Prospective Study of Air Pollution and Bronchitic Symptoms in Children with Asthma

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The relationship of bronchitic symptoms to ambient particulate matter and to particulate elemental and organic carbon (OC), nitrogen dioxide (NO_2), and other gaseous pollutants was examined in a cohort of children with asthma in 12 Southern California communities. Symptoms, assessed yearly by questionnaire from 1996 to 1999, were associated with the yearly variability of particulate matter with aerodynamic diameter less than 2.5 μm (odds ratio [OR] 1.09/μg/m^3; 95% confidence interval [CI] 1.01–1.17), OC (OR 1.41/μg/m^3; 95% CI 1.12–1.78), NO_2 (OR 1.07/ppb; 95% CI 1.02–1.13), and ozone (OR 1.06/ppb; 95% CI 1.00–1.12). The ORs associated with yearly within-community variability in air pollution were larger than the effect of the between-community 4-year average concentrations. In two pollutant models, the effects of yearly variation in OC and NO_2 were only modestly reduced by adjusting for other pollutants, except in a model containing both OC and NO_2; the effects of all other pollutants were reduced after adjusting for OC or NO_2. We conclude that OC and NO_2 deserve greater attention as potential causes of the chronic symptoms of bronchitis in children with asthma and that previous cross-sectional studies may have underestimated the risks associated with air pollution.

Keywords: asthma; epidemiology; air pollution; child; particulate matter

Several cross-sectional studies have examined the relationship of average levels of particulate matter (PM) in different communities and the prevalence of bronchitis and chronic cough or phlegm production in children (1–6). However, there has been little investigation of the effects of components of PM on these symptoms or of whether other gaseous pollutants could be responsible for the observed effects. Bronchitis was reported to be more prevalent among children with asthma living in communities with high ambient PM_{10} (particulate mass less than 10 μm in diameter) in combination with high sulfur dioxide and sulfate PM in the 6 and 24 cities studies in the eastern United States (3, 7). We reported similar effects of particulate exposure in a cross-sectional evaluation of children in the 12 communities of the Children's Health Study in Southern California, where there is little ambient sulfur dioxide or particulate sulfate (5). This suggests that these sulfur compounds are not necessary to produce bronchitic symptoms. We also observed associations of bronchitic symptoms with nitrogen dioxide (NO_2), which were as strong as those for PM_{10} and fine particulate mass less than 2.5 μm in diameter ($PM_{2.5}$). In Southern California, the primary source both for PM and NO_2 is vehicular traffic, which distinguishes this region from polluted areas in the eastern United States, where there are other important sources for particulate air pollution.

Recent toxicologic evidence indicates that organic carbon (OC) in PM may play an important role in the effects of PM. OC extracted from ambient PM in Los Angeles has been shown to elicit oxidative stress responses potentially important for asthma exacerbation and similar to the response to diesel exhaust particulate (8), which is known to promote an allergic response (9, 10). The Children's Health Study offers the opportunity to examine the effect on bronchitic symptoms of different size fractions of PM and of particulate OC, elemental carbon (EC), and of other traffic-related pollutants, including NO_2, after adjusting for other co-pollutants. Using data collected longitudinally and a novel statistical approach, we have investigated the effects on children with asthma both of differences between communities and of the yearly variation in pollutants within communities. Some of the results of this study have been previously reported in the form of an abstract (11).

METHODS

Twelve communities in Southern California were selected for study, on the basis of the historic levels of criteria air pollutants, as described previously (12). In 1993 approximately 150 fourth graders (aged 9–10 years) and 75 seventh graders (12–13 years) were recruited from schools in each of 12 neighborhoods with low residential mobility on the basis of the 1990 census. All children from targeted classrooms were invited to participate, and a baseline questionnaire was sent home for completion with the help of parents of participating children. In early 1996 an additional cohort of approximately 175 fourth graders from each community was recruited. There was an overall participation rate in the surveyed classrooms of 82%. Each child was administered a follow-up questionnaire each year between January and June through 1999. Children with a history of asthma at study entry, who completed two or more follow-up questionnaires any time during the years 1996 to 1999 (n = 475) were included in the current analysis.

