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Authors
Delfino, Ralph J
Zeiger, Robert S
Seltzer, James M
et al.

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Association of Asthma Symptoms with Peak Particulate Air Pollution and Effect Modification by Anti-inflammatory Medication Use

Ralph J. Delfino,[1] Robert S. Zeiger,[2,3] James M. Seltzer,[2,4] Donald H. Street,[5] and Christine E. McLaren[1]

[1]Epidemiology Division, Department of Medicine, University of California, Irvine, Irvine, California, USA; [2]Department of Pediatrics, University of California, San Diego, School of Medicine, La Jolla, California, USA; [3]Department of Allergy, Southern California Permanente Medical Group, San Diego, California, USA; [4]Indoor Hygienic Technologies Corporation, Rancho Santa Fe, California, USA; [5]Hollistier-Stier Laboratories LLC, Allergy Products, Independence, Oregon, USA

Maxima of hourly data from outdoor monitors may capture adverse effects of outdoor particulate matter (PM) exposures in asthmatic children better than do 24-hr PM averages, which form the basis of current regulations in the United States. Also, asthmatic children on anti-inflammatory medications may be protected against the proinflammatory effects of air pollutants and aeroallergens. We examined strengths of pollutant associations with asthma symptoms between subgroups of asthmatic children who were on versus not on regularly scheduled anti-inflammatory medications, and tested associations for different particle averaging times. This is a daily panel study of 22 asthmatic children (9–19 years of age) followed March through April 1996 (1,248 person-days). They lived in nonsmoking households in a semirural area of Southern California within the air inversion mixing zone (range, 1,200–2,100 feet) with transported air pollution from urban areas of Southern California. The dependent variable derived from diary ordinal scores is episodes of asthma symptoms that interfered with daily activities. Minimum to 90th-percentile levels of exposures at the outdoor monitoring site were 12–63 μg/m^3 for 1-hr PM < 10 μm in aerodynamic diameter (PM_{10}); 8–46 μg/m^3 for 8-hr PM_{10}; 7–32 μg/m^3 for 24-hr PM_{10}; 45–88 ppb for 1-hr O_3; 6–26 ppb for 8-hr NO_2; 70–4,714 particles/m^3 for 12-hr daytime fungi; and 12–744 particles/m^3 for 24-hr pollen. Data were analyzed with generalized estimating equations controlling for autocorrelation. There was no confounding by weather, day of week, or linear time trend. Associations were notably stronger in 12 asthmatic children who were not taking anti-inflammatory medications versus 10 subjects who were. Odds ratios (95% confidence intervals) for asthma episodes in relation to lag 0 minimum to 90th-percentile pollutant changes were, respectively, 1-hr maximum PM_{10}, 1.92 (1.22–3.02) versus 0.96 (0.25–3.69); 8-hr maximum PM_{10}, 1.68 (0.91–3.09) versus 0.75 (0.18–3.04); 24-hr average PM_{10}, 1.35 (0.82–2.22) versus 0.80 (0.24–2.69); 1-hr maximum O_3, 1.28 (0.75–2.17) versus 0.76 (0.24–2.44); 8-hr maximum NO_2, 1.91 (1.07–3.39) versus 1.08 (0.30–3.93); 12-hr fungi, 1.89 (1.24–2.89) versus 0.90 (0.35–2.30); 24-hr pollen, 1.90 (0.99–3.67) versus 0.85 (0.18–3.91). Pollutant associations were stronger during respiratory infections in subjects not on anti-inflammatory medications. Although lag 0 1-hr maximum PM_{10} showed the strongest association, the most robust associations were for lag 0 and 3-day moving averages (lags 0–2) of 8-hr maximum and 24-hr mean PM_{10} in sensitivity analyses testing for thresholds. Most pollutant effects were largely driven by concentrations in the upper quintile. The divergence of exposure–response relationships by anti-inflammatory medication use is consistent with experimental data on inflammatory mechanisms of airborne pollutants and allergens. *Key words:* **asthma, epidemiology, longitudinal data analysis, ozone, panel study, particulate air pollution.** *Environ Health Perspect* **110:A607–A617 (2002). [Online 13 September 2002]** *http://ehpnet1.niehs.nih.gov/docs/2002/110pA607-A617delfino/abstract.html*

Experimental studies in animals and humans have shown that exposures to particulate air pollutants on a time scale of minutes to several hours can cause adverse respiratory effects. However, there is no direct experimental evaluation of differences in biologic responses to particulate air pollution (particulate matter; PM) from time-varying exposures (with peaks) versus time-invariant exposures controlling for cumulative exposure. Biologic responses may intensify with high peaks in concentrations of pollutants that overwhelm certain lung defense mechanisms. In epidemiologic research, daily peak particle concentrations measured at central outdoor sites may also serve as a better indicator for personal outdoor exposures during the daytime compared with daylong averages. Most epidemiologic studies have relied on particle averaging times of 24 hr. There are few epidemiologic studies examining respiratory effects from peak particle exposures (*1,2*). The present epidemiologic study examined effects of maximum hourly concentrations of outdoor particulate matter < 10 μm in aerodynamic diameter (PM_{10}) on asthma symptoms in children to assess the utility of peak versus daily average exposure data.

Based on our previous findings (*1*), we hypothesized that peak hourly exposures to PM of outdoor origin will be more closely associated with acute asthmatic symptoms in some susceptible children than will 24-hr average exposures. We further hypothesize that the proinflammatory effects of air pollutants will likely vary across individual asthmatic children, with greater responses in those with more severe disease. The severity of asthma depends largely on the magnitude of underlying pulmonary inflammation (*3*). Therefore, subjects taking anti-inflammatory medications may be protected against proinflammatory effects of airborne agents and may show smaller responses to air pollutants, including O_3, nitrogen dioxide (NO_2), and some particle components. Experimental evidence in asthmatic patients identifies the proinflammatory effects of O_3 as a major mechanism for adverse effects of O_3 (*4,5*), and emerging experimental evidence for particulate air pollution is beginning to characterize the proinflammatory nature of causal components [e.g., (*6*)].

In the present article, we again examine the relationships of daily asthma symptom severity to 1-hr maximum, 8-hr maximum, and 24-hr mean PM_{10} measured March through April 1996 in Alpine, California. This panel study included 22 children with asthma (9–19 years old) living in nonsmoking households (1,248 person-days). Strengths of association are compared between the different particle averaging times. In addition, strengths of association for the relationship of asthma symptom severity to air pollutants and aeroallergens are compared between subgroups of asthmatic children divided into

Address correspondence to R.J. Delfino, Epidemiology Division, Department of Medicine, College of Medicine, 224 Irvine Hall, University of California, Irvine, Irvine, CA 92697-7550 USA. Telephone: (949) 824-1767. Fax: (949) 824-1343. E-mail: rdelfino@uci.edu

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a) those who were taking regularly scheduled anti-inflammatory medications during the panel follow-up period and *b*) those who did not take anti-inflammatory medications. This study was conducted in the same region as the above-cited study (*1*), a semirural area of southern California around the small town of Alpine that lies within the air inversion mixing zone (town elevation, 1,800 ft; range, 1,200–2,100 ft) with transported air pollution from urban areas of southern California. The "early spring season" of March through April was chosen because it is the peak pollen period in southern California. This time period differs from those of our previous studies, when low pollen concentrations were found and no pollen effects were seen (*1,7,8*). This provided us the opportunity to examine differences in response to pollen by subject medication use and to test putative interactions between O_3 and pollen in relation to asthma outcomes (*9,10*).

Methods

Design. The present design is a panel study, which involves repeated measurements of outcomes and exposures in individuals. The repeated measurements make it possible to establish, with some detail, the temporality of causal associations and to examine acute exposure–response relationships at the level of an individual subject. Subjects can act as their own control over time, analogous to a clinical crossover trial. Panel designs with a large number of repeated measures can be an efficient way to maximize information derived from a small number of subjects. Power and precision can be enhanced because the repeated measures reduce the variability of the response variable compared with strictly between-subject comparisons, without reducing the magnitude of the true exposure–response relationships (*11*).

Population. The institutional review boards of the University of California, Irvine, San Diego State University, and Kaiser Permanente approved the study protocol. Informed written consent was obtained from all subjects and one of their legal guardians. Recruitment of subjects was done with the assistance of the Alpine School District nurse (four grade schools), with referrals from the Kaiser Permanente Health Plan, Inc., San Diego Area, Department of Allergy, and with newspaper advertisements. Monetary incentives were an essential component of both recruiting and retaining subjects. Subjects were not blinded to the study but were simply told that it involved the examination of environmental agents, including outdoor allergens. Eligibility criteria were as follows: *a*) physician-diagnosed asthma with ≥ 1-year history, including episodic symptoms of wheezing, cough, and dyspnea; *b*) a history of at least several weeks during the warm seasons (March–October) when the subject required the use of prescribed asthma medications for asthma exacerbations apart from respiratory infections; *c*) age from 9 to 18 years; *d*) home and school addresses in the Alpine or adjacent areas; and *e*) no history of smoking by the subject and no person smoking in the subject's home. One participant was recruited at age 18 but turned 19 at the panel follow-up.

