoms and particle levels in winter months when ozone is not a factor would help us better understand the role of exposure to small particles on respiratory health.

There is little doubt that children with asthma are especially vulnerable to high levels of air pollution. Among a group of asthmatic children (n=71) living in Mexico City, where levels of ozone have regularly exceeded the EPA standard, multivariate regression analyses of same-day ambient air pollution and separate models of previous-day pollution all revealed significant effects of ozone and fine particles on the likelihood of cough (an increase of 8% for each 50-ppb increase in ozone on either the same day or previous day; an increase of 6% or 8% for each 10-μg/m^3 increase in $PM_{2.5}$ on the same day or previous day) and lower respiratory tract illness (by 7% for each pollutant on the same day or previous day).[2] The effects seen for $PM_{2.5}$ in Mexico City, but not in our study, could be explained by the large difference between the mean (SD) 24-hour concentration of $PM_{2.5}$ in Mexico City (85.7 [30.2] μg/m^3), which was above the EPA standard of 65 μg/m^3 and was well above the mean of 13.1 (7.9) μg/m^3 observed in the current study. In addition, the chemical composition of the fine particles in each region may be different.[2,10] The larger effect of 1-hour ozone that we found could be explained in part by the fact that we stratified our analysis by asthma severity, thereby observing a consistent pattern of increased likelihood of some symptoms of more than 40% in the group with more severe disease and no significant effects among the group with less severe disease.

Our results are consistent with recent studies[7,10] that suggest exposure to lower levels of ozone is associated with respiratory symptoms in children with asthma. Children with asthma who attended a week-long asthma summer camp (a total of 166 children during three 1-week periods compared with our 183-day observation period) in the Connecticut River Valley (the same geographic area as the current study) were exposed to levels of ozone somewhat higher than the current study (mean [SD] 1-hour average, 84 [38] ppb; range, 20-160 ppb). In single-pollutant models, daily levels of same-day ozone were significantly associated with increased chest symptoms, β-agonist use, and decreased lung function.[10] These associations did not change when same-day levels of sulfate (a primary constituent of $PM_{2.5}$ in this region) were added to the model. In a recent study[7] of 846 children with asthma living in 8 urban areas around the country, ozone at levels comparable to those observed in the current study (mean 8-hour average of 48 ppb compared with our mean of 51 ppb with <5% of the days exceeding the EPA standard of 80 ppb in both studies) was associated, in single-pollutant models, with morning respiratory symptoms (wheeze, cough, or chest tightness). Al-

though the data were not shown, the authors of each study also noted that adding copollutants to their models did not appreciably confound the effect of ozone. Both studies concluded that ozone, even at levels lower than current EPA standards, is strongly associated with adverse respiratory health effects in children with asthma.

Previous environmental chamber studies[19-21] of adults with asthma exposed to ozone for 1 to a few hours have shown relatively little effect on symptoms or lung function. On the other hand, short-term exposure to elevated levels of ozone and particulates in outdoor air has been associated with reduced pulmonary function in otherwise healthy children.[1,22,23] Our study of asthmatic children under ambient exposure conditions in areas of lower pollution suggests that the more prolonged exposures associated with summertime ozone produce a greater stimulus than chamber exposures, that asthmatic children are more susceptible than asthmatic adults, that effects are delayed and not captured by short-term chamber studies, or that coexposures to other unidentified constituents of ambient air enhance the response to ozone. A recent study supporting this view examined the impact of traffic-reducing changes in Atlanta, Ga, during the 1996 summer Olympic Games.[24] Significant reductions in ozone and particles were associated with significant reductions in acute asthma care events (physician, clinic, or hospital visits) among children aged 1 to 16 years. In analyses including days before, during, and after the Olympics, an increase in daily acute asthma events was associated with levels of 1-hour ozone concentrations beginning at 60 to 89 ppb. Our findings indicate that comparable levels were associated with an increased likelihood of wheeze (≥58.9 ppb), chest tightness (≥58.9 ppb), shortness of breath, and rescue medication use (≥72.7 ppb).

In our study, we defined 2 levels of asthma severity based on maintenance medication use. We reasoned that since we were examining the association of air pollution and symptoms, we did not want to use symptoms to define severity. Instead, we used maintenance medication as a proxy for disease severity even though medication use and symptoms will be related. Maintenance medication users had significantly more wheeze, persistent cough, chest tightness, and shortness of breath than the nonusers and used rescue medication significantly more often. Our results strongly suggest that this definition of asthma severity divides the group into 2 levels of vulnerability to air pollution.

Our study is a unique combination of a sample of asthmatic children with detailed symptom and medication use followed for a long period and well-measured daily ambient copollutants. These results add to others that suggest that, even at low levels of ambient ozone and controlling for ambient fine particle concentration, children with severe asthma are at a significantly increased risk of experiencing respiratory symptoms.