Bronchitic symptoms were assessed in the yearly follow-up questionnaire. A child was considered to have had chronic bronchitic symptoms during the previous year, on the basis of the child's report of a daily cough for 3 months in a row, congestion or phlegm for at least 3 months in a row, or bronchitis. Therefore, although these symptoms may have started with an acute exacerbation of asthma, they were likely to represent chronic, indolent symptoms. Children who answered no to all 3 of these questions were considered not to have bronchitic symptoms for the corresponding year. Information on current secondhand tobacco smoke exposure in the home and on the child's personal smoking

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was obtained from the yearly questionnaire completed by the child. Participation in team sports before the first year a child contributed information on bronchitis for this analysis was also assessed from the child's completed questionnaire.

A history of asthma for each child was assessed on the basis of the report in the baseline questionnaire. Children were considered to have a history of asthma, if there was a yes answer to the question "Has a doctor *ever* diagnosed this child as having asthma? " Information on potential confounders also was collected in the baseline questionnaire, including the child's sex, age, race and ethnicity, history of allergies, whether the child smoked, *in utero* tobacco smoke exposure (from maternal smoking), family history of asthma in either parent, membership in a health insurance plan, and socioeconomic status. Families were considered to be of low socioeconomic status, if family income was less than $15,000 (or, if income was not reported, if the responding parent had less than a 12th grade education). High socioeconomic status was defined by family income of $100,000 or more (or, if income was not reported, by postgraduate training). Remaining families were classified as middle socioeconomic status. Information on each child's participation in team sports during the past year and on the amount of time routinely spent outside in the afternoon from 2:00 to 6:00 P.M. (divided at the median for all participants) was collected because exercise and time outside might modify the effect of ambient pollution by increasing the dose to the lungs.

Air pollution monitoring stations were established in each of the 12 communities. For each year of follow-up, measurements were made for each pollutant, as described previously (12, 13). Each station monitored hourly levels of ozone (O_3), PM_{10}, and NO_2. $PM_{2.5}$ and acid vapor were measured using 2-week integrated samplers. PM_{10} EC and OC were collected in 2-week integrated samples and subsequently analyzed by the National Institute for Occupational Safety and Health method (14–16). Annual averages were computed of the 24-hour PM_{10} and NO_2 and of the 10:00 A.M. to 6:00 P.M. averages of O_3. This O_3 metric was selected because O_3 has a marked diurnal pattern, with highest concentrations occurring during midday and afternoon periods, when children were likely to be outside and, therefore, more exposed. Annual averages also were computed from 2-week averages of $PM_{2.5}$, of coarse $PM_{10\text{-}2.5}$ (PM_{10}–$PM_{2.5}$), of inorganic hydrochloric plus nitric acid vapor, of organic acetic plus formic acid vapor, and of EC and OC. Four-year mean levels (1996–1999) in each community were computed for each pollutant metric. The yearly deviations from the 4-year mean were computed each year for each community.

Data Analysis

The associations of demographic and other personal and family characteristics with bronchitic symptoms at study entry were examined, and the between-pollutant correlation structure was examined, using descriptive statistics and tests for overall associations.

We examined the associations of bronchitic symptoms both with yearly variation in air pollution within communities and with the 4-year average of air pollutants across the 12 study communities. The modeling strategy can be conceptualized as a three-stage regression (13, 17), in which the effects of individual time-dependent covariates, including within-community variability in air pollution, were assessed in the first stage; individual level time-independent confounders were assessed in the second stage; and the effects of 4-year average air pollutants were examined in the third stage. For years in which children were not available to complete the questionnaire, they did not contribute to the analysis.