Twenty-five asthmatic children agreed to participate, 16 boys and 9 girls. A 10-year-old boy and a 17-year-old girl dropped out after the second week of study and are not retained for analysis. Remaining subjects were 18 white non-Hispanic Americans, 3 Hispanic Americans, and 2 Asian Americans. One white 10-year-old male was asymptomatic throughout the panel period and therefore contributed no information to the repeated-measures analysis. This subject is not included in the following analyses involving 22 subjects. Subjects lived an average of 1.9 miles (SD, 0.22) from the central site, ranging from 0.6 to 2.9 miles, except one subject at 5.45 miles. The panel period was 1 March through 30 April 1996 (61 days). Subjects were followed up weekly during the first 2–3 weeks, then biweekly at their home to check the accuracy of diaries and compliance with the study protocol and to ask questions of subjects and resolve problems. Two subjects started in the second week of March, and all volunteers completed the full follow-up through March and April 1996. Missing symptom score data occurred on 51 person-days (3.8% of total expected follow-up of 1,328 person-days) because subjects had left the study area all day, and on 29 person-days because of noncompliance with diary completion (2.2%), leaving 1,248 person-days of observation.

Classification of allergy among subjects was based on the presence or absence of positive allergen reactivity as assessed using epicutaneous skin prick tests (SPTs) for house dust mites, cat, and various pollens and molds common to the study area (*12*). Positive SPT reactivity was defined as a wheal 3 mm greater than the saline control or having a diameter ≥ 50% of a histamine dihydrochloride control. The SPTs for locally relevant pollens consisted of standardized allergen extracts of nine trees, Bermuda grass, a grass mix without Bermuda grass, and two weed mixes. There were 13 SPTs for fungal spore taxa.

Asthma diary. At the end of each day, subjects recorded medication use, presence of respiratory infection or allergic rhinitis symptoms (hay fever), and the maximum level of asthma symptom severity since the last entry on the previous evening. Asthma symptoms served as the main outcome variable in this article. Our diary questions concerning asthma symptoms focused on the impact of the clinical severity of asthma on a subject's normal daily activities. Subjects received training in interpreting the scoring system so that it was meaningful in relation to their activities and asthma. This is important because of interindividual differences in the types and characteristics of symptoms recognized or experienced by asthmatic patients. The approach used combines the rating of various symptoms into one score that is relevant to the impact of asthma on a subject's daily well-being. Asthma symptoms (cough,

Table 1. Descriptive statistics for 22 asthmatic subjects, 1 March through 30 April 1996, Alpine, California.

Subject characteristic	On anti-inflammatory medication: Yes (*n* = 10)	On anti-inflammatory medication: No (*n* = 12)
Median age (age range, years)	12.5 (9–17)	15.0 (11–19)
No. males/females	6/4	8/4
No. allergic to fungi or pollen	8	9
No. days at symptom score (%)		
0: No asthma symptoms present	282 (49.4)	241 (35.6)
1: Asthma symptoms present but caused no discomfort	160 (28.1)	149 (22.0)
2: Asthma symptoms caused discomfort but did not interfere with daily activities or sleep	42 (7.4)	178 (26.2)
3: Asthma symptoms interfered somewhat with daily activities or sleep	74 (13.0)	105 (15.5)
4: Asthma symptoms interfered with most activities (may have stayed home in bed, returned home early from school, or called a doctor or nurse for advice)	11 (1.9)	5 (0.7)
5: Asthma symptoms required going to a hospital, emergency department, or outpatient clinic	1 (0.2)	0 (0)
Missing days (subject range)	40 (0–12)	40 (0–16)
Average symptom score (range)	0.90 (0.05–3.1)	1.24 (0.15–2.4)
No. asthma episodes[a]/person-days (%)	86/570 (15)	110/678 (16)
No. subjects with mild persistent or more severe asthma (%)[b]	2 (20.0)	6 (50.0)
No. subjects with any respiratory infections (%)	5 (50)	6 (50)
No. days with any respiratory infections (%)/subject range	24 (4.2)/0–10	46 (6.8)/0–18
Mean daily as-needed β-agonist inhaler puffs (SD)	1.47 (2.34)	1.01 (1.57)

[a]Defined as having asthma symptoms that interfered with daily activities (symptom score > 2). [b]Defined as daily diary reports of bothersome symptoms or worse more than twice a week throughout the study (*16*), irrespective of asthma medication regimen.

wheeze, sputum production, shortness of breath, and chest tightness) were rated by the subjects according to their global severity on a scale from 0 to 5. Our classification, which we developed for use in previous studies (*1,7,8*), supplants the usual asthma panel study approach of dichotomizing each individual symptom into present or absent. Subjects classified their asthma symptom severity across six levels, as described in Table 1 (see "Results"). For the purposes of this article, we will say "on versus not on anti-inflammatory medications" when comparing those who were taking regularly scheduled anti-inflammatory medications with those who did not take anti-inflammatory medications. Rather than using prescribed medications at baseline, the grouping was ascertained by examining regular daily or near-daily medication use, which subjects entered into their diaries by medication name. Subjects and parents were assisted in labeling medication entry lines, and any changes were evaluated during follow-up home visits. Twelve subjects who were classified as not using anti-inflammatory medications reported no use during the panel follow-up period. For 10 subjects on regularly scheduled preventive medications, four used inhaled cromolyn or nedocromil sodium, and six used inhaled corticosteroids.

Subjects also entered yes or no regarding whether they had a respiratory infection that day. Diary instructions below the question stated: "Were any of the following conditions present today: a cold, sore throat, fever, doctor-diagnosed flu, doctor-diagnosed respiratory infection (pneumonia, bronchitis, croup, pharyngitis, laryngitis, tracheitis, middle ear infection, upper respiratory tract infection, or sinus infection)?" This question was distinguished from a preceding question on allergy symptoms that asked the yes or no question "Did you have symptoms of hay fever today, which were not due to a cold or flu?" Instructions clarifying the hay fever question stated: "Those symptoms should include more than one of the following: sneezing, runny nose (including postnasal drip), sinus or nasal congestion, itchy and watery eyes, itchy throat."

Environmental variables. The PM_{10} concentrations were measured with a tapered-element oscillating microbalance (TEOM), at a stationary outdoor monitoring station located centrally in Alpine and operated by the San Diego Air Pollution Control District (SDAPCD). The TEOM is an inertial instrument that measures particle mass in real time on an exchangeable filter cartridge by monitoring frequency changes of a tapered element (*13*). The PM_{10} data were used as 1-hr averaged data, similar to O_3 monitoring, but in contrast to the standard 24-hr PM_{10} collected on filters and weighed on a scale. The U.S. Environmental Protection Agency has certified the TEOM for measuring PM_{10} concentration. The TEOM sampler inlet was operated at 16.7 L/min, and the inlet air stream was heated to a constant 50°C to keep water in the vapor phase. We did not collect samples for daily gravimetric mass, particle composition, or size fractions. Sampling, analysis, and data-processing protocols for PM_{10} were carried out as part of another ongoing project at the University of Southern California (*14*). Five days of TEOM data were missing because of equipment malfunction. At the same central site, outdoor O_3 was monitored continuously using ultraviolet photometry, and outdoor NO_2 was monitored continuously using chemiluminescence. Hourly temperature, relative humidity, and wind speed and direction were also measured there.

Measurements of aeroallergens were made using the Burkard 7-day recording volumetric pollen and fungal spore collector with a sample flow rate of 10 L/min (Burkard Manufacturing Co. Ltd., Rickmansworth, Hertfordshire, England). Placement of the pollen and fungal spore sampler at the SDAPCD site ensured no nearby upwind obstructions and was 4 m above the ground. To prepare the sampler for pollen and fungal spore collection, Melenex tape was placed on the mounted drum of the sampler and coated with silicone solution evenly applied with an artist's brush. After 7 days of continuous sample collection, the tape was cut and mounted onto microscope slides as 14 12-hr segments from 0900 hr to 2100 hr for daytime counts and 2100 hr to 0900 hr for nighttime counts. The various fungal spores and pollen grains were then counted and identified by using a compound microscope at 500× and 1,000×. The pollen and fungal spore counts were then converted into particles per cubic meter of air for each 12-hr time period. One day of data was lost because of slide damage. Two analytic variables were the total fungal spore and total pollen concentrations, which were the sum of the daily concentrations of all identified and unidentified types of each of these two allergen groups. The airborne exposure variables in regression models were outdoor ambient measurements of 1-hr and 8-hr maximum and 24-hr mean PM_{10}, 1-hr and 8-hr maximum O_3 and NO_2, and 12-hr daytime mean and 24-hr daily mean total fungal spore and total pollen concentrations.