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Analysis and interpretation of data: Gent, Triche, Holford, Belanger, Bracken, Leaderer.
Drafting of the manuscript: Gent, Bracken, Leaderer.
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Study supervision: Bracken, Leaderer.
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REFERENCES

1. Gold DR, Damokosh AI, Pope CA III, et al. Particulate and ozone pollutant effects on the respiratory function of children in southwest Mexico City. *Epidemiology.* 1999;10:8-16.
2. Romieu I, Meneses F, Ruiz S, et al. Effects of air pollution on the respiratory health of asthmatic children living in Mexico City. *Am J Respir Crit Care Med.* 1996;154:300-307.
3. Romieu I, Meneses F, Ruiz S, et al. Effects of intermittent ozone exposure on peak expiratory flow and respiratory symptoms among asthmatic children in Mexico City. *Arch Environ Health.* 1997;52:368-376.
4. Peters A, Dockery DW, Heinrich J, Wichmann HE. Medication use modifies the health effects of particulate sulfate air pollution in children with asthma. *Environ Health Perspect.* 1997;105:430-435.
5. Ostro BD, Lipsett MJ, Mann JK, Braxton-Owens H, White MC. Air pollution and asthma exacerbations among African-American children in Los Angeles. *Inhal Toxicol.* 1995;7:711-722.
6. Ostro B, Lipsett M, Mann J, Braxton-Owens H, White M. Air pollution and exacerbation of asthma in African-American children in Los Angeles. *Epidemiology.* 2001;12:200-208.
7. Mortimer KM, Tager IB, Dockery DW, Neas LM, Redline S. The effect of ozone on inner-city children with asthma: identification of susceptible subgroups. *Am J Respir Crit Care Med.* 2000;162:1838-1845.
8. Delfino RJ, Zeiger RS, Seltzer JM, Street DH. Symptoms in pediatric asthmatics and air pollution: differences in effects by symptom severity, anti-inflammatory medication use and particulate averaging time. *Environ Health Perspect.* 1998;106:751-761.
9. Gielen MH, van der Zee SC, van Wijnen JH, van Steen CJ. Acute effects of summer air pollution on respiratory health of asthmatic children. *Am J Respir Crit Care Med.* 1997;155:2105-2108.
10. Thurston GD, Lippmann M, Scott MB, Fine JM. Summertime haze air pollution and children with asthma. *Am J Respir Crit Care Med.* 1997;155:654-660.
11. Gent JF, Ren P, Belanger K, et al. Levels of household mold associated with respiratory symptoms in the first year of life in a cohort at risk for asthma. *Environ Health Perspect.* 2002;110:A781-A786.
12. Belanger K, Beckett W, Triche E, et al. Symptoms of wheeze and persistent cough in the first year of life: associations with indoor allergens, air contaminants, and maternal history of asthma. *Am J Epidemiol.* 2003;158:195-202.
13. US Environmental Protection Agency. *Air Quality Criteria for Ozone and Related Photochemical Oxidants.* Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; 1996. EPA report EPA/600/AP-93/004a-c.
14. State of Connecticut Department of Environmental Protection. Annual Air Quality Summary (1999). Available at: http://dep.state.ct.us/air2/ozone/99aqs.pdf. Accessed November 18, 2002.
15. Commonwealth of Massachusetts Department of Environmental Protection. Air Quality Report (2000). Available at: http://www.mass.gov/dep/bwp/daqc. Accessed November 18, 2002.
16. SAS Version 8. Cary, NC: SAS Institute Inc; 2001.
17. Liang K-Y, Zeger SL. Longitudinal data analysis using generalized linear models. *Biometrika.* 1986;73:13-22.
18. Allison PD. *Logistic Regression Using the SAS System: Theory and Application*. Cary, NC: SAS Institute Inc; 1999.
19. Silverman F. Asthma and respiratory irritants (ozone). *Environ Health Perspect.* 1979;29:131-136.
20. Hanania NA, Tarlo SM, Silverman F, Urch B, Senathirajah N, Zamel N, Corey P. Effect of exposure to low levels of ozone on the response to inhaled allergen in allergic asthmatic patients. *Chest.* 1998;114:752-756.
21. Kehrl HR, Peden DB, Ball B, Folinsbee LJ, Horstman D. Increased specific airway reactivity of persons with mild allergic asthma after 7.6 hours of exposure to 0.16 ppm ozone. *J Allergy Clin Immunol.* 1999;104:1198-1199.
22. Spektor DM, Lippmann M, Lioy PJ, et al. Effects of ambient ozone on respiratory function in active normal children. *Am Rev Respir Dis.* 1988;137:313-320.
23. Ulmer C, Kopp M, Ihorst G, Frischer T, Forster J, Kuehr J. Effects of ambient ozone exposures during the spring and summer of 1994 on pulmonary function of schoolchildren. *Pediatr Pulmonol.* 1997;23:344-353.
24. Friedman MS, Powell KE, Hutwagner L, Graham LM, Teague WG. Impact of changes in transportation and commuting behaviors during the 1996 summer Olympic Games in Atlanta on air quality and childhood asthma. *JAMA.* 2001;285:897-905.