Let c, i, j denote the community, subject, and year of visit, respectively. In the first level, we modeled bronchitic symptoms as a function of time-dependent covariates z_{cij} and the deviation of yearly average air pollution from the 4-year average for each community (a key parameter of interest), $X_{cj} - \bar{X}_c$, where $\bar{X}_c$ represents the 4-year average level of air pollution for each community, using logistic regression. The superscript T on the parameters in the model specifications denotes transposes of the parameter vectors. This model includes subject-specific intercepts A_{ci} to be used in the second-level models. Time-dependent covariates include age (centered at 12 years), children's smoking history, and secondhand tobacco smoke exposure. The model thus has the following form:

$$\text{logit}[\Pr(\text{symptoms}_{cij})] = A_{ci} + \gamma^T z_{cij} + \delta^T(X_{cj} - \bar{X}_c)$$

In the second-level model, we used a linear regression model to adjust for effects of subject-specific covariates z_{ci} that did not vary with time. This model has the following form:

$$A_{ci} = A_c + \eta^T z_{ci} + e_{ci}$$

Here, subject-specific adjusted intercepts (A_{ci} from level one) were modeled as functions of time-independent covariates, which included sex and race/ethnicity, in addition to community-specific intercepts (to be used in the third-level models). In the third level, the 12 community-specific intercepts A_c from Level 2 (from which community-specific prevalence can be calculated) were regressed as functions of the 4-year averages of air pollution for each community, leading to the following ecologic model:

$$A_c = \alpha + \beta^T\bar{X}_c + e_c$$

These three regression models were combined to yield a more efficient logistic mixed-effects model of the form:

$$\text{logit}[\Pr(\text{symptoms}_{cij})] = \alpha + \beta^T\bar{X}_c + \eta^T z_{ci} + \gamma^T z_{cij} + \delta^T(X_{cj} - \bar{X}_c) + e_c + e_{ci} + e_{cj}$$

where e_c, e_{ci}, and e_{cj} are three random effects for community, subject, and year, assumed to be randomly distributed with zero means and variances σ^2_c, σ^2_{ci}, σ^2_{cj} respectively. Note that the combined mixed effects modeling structure allowed us to include the year random effect e_{cj} to account for effects of any temporal trends in pollution and symptoms. The parameters of primary interest are δ^T (the effect on bronchitic symptoms of the yearly variation in air pollutants within communities from the 4-year average) and β^T (the effect of 4-year average air pollution across the 12 communities). Heterogeneity of effects in different communities was also assessed by including additional random effects that allowed intracommunity variability. In all models, missing data were assumed to be missing at random (17).

Confounding was assessed by examining models with and without the potential confounder to see if the coefficient of the pollutant of interest changed by more than 10%. Effect modification was assessed by examining pairwise interaction terms with the within- and between-community pollution variables.

All analyses were conducted by using the SAS software 2 (18). The GLIMMIX macro in SAS was used in fitting the logistic mixed effects regression models. As a sensitivity analysis, the final models were also fitted using a comparable conditional logistic model for the presence of symptoms each year, conditional on the total numbers of years in which symptoms were reported. This method essentially treats each subject as a separate stratum and automatically adjusts for all subject-specific time constant covariates. The results were very similar to those obtained from the logistic mixed effects models. To assess the sensitivity of results to the normality assumptions on the random effects, marginal models in the style of the generalized estimating equations (17) were also fitted. There was no noticeable bias in the regression estimates, so only the results from the mixed effects models are presented.

RESULTS

Among the 475 children with asthma, 184 (38.7%) had bronchitic symptoms during the first year they contributed to the analysis. Children with a history of wheeze during the year before study entry or allergies in the past were significantly more likely to report symptoms (Table 1). Demographic and socioeconomic characteristics, history of asthma in a parent, and secondhand tobacco smoke exposure in the home were not significantly associated with bronchitic symptoms at study entry. There were few children who smoked. Children with symptoms (12.9 years; SD 2.0) were older than children without symptoms (12.4; SD 1.8) ($T = 3.25$; $p = 0.001$).