Statistical analysis. We used descriptive statistics on individual subjects to summarize the severity of asthma symptoms over time. We examined temporal trends for daily and hourly pollutant concentrations and constructed exposure correlation matrices for pollutant and weather variables to assess the potential for confounding or multicollinearity in regression analyses.

We used the asthma symptom score to create a dichotomous response variable representing the occurrence of clinically meaningful asthma episodes: "no episode," no asthma symptoms, symptoms not bothersome or not interfering with daily activities (score < 3); versus "episode," symptoms that interfered somewhat with daily activities or worse (score ≥ 3).

A cut point between a score of 0 and 1 was not informative, probably because symptoms not considered by the subject to be bothersome (score = 1) may not be clinically meaningful. A cutoff point between a score of 1 and 2 was examined in regression models. Regression parameters for this binary variable versus exposures were consistent with but smaller than the episode cutoff point. Therefore, results presented are for the analysis of asthma symptom episodes only.

We performed regression analyses of effects of air pollutants on binary symptom scores using generalized estimating equations (GEEs). The GEE approach can model nonnormal response data that are discrete and correlated (*15*). The present data are correlated because repeated daily measurements over time in each individual constitutes a cluster of dependent observations. The GEE models were tested using the logit link in the SAS (version 8; SAS Institute, Cary, NC) generalized linear model procedure Genmod, which uses a ridge-stabilized Newton-Raphson algorithm to maximize the log-likelihood function for the regression parameters. Deviance statistics for GEE models were used to assess the fit of various models. GEE models for the time-varying predictors (air pollutants) were best fitted with an autoregressive lag 1 working correlation matrix. Serial correlation was thus accounted for to control autocorrelation of residual errors, a potential source of bias. The GEE model for medication group alone, a time-invariant predictor, was best fitted with an exchangeable correlation. We evaluated the potential for confounding by temperature, relative humidity, day-of-week trends, linear time trend across the 61 days, and upper or lower respiratory infection. This was done after testing for interaction with the pollutant or aeroallergen variables. Confounding was defined as at least a 15% change in the parameter estimate. Two-pollutant and pollutant-aeroallergen models were also examined after testing for interaction. Model regression parameters were multiplied by an increase in the pollutant of interest from the minimum to the 90th percentile of its distribution. The magnitude of effect is expressed as the symptom odds ratios (ORs) for this increase to express what may be among the largest effects for the study population.

We first performed regression analyses on all subjects with single pollutants in the model. We then tested for interaction between whether a subject was on versus not on anti-inflammatory medications and each of

the continuous exposure variables. We compared the regression coefficients of subjects on anti-inflammatory medications with those not on anti-inflammatory medications to test the null hypothesis of no difference in regression coefficients between the two groups. To do this analysis, we first made a dummy variable for medication group that is coded 1 for subjects on anti-inflammatory medications and 0 for those not on anti-inflammatory medications. We then used the pollutant variable, medication group, and a product term between pollutant variable and medication group as predictors in the regression equation. We present disaggregated effects for the two subgroups from this model.

The analysis focuses on effects of air pollutant concentrations on the day of symptom reports (lag 0). We also examined effects of air pollution levels on days before the day of the diary symptom report to assess the potential for delayed or cumulative air pollutant health effects. This was accomplished by regressing symptoms on pollution levels measured up to 5 days before the day of symptom reporting (lags 1–5). We then examined moving pollutant averages that combined air pollution levels on current and lag days. The moving average length was chosen after examining the distribution of individual day lag effects. Because pollutants were measured on 5 days before the start of the study, it was possible to test lag effects from the first day of follow-up. However, lags and moving averages for PM_{10} were missing for up to 5 days after the time the TEOM was malfunctioning.

Results

Descriptive statistics. Table 1 shows the characteristics of subjects. We compared the two groups on versus not on anti-inflammatory medications. Subjects on anti-inflammatory medications were somewhat younger than other subjects, and in both groups there were more boys than girls, which is the typical gender distribution in pediatric asthma. Most subjects were allergic to pollens or molds. The overall proportion of days with asthma episodes was similar between the two medication groups (15–16%). Two subjects on anti-inflammatory medications had no episodes, and one subject not on anti-inflammatory medications had no episodes. We also used daily symptom reports to classify a subject's asthma severity in a manner consistent with the National Heart, Lung, and Blood Institute (NHLBI) symptom-based criteria (*16*), irrespective of asthma medication regimen. Subjects with mild persistent or more severe asthma were defined as having daily diary reports of bothersome or more severe symptoms (score > 1) more than twice a week throughout the study. Remaining subjects were considered to have mild intermittent asthma. There were more subjects not taking anti-inflammatory medications who fitted the NHLBI classification of persistent asthma. However, there was no significant difference in GEE models for medication classification predicting either symptom scores > 1 or symptom scores > 2 ($p > 0.16$). An equal proportion of subjects in the two groups reported respiratory infections. There was no significant difference in use of as-needed β-agonist inhalers between anti-inflammatory medication groups (Table 1).

Table 2 describes the exposure concentrations. No days had ozone concentrations > 120 ppb, which is the current U.S. National Ambient Air Quality Standard (NAAQS) (*17*). PM_{10} levels were very low compared with urban areas of southern California. The highest 24-hr mean PM_{10} was less that a fourth of the current NAAQS of 150 μg/m^3 (*17*). As expected, the PM_{10} data show different distributions depending on the averaging time. The highest 24-hr mean PM_{10} measurement was 42 μg/m^3, compared with the mean of 1-hr maximum PM_{10} of 38 μg/m^3. Levels of NO_2 were fairly modest, with the highest 1-hr maximum just reaching the NAAQS for the annual arithmetic mean (53 ppb) (*17*). Looking at the overall average by hour of day, we found the highest PM_{10} hourly exposures were from 1300 to 2000 hr (> 22 μg/m^3). The highest O_3 hourly exposures were from 0100 to 1700 hr (> 50 ppb). These are times when children are most likely to be outdoors and playing. Figure 1 shows time plots of selected pollutant measurements across the days of study.

The exposure correlation matrix is shown in Table 3. Variables were approximately normally distributed, so Pearson correlation coefficients were computed. Because of photochemical oxidation processes, both O_3 and PM_{10} are often jointly higher on hotter and dryer days, which explain the correlations among the pollutant and weather variables. Pollen was also moderately correlated with O_3 and PM_{10} because pollination of many native plants is greatest on hot, dry days. In our region of study, the months of March and April studied represent the period of greatest pollination. Fungal concentrations were significantly but weakly correlated with the pollutants. PM_{10} was moderately correlated with NO_2, showing that upwind combustion sources from urban areas of southern California (largely traffic related) are important.

Regression analysis. **Single-pollutant regression models.** Symptoms were not associated with day of week, linear trend, temperature, or relative humidity, and these variables did not confound exposures. Models testing lag days for aeroallergens, for PM_{10}, and for the gaseous pollutants were not significant in regression models fitted with each exposure alone, including 1–5 days before the day of symptom reports (lags 1–5). The largest and most robust effects were found for exposures on the same day (lag 0) of the subject's asthma symptom report. However, findings in a regression model fitted with a product term for anti-inflammatory medication by exposure showed lag effects for the group not on anti-inflammatory medications. Effects were suggested for PM_{10} at lags 1 and 2 ($p < 0.1$), with robust associations for the 3-day moving average of PM_{10} lags 0–2. Therefore, for simplicity, models are presented for lag 0 and the 3-day moving average of PM_{10} for each of the daily averaging times (maximum 1-hr, maximum 8-hr, and 24-hr mean). Lag 0 effects of 12-hr daytime total fungi were slightly greater than 24-hr average total fungi, whereas effects of 24-hr total pollen were slightly greater than 12-hr daytime total pollen. Therefore, for simplicity, models are presented for 12-hr total fungi and 24-hr total pollen.

There was no association between symptoms and medication group in a GEE model

Table 2. Daily air pollution and weather measurements, 1 March through 30 April 1996, Alpine, California.[a]

Exposure and averaging time	No. observations	Mean (SD)	Min/max	90th percentile
PM_{10} 1-hr max (μg/m^3)[b]	56	38 (15)	12/69	63
PM_{10} 8-hr max (μg/m^3)	56	28 (12)	8/57	46
PM_{10} 24-hr mean (μg/m^3)	56	20 (9)	7/42	32
O_3 1-hr max (ppb)	61	69 (16)	45/108	88
O_3 8-hr max (ppb)	61	60 (12)	39/97	75
NO_2 1-hr max (ppb)	61	24 (10)	8/53	42
NO_2 8-hr max (ppb)	61	15 (7)	6/34	26
Fungi 12-hr daytime mean (particles/m^3)[c]	60	3,132 (1,647)	70/8,147	4,714
Fungi 24-hr mean (particles/m^3)	60	2,973 (1,542)	757/7,975	5,380
Pollen 12-hr daytime mean (particles/m^3)	60	427 (314)	17/1,310	875
Pollen 24-hr mean (particles/m^3)	60	345 (292)	12/1,257	744
Temperature 1-hr max (°F)	61	71 (10)	50/91	85
Relative humidity 24-hr mean (%)	61	59 (24)	12/97	86

Abbreviations: max, maximum; min, minimum.
[a]Measurements were taken at the stationary outdoor monitoring site of the SDAPCD. [b]Five days are missing because of TEOM equipment malfunction. [c]12-hr levels for fungi and pollen are for the sampling period of 0900 to 2100 hr; 24-hr levels for fungi and pollen are from 2100 hr of the previous day to 2100 hr of the current day. One day is missing because of slide damage.

that included only a medication indicator variable: OR = 1.06; 95% confidence interval (CI) = 0.25–4.43. However, we found significant interactions between exposures (air pollutants or aeroallergens) and classification of subjects by regular use versus nonuse of anti-inflammatory medications. Therefore, we present GEE models without the product term of medication group by pollutant concentration (model 1) to serve as a comparison for relationships disaggregated by medication use (Table 4, model 2). GEE results for the models with each pollutant alone (model 1) show that the lower 95% confidence limits fall below 1.00 for relationships between symptoms and pollutants or aeroallergens. Nevertheless, several models suggest that risk of an asthma symptom episode is greater with elevations in exposures, including 1-hr maximum PM_{10}, 3-day moving averages of all PM_{10} daily averaging times, NO_2, and the aeroallergens. Exposure–response relationships in model 2 are presented separately for the two medication groups in Table 4. For all pollutants and aeroallergens, ORs were larger for subjects not taking anti-inflammatory medications. A divergence in effects is suggested for all models, with several showing significant between-group product terms ($p < 0.05$). In summary, results in Table 4 show that only the group of children not on anti-inflammatory medications had positive associations between asthma symptoms and air pollutants or aeroallergens. For all exposures except O_3 in this group, the lower 95% CIs are either above 1.00 or do not fall far below 1.00. Therefore, models below focus on this group to test effects of multiple exposures and to test sensitivity to high concentrations. Subgroup models for these subjects showed narrower confidence limits for every exposure. For instance, asthma symptoms were more clearly associated with O_3 (OR, 1.45; 95% CI, 0.97–2.11), and the lower 95% confidence limits for 8-hr PM_{10} and 24-hr pollen were above 1.00.

Symptoms were not associated with day of week, linear trend, temperature, or relative humidity in either model 1 or model 2. Inclusion of temperature in the models led to instability in all variance estimates, suggesting problems of multicollinearity, but did not confound air pollution variables. Deviance was not substantially changed (deviance difference < 4.0) when adding day of week, linear trend, temperature, or relative humidity to models with the exposure alone. Symptoms were associated with respiratory infections in both groups: for the group not on anti-inflammatory medications, OR = 2.80 (95% CI, 0.92–8.49), and for the group on anti-inflammatory medications, OR = 1.93 (95% CI, 1.01–3.71). In exposure models including respiratory infections, parameter estimates shown in Table 4 increased in all models for the group not on anti-inflammatory medications. However, we found significant interactions between exposures and respiratory infections, making it more informative to present the magnitude of increase in the ORs for exposure given the presence versus absence of a respiratory infection among subjects not on anti-inflammatory medications (Table 5). ORs were around three times greater or more during respiratory infections than at other times for all exposures except total pollen (OR, 0.95). Pollutant exposures were not associated with risk of respiratory infections in GEE models, suggesting that risk of infection onset was independent of the exposures, but the probability of an asthmatic response to respiratory infection was enhanced on high air pollution days.

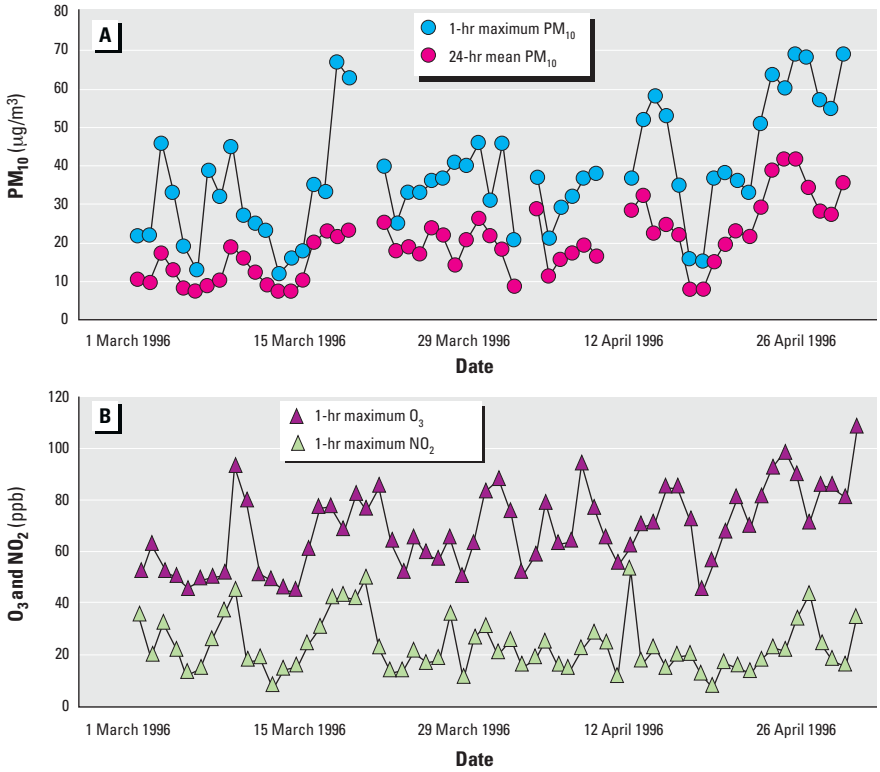

Figure 1. Time plot of air pollutant exposures, (*A*) PM_{10} and (*B*) 0_3 and NO_2, Alpine, California, panel study, 1 March through 30 April 1996.

Table 3. Air pollution and weather correlation matrix,[a] 1 March through 30 April 1996, Alpine, California.

	8-hr max O_3	1-hr max PM_{10}	8-hr max PM_{10}	24-hr mean PM_{10}	1-hr max NO_2	8-hr max NO_2	12-hr daytime fungi[b]	24-hr pollen[b]	Max temp	24-hr mean RH
1-hr max O_3	0.95#	0.68#	0.72#	0.74#	0.31*	0.36**	0.30*	0.56#	0.76#	–0.49#
8-hr max O_3		0.62#	0.65#	0.71#	0.25	0.26*	0.26*	0.57#	0.76#	–0.52#
1-hr max PM_{10}			0.93#	0.84#	0.49#	0.55#	0.24	0.47#	0.69#	–0.34*
8-hr max PM_{10}				0.95#	0.48#	0.55#	0.28*	0.45#	0.66#	–0.23
24-hr PM_{10}					0.37**	0.44#	0.21	0.47#	0.64#	–0.17
1-hr max NO_2						0.91#	0.29*	0.27*	0.33**	–0.28*
8-hr max NO_2							0.32*	0.28*	0.36**	–0.28*
12-hr fungi								0.29*	0.12	–0.07
24-hr pollen									0.68#	–0.50#
Max temp										–0.75**

Abbreviations: max, maximum; RH, relative humidity; temp, termperature.
[a]Pearson correlation coefficients (*p*-value); *n* is 61 for O_3, NO_2, and weather, 60 for fungi and pollen, and 56 for PM_{10} observations. [b]Correlations for 24-hr fungi and 12-hr pollen were similar. *$p < 0.05$; **$p < 0.01$; #$p < 0.001$.

Multiple exposure regression models. For the group not on anti-inflammatory medications, we then tested multivariate models involving multiple exposures. The aim was to explore possible copollutant confounding and interactions. This information could indicate underlying effects of an air pollutant mixture not fully captured by any one criteria air pollutant. Regressions of two air pollutants generally led to decreases in both regression parameters, likely the result of multicollinearity. For example, the model including both 8-hr PM_{10} and 8-hr NO_2 showed ORs (95% CIs) of 1.19 (0.75–1.88) and 1.50 (0.80–2.82), respectively. Differences in the fit of single-pollutant versus two-pollutant models were not significant. However, there were significant positive multiplicative interactions between the pollutants, which make interpretation of the simple joint regression models difficult. The interaction was significant between 1-hr maximum PM_{10} and 8-hr maximum NO_2 ($p < 0.01$). Figure 2 shows this pollutant interaction in relation to the probability of a symptom response on the vertical axis (scaled to the log odds). The mesh plot was smoothed using a Loess transform function. For example, if 1-hr maximum PM_{10} was 69 μg/m^3 and 8-hr maximum NO_2 was at 31 ppb, the predicted probability of an asthma symptom response is 33%. This can be compared with an overall average probability during the study of 17% (105 asthma episodes/622 person-days of PM_{10} and NO_2 observations) in the 12 subjects not on anti-inflammatory medications.