The between-community range of 4-year average pollutant concentrations was 4- to 10-fold across the 12 communities, with the exception of O_3 and of $PM_{10\text{-}2.5}$, which had approximately twofold and 3.5-fold ranges, respectively (Table 2). The within-community ranges, i.e., the range of the yearly deviation from the 4-year mean of pollutants in each of the 12 communities

TABLE 1. DISTRIBUTION OF DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS BY BRONCHITIC SYMPTOMS AMONG CHILDREN WITH ASTHMA

	n (%) with Symptoms	Total
Sex (p* = 0.58)		
Girls	73 (37.2)	196
Boys	111 (39.8)	279
Ethnicity (p = 0.73)		
Non-Hispanic white	109 (39.1)	279
Hispanic	47 (37.9)	124
Black	10 (35.7)	28
Asian	14 (48.3)	29
Others	4 (26.7)	15
Allergies (p = 0.002)		
No	55 (30.4)	181
Yes	126 (44.7)	282
Asthma in family (p = 0.08)		
No	98 (36.4)	269
Yes	78 (44.8)	174
SES (p = 0.87)		
Low	31 (42.5)	73
Medium	121 (36.7)	330
High	30 (44.1)	68
Insurance (p = 0.83)		
No	13 (37.1)	35
Yes	169 (38.9)	434
Current wheeze (p = 0.02)		
No	48 (30.8)	156
Yes	129 (42.0)	307
Current ETS (p = 0.66)		
No	135 (38.0)	355
Yes	44 (40.4)	109
Personal smoking (p = 0.07)		
No	161 (37.0)	435
Yes	7 (63.6)	11

Definition of abbreviations: ETS = environmental (secondhand) tobaco smoke; SES = socioeconomic status.

Distribution at year child first contributed to the analyses.

* p Value for χ^2 test of homogeneity.

TABLE 2. VARIABILITY IN THE 4-YEAR AVERAGE AIR POLLUTANT CONCENTRATIONS ACROSS THE 12 COMMUNITIES, AND VARIABILITY IN THE YEARLY DEVIATION FROM THE 4-YEAR MEAN WITHIN EACH OF THE 12 COMMUNITIES

	4-Year Average across 12 Communities*		Range of Yearly Variability within the 12 Communities†	
Pollutant‡	Mean (SD)	Min–Max	Mean (SD)	Min–Max
NO_2	19.4 (11.3)	4.2–38.0	4.9 (4.0)	1.1–12.8
O_3	47.2 (11.3)	28.3–65.8	5.3 (3.2)	1.7–13.2
PM_{10}	30.8 (13.4)	15.7–63.5	7.0 (3.9)	2.3–14.7
$PM_{2.5}$	13.8 (7.7)	5.5–28.5	3.9 (2.8)	0.9–8.7
$PM_{10-2.5}$	17.0 (6.4)	10.2–35.0	4.2 (2.2)	1.3–9.7
Inorganic acid	2.7 (1.3)	0.7–4.7	0.58 (0.42)	0.1–1.4
Organic acid	4.4 (2.2)	1.0–7.4	0.83 (0.57)	0.3–2.1
EC	0.71 (0.41)	0.1–1.2	0.32 (0.19)	0.1–0.7
OC	4.5 (2.7)	1.4–11.6	1.5 (0.76)	0.5–2.3

Definition of abbreviations: EC = elemental carbon; NO_2 = nitrogen dioxide; O_3 = ozone; OC= organic carbon; $PM_{2.5}$ = particulate mass less than 2.5 μm in diameter; PM_{10} = particulate mass less than 10 μm in diameter; $PM_{10-2.5}$ = particulate mass between 10 and 2.5 μm in diameter.

* Mean and SD of the 4-year average across the 12 communities.

† Mean and SD of the range of the deviation from the 4-year mean within each of the 12 communities; min, max are the ranges in the communities with the smallest and largest range of deviation from the mean.

‡ NO_2, O_3, acid in ppb; PM, EC, and OC in μg/m^3.

($X_{cj} - \bar{X}_c$ in the hierarchic model described previously) were small. For OC, for example, the within-community range was only 0.5 μg/m^3 in the community with the least variability, and this would not have contributed substantially to the observed within-community risk of symptoms. Even in the community with the largest yearly deviations from the 4-year mean, the range was modest (2.3 μg/m^3), compared with the large between-community variability (1.4–11.6 μg/m^3).

The correlation of 4-year average pollution across the 12 communities was low for O_3 with each of the other pollutants (*see* Table E1 in the online supplement). Most other pollutants were relatively highly correlated with each other ($R > 0.65$).