Regression models including O_3 and any one of the other pollutant variables led to a greater decrease in the O_3 parameter than in the copollutant parameter (e.g., 1-hr maximum NO_2, OR decreased from 1.93 to 1.81, whereas 1-hr maximum O_3, OR decreased from 1.43 to 1.23). Differences in the fit of single-pollutant versus this two-pollutant model were not significant. There was a dramatic decrease in the O_3 regression parameter when regressed with PM_{10}, which did not change from the model with PM_{10} alone [e.g., 1-hr maximum PM_{10}, OR = 1.73 (95% CI, 1.03–2.92); 1-hr maximum O_3, OR = 0.99 (95% CI, 0.56–1.77)]. There were no significant product terms of PM_{10} or NO_2 with O_3; however, there was a suggestion of a positive interaction between O_3 and NO_2 ($p = 0.12$). The interaction is shown in Figure 3 in relation to the probability of a symptom response on the vertical axis (scaled to the log odds).

Models including pollutants and aeroallergens. We also tested multivariate models including pollutants and aeroallergens for the group not on anti-inflammatory medications. Joint regression models were tested for pollutants and total pollen in nine pollen-allergic subjects and for pollutants and total fungi in eight fungus-allergic subjects. Only one of the pollen-allergic subjects was not in the fungus-allergic group. Effect magnitudes for aeroallergens were greater in the allergic group than in all 12 subjects not on anti-inflammatory medications, but differences were small (~15%). There were no significant multiplicative interactions between the aeroallergens and pollutants. Including both aeroallergens and air pollutants in the same model generally led to a decrease in regression parameters for both exposures. In the case of regressions of total pollen with O_3, or with any of the 3-day moving averages of PM_{10}, all standard errors were inflated by over two times, suggesting multicollinearity. The aeroallergens did not confound the product term for O_3 and NO_2 or

Table 5. ORs for risk of asthma symptoms[a] from a 90th percentile increase in pollutants or aeroallergens in those who report a respiratory infection compared with those who do not have respiratory infections.

Pollutant and aeroallergen variables	Air pollutant level[b]	OR (95% CI)[c]
1-hr max PM_{10} lag 0	51 μg/m^3	4.88 (1.31–18.2)
8-hr max PM_{10} lag 0	38 μg/m^3	6.78 (1.38–33.3)
24-hr mean PM_{10} lag 0	25 μg/m^3	4.68 (0.71–30.7)
3-day moving average 1-hr max PM_{10}	51 μg/m^3	11.1 (1.10–112)
3-day moving average 8-hr max PM_{10}	38 μg/m^3	10.1 (1.42–72.0)
3-day moving average 24-hr mean PM_{10}	25 μg/m^3	2.67 (0.60–11.8)
1-hr max O_3 lag 0	43 ppb	3.27 (1.00–10.7)
8-hr max O_3 lag 0	36 ppb	2.72 (0.67–11.0)
1-hr max NO_2 lag 0	34 ppb	3.46 (0.45–26.6)
8-hr max NO_2 lag 0	20 ppb	6.72 (1.73–26.1)
12-hr fungi lag 0	4,644 particles/m^3	6.38 (1.03–39.6)
24-hr pollen lag 0	732 particles/m^3	0.95 (0.16–5.74)

Max, maximum. Effect modification of respiratory infection in children not on anti-inflammatory medications, Alpine, California, panel study, 1 March through 30 April 1996.
[a]The asthma symptom severity score was dichotomized to *a*) no symptoms or symptoms not bothersome or not interfering with daily activities, versus *b*) symptoms interfering with daily activities. [b]90th percentile minus the minimum. [c]Per increase to 90th percentile concentration of pollutant or aeroallergen given the presence vs. absence of a respiratory infection from GEE models including the pollutant or aeroallergen, an indicator variable for respiratory infection and a product term between them. Models involve 12 subjects with 678 person-days of O_3 and NO_2 observations, 622 person-days of PM_{10} observations, and 666 person-days of aeroallergen observations.

Table 4. Effect modification by anti-inflammatory medication use on the relationship of asthma symptoms[a] in children to increases in PM_{10}, O_3, NO_2, and aeroallergen concentrations, Alpine, California panel study, 1 March through 30 April 1996.

Pollutant and aeroallergen variables	Exposure concentration[d]	OR (95% CI) per increase to 90th percentile of exposure[b]			
		Model 1[e]	Model 2[c]		
			On medication[f]	Not on medication[g]	*p*-Value[h]
1-hr max PM_{10} lag 0	51 μg/m^3	1.41 (0.87–2.30)	0.96 (0.25–3.69)	1.92 (1.22–3.02)**	0.13
8-hr max PM_{10} lag 0	38 μg/m^3	1.19 (0.74–1.94)	0.75 (0.18–3.04)	1.68 (0.91–3.09)	0.05
24-hr mean PM_{10} lag 0	25 μg/m^3	1.08 (0.73–1.61)	0.80 (0.24–2.69)	1.35 (0.82–2.22)	0.15
3-day moving average 1-hr max PM_{10}	51 μg/m^3	1.45 (0.76–2.76)	1.01 (0.14–7.02)	1.92 (0.99–3.71)	0.33
3-day moving average 8-hr max PM_{10}	38 μg/m^3	1.32 (0.76–2.29)	0.82 (0.17–3.94)	1.89 (1.10–3.24)*	0.11
3-day moving average 24-hr mean PM_{10}	25 μg/m^3	1.22 (0.84–1.77)	0.75 (0.26–2.14)	1.75 (1.15–2.68)**	0.008
1-hr max O_3 lag 0	43 ppb	1.02 (0.71–1.47)	0.76 (0.24–2.44)	1.28 (0.75–2.17)	0.11
8-hr max O_3 lag 0	36 ppb	0.94 (0.64–1.40)	0.73 (0.20–2.67)	1.14 (0.62–2.09)	0.21
1-hr max NO_2 lag 0	34 ppb	1.40 (0.80–2.47)	0.90 (0.17–4.78)	1.95 (0.88–4.32)	0.08
8-hr max NO_2 lag 0	20 ppb	1.49 (0.95–2.33)	1.08 (0.30–3.93)	1.91 (1.07–3.39)*	0.12
12-hr fungi lag 0	4,644 particles/m^3	1.37 (0.95–1.97)	0.90 (0.35–2.30)	1.89 (1.24–2.89)**	0.005
24-hr pollen lag 0	732 particles/m^3	1.37 (0.84–2.21)	0.85 (0.18–3.91)	1.90 (0.99–3.67)	0.07

Max, maximum.
[a]The asthma symptom severity score was dichotomized to *a*) no symptoms or symptoms not bothersome or not interfering with daily activities, versus *b*) symptoms interfering with daily activities. [b]GEE models involve 56 days for PM_{10}, 61 days for O_3 and NO_2, and 60 days for aeroallergens; lag 0 concentrations are from the same day as the symptom reports. [c]Pollutant, indicator for medication group, and interaction term for pollutant by medication group. [d]90th percentile minus the minimum. [e]Pollutant alone. [f]On anti-inflammatory medications; six subjects on inhaled corticosteroids and four subjects on cromolyn or nedocromil; total of 570 person-days of O_3 and NO_2 observations, 524 person-days of PM_{10} observations, and 560 person-days of aeroallergen observations. [g]Not on anti-inflammatory medications; twelve subjects with 678 person-days of O_3 and NO_2 observations, 622 person-days of PM_{10} observations, and 666 person-days of aeroallergen observations. [h]For between-group product term in model 2. *$p < 0.05$; **$p < 0.01$.

the product term for PM_{10} and NO_2 described above.

Sensitivity analysis. Effects at low levels of particulate air pollution and NO_2 in the present study may be surprising, whereas there is some expectation of effects for O_3 given that the 1-hr maximum approached the NAAQS (*17*) (120 ppb) on 3 days (94–108 ppb). We did not identify any statistical outliers in pollutant distributions (> 3 SD above the mean). However, it is possible that only the highest concentrations drove associations. Therefore, models for subjects not on anti-inflammatory medications were further tested by progressively dropping the upper 5% of pollutant concentrations (2–3 days) to test for a "threshold effect." We found that dropping the upper 5% of 1-hr maximum PM_{10} (2 days at 69 μg/m^3) led to a marked reduction in the OR from 1.72 to 1.27, but there was little change in ORs for 8-hr maximum PM_{10} and 24-hr mean PM_{10}. There were no decreases in parameters for the 3-day moving averages of PM_{10}. Dropping the upper 10% led to a further reduction in the OR for 1-hr maximum PM_{10} to 0.97, but not for 8-hr maximum PM_{10} or 24-hr mean PM_{10}. Again, the 3-day moving average PM_{10} effects remained above an OR of 1.5. No reductions in effect magnitudes were found after dropping the upper 15% of 8-hr maximum PM_{10} or 24-hr mean PM_{10}. Dropping the upper 15% of 3-day moving average PM_{10} variables notably dropped the effect of the 1-hr maximum to an OR of 1.11, but not the 3-day 8-hr maximum or the 3-day 24-hr mean.

Dropping the upper 5% also led to a marked reduction in the OR for 1-hr maximum O_3 from 1.43 to 1.19 and for 8-hr maximum NO_2 from 1.73 to 1.17, and similar reductions were seen for other averaging times. We found no further reductions in ORs after dropping the upper 10% of O_3 and NO_2. After we dropped the upper 15%, the OR for NO_2 dropped to near unity, but O_3 showed an increase. After we dropped the upper 10% of PM_{10}, NO_2, and O_3, pollutant interactions noted above were still significant between PM_{10} and NO_2 and were borderline significant ($p < 0.1$) between NO_2 and O_3. All of the pollutant interactions were nonsignificant after dropping the upper 15%.

Dropping the upper 5% of fungal spores did not reduce its effect (OR, 2.03), and the same was found for total pollen (OR, 1.87). Further dropping the upper 10% of fungal spores markedly reduced the OR to 1.37, but the reduction was less for total pollen (OR, 1.57). Dropping the upper 15% of fungi eliminated any association (OR, 1.18; $p = 0.7$). However, dropping the upper 15% of total pollen did not reduce the effect magnitude (OR, 1.82).

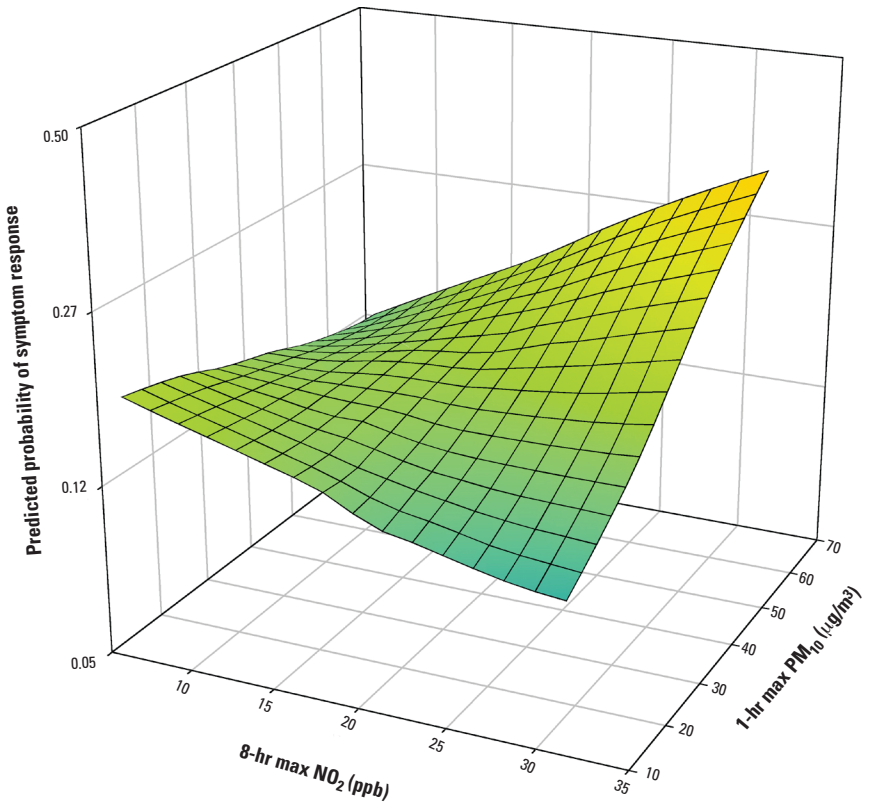

Figure 2. Predicted probability of an asthma symptom response and interaction between PM_{10} and NO_2 in asthmatics not on anti-inflammatory medications. The probability of a symptom response is on the vertical axis and is scaled to the log odds from the GEE model. The plot was smoothed using a Loess transform function.

Further exclusions below the 15th percentile led to additional reductions in most ORs and wide confidence intervals below the fifth quintile. Exceptions to this were found for the 3-day moving average of 24-hr mean PM_{10} and total pollen, which showed associations for the fourth compared with the lowest quintile [PM_{10} OR = 1.93 (95% CI, 1.34–2.79); pollen OR = 1.50 (95% CI, 1.04–2.14)] but not the third quintile.

Discussion

Overview of findings. These findings confirm the acute adverse effects of air pollutants on asthmatic symptoms and suggest that the irritant potential of PM_{10} at inversion layer elevations is greater than expected based upon mass concentration. Our findings also point to the potential relevance of peak PM_{10} exposures to acute respiratory effects. Magnitudes of association for current-day PM_{10} showed modest graded differences of 1-hr maximum > 8-hr maximum > 24-hr mean PM_{10}. However, confidence intervals overlapped markedly, and findings for the 1-hr maximum were sensitive to removal of the two highest days at 69 μg/m^3.

Our strongest lag day associations for PM_{10} were found with lag 0 (the current day's exposure) and a 3-day moving average. Given that the time coarse of lung function and symptom changes can be on the order of minutes to hours for early- to late-phase asthmatic reactions (*18*), asthma is expected to be acutely related to airborne exposure on the day of an exacerbation (lag 0). We found slightly stronger associations with a 3-day moving average than with lag 0 of 24-hr mean PM_{10}, suggesting some cumulative or delayed effects as well. The lag 0 and multiday moving average findings are consistent with results of our previous asthma panel study during fall 1995 in the same region (*1*). Sixteen of 22 subjects in the present study were subjects in this previous study.

Associations of asthma symptoms with PM_{10}, NO_2, O_3, fungi, and pollen were largely isolated to asthmatic children not taking anti-inflammatory medications, with significant or near-significant differences in regression slopes from subjects who were taking anti-inflammatory medications (Table 4). This is consistent with a similar divergence of association by anti-inflammatory medication use found in our earlier asthma panel (*1*). The present study also showed a further enhancement of symptom responses to pollutant exposures among subjects not on anti-inflammatory medication during respiratory infections.

Asthma symptoms were more clearly associated with O_3 in a subgroup model including only subjects not on anti-inflammatory medications. Positive associations between asthma outcomes and O_3 have been consistently

reported in the literature (*19*) and in two of our previous studies in the same region (*1,7*), but not in another study in Alpine (*8*).

Asthma symptoms were associated with combined elevations of NO_2 and O_3. This suggests either a pollutant interaction or that underlying effects of an air pollutant mixture on days with joint elevations are not fully captured by any one of these criteria air pollutants. In two-pollutant models, there was a loss of O_3 association in joint regressions with PM_{10}, but this may have been caused by collinearity effects. Significant interactions were also found between PM_{10} and NO_2. Again, this suggests that the product term represented either a pollutant interaction or underlying effects of an air pollutant mixture. Outdoor fungal and pollen particles were associated with asthma symptoms as well, but there were no interactions with any air pollutant.

Results of testing for a threshold suggest that effects from lag 0 1-hr maximum PM_{10}, O_3, and NO_2 were attributable primarily to 2–3 days of elevated concentrations for each variable. For these days, one day showed both higher PM_{10} and NO_2 levels, and one day showed both higher PM_{10} and O_3 levels. These were all warm, dry days with maximum temperatures from 74°F to 91°F and minimum relative humidity from 11% to 26%. Winds were 2–3 mph, all out of the west (urban areas). More days, including the upper 15th percentile, were driving associations for lag 0 8-hr maximum PM_{10} and 24-hr mean PM_{10}, as well as the 3-day moving averages of 8-hr average PM_{10} (down to 38 $\mu g/m^3$). Effects were found down to the fourth quintile for the 3-day moving average of 24-hr average PM_{10} (20–23 $\mu g/m^3$) and to the fourth quintile of lag 0 pollen 345–590 particles/m^3. Fungal spores had no effect below the 90th percentile. Our aim in this sensitivity analysis was to examine whether there was an apparent threshold in the models. As stated above, higher concentrations were not statistical outliers in pollutant distributions. Results after discarding valid concentrations at the upper end of the pollutant distribution were exploratory in nature. The sensitivity analysis identified the need for both a greater amount of data to model the shape of the exposure–response curve and better modeling strategies to determine that shape.

Limitations. The external validity of differences in results by subjects on versus not on anti-inflammatory medications is limited by small numbers of subjects (10 vs. 12, respectively). The major limitation in the present study is reliance on outdoor central site exposures to represent individual exposures. The magnitude of exposure misclassification is expected to be greatest for the gaseous pollutants. In the case of O_3, this is because of low indoor-to-outdoor concentration ratios. We previously conducted an exposure assessment study for two seasons (spring and fall 1994) in Alpine using personal passive O_3 badges. We found relatively low correlations between personal (1,175 samples) and outdoor central site O_3 concentrations even after incorporating time–activity, traffic, and spatial data in microenvironmental models (adjusted R^2 = 0.22 and 0.19 in the two seasons) (*20*). The present study lacked personal exposure measurements, although we aim to provide predictive PM_{10} data for this and earlier studies using data from our ongoing investigations in Alpine with personal real-time particle measurements from nephelometers (*21*).

The present measurements of particle exposures (PM_{10}) were additionally limited by an inability to separate fine ($PM_{2.5}$) from coarse ($PM_{2.5–10}$) particle fractions. Fine particles have been found to be a stronger predictor of asthma-related responses than are coarse particles in the Harvard Six Cities Diary Study (*22*). This difference is expected because the deposition fraction in the lower respiratory tract and alveoli of the lungs is greater for fine particles and because toxic irritants in air pollution formed from combustion and photochemical processes are generally found in the fine particle fraction (SO_4^{2-}, NO_3^-, H^+, metals, and organic compounds). Nevertheless, coarse particle components, including crustal elements and some bioaerosols, may also be important respiratory irritants for asthmatic patients. An additional weakness in the PM exposure metric is that TEOM measurements of PM_{10} could have potentially underestimated concentrations at key times because of the expected volatilization of important semivolatile particle components as they cross the 50°C heating element (*23*).

Particle effects by hourly averaging time. Our findings of modestly stronger effects for shorter PM_{10} averaging times are tempered by the fact that confidence intervals overlapped markedly and stronger effects of the 1-hr maximum were driven by 2 of 56 observed days whereas at least 8 days were driving associations for 8-hr maximum PM_{10} and 24-hr mean PM_{10}. Also, there was no difference in magnitude of association for the 3-day moving averages of the different PM_{10} variables, and only the 8-hr and 24-hr PM_{10} 3-day moving averages maintained their effect magnitudes after dropping up to 15% of the highest values.

In our previous Fall 1995 panel study (*1*), analyses in all 24 children showed statistically significant risks of asthma symptoms from increases in daily 1-hr and 8-hr maximum

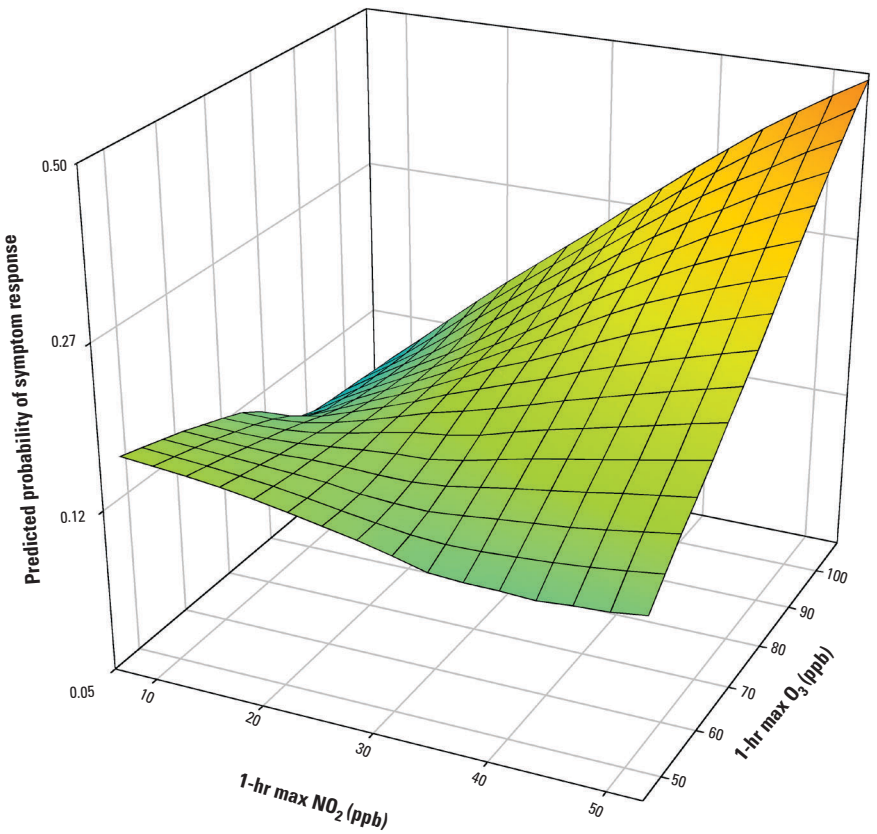

Figure 3. Predicted probability of an asthma symptom response and interaction between O_3 and NO_2 in asthmatics not on anti-inflammatory medications. The probability of a symptom response is on the vertical axis and is scaled to the log odds from the GEE model. The plot was smoothed using a Loess transform function.

PM_{10}. Effects were smaller and nonsignificant for the 24-hr PM_{10} average. However, subgroup analyses showed this difference only in 10 more symptomatic asthmatic subjects, only one of whom was on an anti-inflammatory medication. Among less symptomatic subjects, particle effects were generally weaker for the 1-hr compared with the 8-hr maximum or 24-hr average. Dropping the upper 10% of observations did not alter these previous findings. One other asthma panel study has examined hourly maximum PM_{10} measured using β-attenuation monitors. Ostro et al. (*2*) reported results of an asthma panel study of 138 African-American children living in Los Angeles and Pasadena, California. Diary reports of wheezing, cough, and dyspnea were associated somewhat more strongly with a 17-μg/m^3 increase in 24-hr PM_{10} (ORs, 1.04–1.25) than with a 31-μg/m^3 increase in 1-hr PM_{10} (ORs, 1.02–1.07). No results were presented for 8-hr maxima.

A reasonable biologic rationale for the hypothesis that maximum hourly particle exposures can induce asthmatic reactions is that changes in personal particle exposure concentrations over the course of a day will alter the dose of particles in the lung in a time-dependent manner. Therefore, it is expected that biologic responses may intensify with high peak excursions that overwhelm lung defense mechanisms (e.g., mucociliary transport, and neutralization or metabolism of toxic substances). However, clinical data on the relevance of particle averaging time to respiratory responses is inadequate to support or refute this rationale. A more defensible rationale for epidemiologic research is that shorter averaging times can be used as better surrogates for population exposures than daylong averages. Peak particle excursions could occur during the daytime when children are outdoors and physically active, thus leading to higher pulmonary doses. The peak concentrations of PM_{10} in the present study occurred between 1300 and 2000 hr. The finding that the most robust particle effects were for the 8-hr maximum exposures over the current and prior 2 days could be the result of maximal personal exposures and doses occurring around the same 8-hr time period. One-hour peaks may be more influenced by local point sources near the monitoring station that are not representative of regional exposures, thus explaining weaker associations with asthma symptoms for multiday 1-hr than for 8-hr maximum PM_{10} in the present study as well as in our previous study (*1*). Sustained high peaks during the day may partly explain epidemiologic associations with 24-hr average PM_{10} at levels below the NAAQS of 150 μg/m^3 (*24*).

Effect modification by anti-inflammatory medication use. Our findings support the view that proinflammatory components of PM are causally related to acute asthma exacerbations. In our earlier study, subjects on inhaled anti-inflammatory medications during follow-up (six on corticosteroids, one on cromolyn) experienced fewer symptoms. To evaluate effect modification by medication use, we therefore compared them with seven other subjects not on anti-inflammatory medications but with a similar frequency of asthma symptom reports (*1*). The OR (95% CI) in the previous report for a 36-μg/m^3 increase (minimum to 90th percentile) in the 5-day moving average of 8-hr maximum PM_{10} was 9.66 (95% CI, 2.80–33.2) among subjects not on anti-inflammatory medications, compared with 2.96 (95% CI, 0.32–27.0) among subjects on anti-inflammatory medications. The OR for a 58-ppb increase (minimum to 90th percentile) in the 1-hr maximum O_3 was 4.14 (95% CI, 1.71–10.0) among subjects not on anti-inflammatory medications, compared with 1.20 (95% CI, 0.46–3.15) among subjects on anti-inflammatory medications. Heterogeneity in effects of other pollutant variables and fungal spores was similar. Air pollution levels were higher then (mean 8-hr PM_{10}, 43 ± 12 μg/m^3; mean O_3, 90 ± 18 ppb), possibly explaining stronger associations than in the present study (Table 4).

Several other panel studies have examined the importance of medication use to air pollutant associations (*2,25–27*). Two of these studies showed stronger associations between asthma outcomes and air pollutants among subjects taking any asthma medication versus subjects not taking asthma medication, but they did not separate subjects by anti-inflammatory medication use (*25,26*). Mortimer et al. (*27*) reported results of a series of 2-week asthma panels in 846 inner-city children. They compared effects on asthma outcomes by outdoor O_3 levels across medication groups based on baseline data for prescribed medication. Associations between incidence of symptoms and an increase of 15 ppb in O_3 were largest among those prescribed cromolyn but not steroids (OR, 1.46; 95% CI, 1.06–2.01) followed by nonsignificant ORs for those prescribed β-agonists or xanthines only (1.18), steroids (1.08), and no medication (1.04). The percent change in peak expiratory flow (PEF) was also greatest among those prescribed cromolyn but not steroids (OR, –1.27%; 95% CI = –2.47to –0.06) followed by nonsignificant PEF changes of around –0.5% for the other groups. Ostro et al. (*2*) reported results of an asthma panel study of 138 African-American children living in Los Angeles and Pasadena, California. Diary reports of daily and new-onset presence or absence of wheezing, cough, and dyspnea were associated with 3-day lagged 24-hr average PM_{10} and *Alternaria* spores. For an interquartile increase in 24-hr PM_{10} of 17 μg/m^3, the OR ranged from 1.10 to 1.30 in subjects with anti-inflammatory prescriptions and from 1.09 to 1.26 in subjects without such medications. For an interquartile increase in *Alternaria* of 20 spores/m^3, the OR ranged from 1.05 to 1.19 in subjects with anti-inflammatory prescriptions and from 0.98 to 1.10 in subjects without such medications. In summary, there is little consistency between the present study and the few other epidemiologic studies examining medication subgroups, possibly because of methodologic differences in the stratification of groups. One major difference is the assessment of medication used at baseline rather than during the days of panel follow-up. If a subject is not taking an anti-inflammatory medication during follow-up, putting that subject in the medication category is exposure misclassification. When outcome data are analyzed as repeated measures, capturing repeated clinical determinants is critically important.

It is biologically plausible that an asthmatic individual taking anti-inflammatory medications would be less susceptible to air pollution health effects that act through proinflammatory mechanisms. Experimental evidence in asthmatic patients identifies the proinflammatory effects of O_3 as a major mechanism for adverse effects of O_3 in asthmatic populations (*4,5*). The proinflammatory nature of PM components is beginning to be clarified, but the large number of organic and inorganic components makes this a major task. Studies examining the proinflammatory effects of the polycyclic aromatic hydrocarbon fraction of diesel exhaust particles serve as an important example [reviewed in Nel et al. (*28*)]. The proinflammatory effects of NO_2 have also been described [reviewed in Bascom et al. (*19*) and Chauhan et al. (*29*)]. Four experimental studies of mild atopic asthmatic adults have shown an enhancement of airway responses to allergens after exposure to 260–400 ppb NO_2 (*30–33*). There is also some evidence that NO_2 exposure leads to persistent neutrophilic infiltration in human airways (*34*) and to increased histamine release in histocultured human nasal mucosa (*35*). The inflammatory mechanisms of pollen and fungal allergens in allergic respiratory disease have also been described (*36–38*). Our finding of a divergence of association in the medication groups for aeroallergens is not unexpected and demonstrates the value of stratifying panel data.

Effect modification by respiratory infections. Our finding that positive associations between asthma symptom severity and air pollution is greater during respiratory infections is supported by experimental data. Rodent models have shown reduced particle

clearance, increased susceptibility to microbe-induced death, and adverse pulmonary responses when pulmonary infections are concurrent with inhalation of PM, including diesel particles and metal-rich particles (*39–41*). There is also some experimental evidence that NO_2 exposure leads to an alteration of lymphocyte subsets and diminution of macrophage inactivation of respiratory viruses (*29*). These effects could enhance the severity of the infectious illness, which in turn could lower the threshold of the asthmatic response to inhaled pollutants. A recent epidemiologic study by Linaker et al. (*42*) of 114 asthmatic children using weekly averaged NO_2 levels from personal passive diffusion samplers showed an increased risk of asthma episodes after respiratory infections that occurred when NO_2 concentrations were higher. Some other coherent data can be found in aggregate time-series data showing associations of increased levels of PM and/or NO_2 with *a*) hospitalization for pneumonia (*43*), *b*) hospitalization for respiratory infections in aggregate (*44*), *c*) increased physician visits for croup in children (*45*), *d*) mortality from pneumonia (*46,47*), and *e*) mortality from respiratory infections in aggregate (*48*). The prevailing view here is that air pollution may have enhanced the severity of ongoing infectious illness, leading to hospitalization or mortality.

Effects of NO_2. The respiratory health effects of NO_2 on asthma are not entirely clear, and there are inconsistencies in the experimental literature. Some studies have shown alterations in lung function, airway responsiveness, or symptoms, whereas others have not, even at high concentrations [reviewed in Bascom et al. (*19*)]. In addition to the study by Linaker et al. (*42*) discussed above, another panel study of 30 asthmatic children found that PEF throughout the day was inversely associated with outdoor home NO_2 levels, whereas only morning PEF was inversely associated with indoor bedroom NO_2 levels (*49*). Several epidemiologic time-series studies have shown an increase in risk of asthma hospital admissions or emergency department visits with increases in outdoor NO_2 levels (*44,50–55*), but many more have reported either no results or results that were nonsignificant for NO_2. This inconsistency may be because of exposure misclassification due to the high spatial variability of NO_2, which is strongly influenced by local traffic density (*56*). The site of the monitoring station in the present study was generally upwind (east) of a two-lane highway accessing a small residential district (343 vehicles/day) (*57*) and was 0.19 mile away and 270 feet higher than an interstate freeway. Although it is possible that on some days local traffic could have influenced NO_2 levels, most of the NO_2 measured at the monitoring station and in the semirural study area is likely transported along with other copollutants from urban areas of San Diego County. This means that local temporal influences on the central site are not likely to be major limitations to the use of NO_2 measurements in the present study.

Pollutant interactions. We found statistical interactions between PM_{10} and NO_2 and between O_3 and NO_2. Copollutant models, however, generally resulted in multicollinearity problems, making interpretation of interaction terms problematic. It is possible that joint elevations in two air pollutant types were acting as an indicator for more causal particle- and gas-phase components at the inversion elevation zone of the study region, but we have no supporting aerometric data. Most other epidemiologic research to date has also not been able to attribute the proportion of adverse respiratory effects to any single air pollutant, which is not inconsistent with the view that a mix of air pollutants may be to some extent acting synergistically (*58*). A simple explanation is that at some jointly high concentrations, the human lung may not be able handle the total pollutant burden contained in the inspired air. Despite a general lack of statistical interaction in observational studies, unmeasured joint effects have been proposed as one explanation for greater relative effects of O_3 on lung function in epidemiologic studies compared with clinical studies (*59*).

Effects of fungi and pollen. Associations between aeroallergens and symptoms were more robust for total pollen than for total fungi in the sensitivity analysis. March and April, the season of study, are the peak pollination months for the native plants in the area of study, where native dry-land brush and canyon trees predominate around the residential areas where subjects lived. One of the original aims of the study was to test the putative interaction between O_3 and pollen that has been suggested in experimental studies (*9,10*). However, there were no pollutant–aeroallergen interactions, which is consistent with our previous studies in southern California in other months of the year with lower pollen counts but equally high fungal spore counts (*1,7,8*). Although effect magnitudes of the air pollutants were in some cases reduced when regressed with the aeroallergens, this was not the case when interaction terms for PM_{10} and NO_2 or for O_3 and NO_2 were included in the models. This suggests that causal components of the pollutant mix were acting independently of aeroallergens. Our previous asthma panel studies did not find confounding of air pollutant associations by outdoor pollen or fungi (*1,7,8*). Several time-series investigations have found associations between asthma hospital admissions and both outdoor air pollutants (particles, NO_2, or O_3) and pollen or fungi, but none has found any confounding between aeroallergens and these pollutants (*54,60,61*). In two studies, there was evidence that SO_2, NO_2, and O_3 enhanced the effect of grass pollen on asthma admissions (*54,60*), although there was a negative interaction between O_3 and tree pollen in one of these studies (*54*). The general inconsistency between epidemiologic and experimental data on the enhancement of allergen-induced respiratory responses by air pollutants may be explained by a lack of temporally resolved data to account for hourly exposures and a lack of spatially resolved data to account for personal exposures to pollutants and aeroallergens.

Conclusions

We have found associations of asthma symptoms in schoolchildren with air pollutants and aeroallergens. A few observed days drove stronger associations of symptoms with 1-hr maximum PM_{10}, but overall, longer averaging times showed more robust associations. The enhancement of exposure–response relationships in subjects not taking anti-inflammatory medications is consistent with experimental data on the inflammatory mechanisms of pollutants and allergens. Our findings are clinically relevant in that the symptom response was defined as symptoms that subjects perceived to have interfered with regular daily activities. We have no information to confirm whether these symptom responses stemmed from enhancements of pulmonary inflammation, although significant interactions of pollutants with respiratory infections suggest that.

Pollutant associations were found at relatively low concentrations and were largely driven by the top exposure quintiles. Ultrafine particles and secondary air pollutant gases and organic aerosols above the base of the temperature inversion layer could be important in these associations found at low mass concentrations of PM_{10}. Could some of these unmeasured pollutants have been the underlying causal agents? Further investigations addressing this question may yield clues.

Our view is that the next phase of epidemiologic research is to more accurately quantify both respiratory responses and airborne exposures in asthmatic children. This includes *a*) the use of biomarkers of response that better capture underlying inflammatory processes in asthma, *b*) the use of better spatially and temporally resolved data that take into account personal time–place–activity patterns and hourly exposures, and *c*) measurements of pollutant components suggested in experimental data to be causally related to irritant and immune responses.

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