The within-community pattern of correlations was somewhat different than between-communities (Table 3). Yearly variation in O_3 was, in general, more highly correlated with PM and with its constituents. However, NO_2 could be distinguished from most other pollutants, except OC and inorganic acid. OC was not as highly correlated with other PM constituents, although the correlation with $PM_{2.5}$ remained strong. OC also was highly correlated with EC and inorganic acid. $PM_{10-2.5}$ was, in general, only modestly correlated with other pollutants.

The odds ratio (OR) of bronchitic symptoms among children with asthma varied from 0.80 (for O_3) to 1.81 (for $PM_{2.5}$) across the large range of pollutants between communities (Table 4). All associations with PM were of similar magnitude, except $PM_{10-2.5}$ (OR 1.38), and ORs were greater than 1.0 for all pollutants except for O_3. Associations were significant ($p < 0.05$) for $PM_{2.5}$ and EC, and for NO_2. Because the yearly variability of pollutants within communities varied by community and was small in some communities, the ORs for within-community effects were arbitrarily expressed as μg/m^3 (or ppb). Within communities, all pollutants were positively associated with symptoms. The ORs for PM within-community effects were significant for $PM_{2.5}$ ($p < 0.05$) and OC ($p < 0.01$). Significant associations were also observed for NO_2 ($p < 0\ 0.01$) and for O_3 ($p < 0.05$). It is possible to compare the size of the effect observed between communities for each pollutant with that observed within communities by examining each effect expressed per unit of each pollutant. The within-community effects were, in general, considerably larger than the between-community effects, especially for OC. Comparisons between pollutants of within-community effects is not appropriate. EC, for example, appears to have the largest within-community OR, but this reflects the relatively narrow range (in μg/m^3) within any community.

Potential confounding of these associations by history of allergy, family history of asthma, *in utero* tobacco smoke exposure, socioeconomic status, and membership in a health insurance plan were examined. The effect estimates for the 4-year average exposures did not change appreciably in models adjusting for any of these covariates (within-community associations cannot be confounded by any time-fixed personal covariates).

The effect of yearly variation in NO_2 was modified by participation in team sports (p value for interaction 0.02). The observed effect of NO_2 was due entirely to the effect among children playing team sports at study entry (OR 1.11, 95% confidence interval 1.05–1.18, compared with 0.99 and 0.91–1.08, respectively, among children not playing team sports). There were no other significant interactions of either within- or between-community pollutant effects with sports or time spent outside (results not shown).

In two pollutant models, the within-community effect estimates for $PM_{2.5}$ and OC, and for NO_2, were significant in the presence of several other pollutants (Table 5). The single-pollutant effect of $PM_{2.5}$ ($\beta = 0.085$/μg/m^3) was only modestly attenuated by other pollutants and remained significant after adjusting

TABLE 3. PEARSON CORRELATION COEFFICIENTS OF YEARLY DEVIATION OF AIR POLLUTANTS FROM 4-YEAR MEAN WITHIN COMMUNITIES (n = 48)

	NO_2	O_3	PM_{10}	$PM_{2.5}$	$PM_{10-2.5}$	Inorganic Acid	Organic Acid	EC	OC
NO_2	1								
O_3	0.59*	1							
PM_{10}	0.20	0.64*	1						
$PM_{2.5}$	0.54*	0.72*	0.79*	1					
$PM_{10-2.5}$	−0.22	0.29†	0.79*	0.24	1				
Inorganic acid	0.65*	0.73*	0.72*	0.76*	0.38*	1			
Organic acid	0.48*	0.69*	0.59*	0.58*	0.35†	0.69*	1		
EC	0.54*	0.68*	0.71*	0.83*	0.30†	0.82*	0.66*	1	
OC	0.67*	0.81*	0.70*	0.84*	0.27	0.83*	0.69*	0.88*	1

Definition of abbreviations: EC = elemental carbon; NO_2 = nitrogen dioxide; O_3 = ozone; OC= organic carbon; $PM_{2.5}$ = particulate mass less than 2.5 μm in diameter; PM_{10} = particulate mass less than 10 μm in diameter; $PM_{10-2.5}$ = particulate mass between 10 and 2.5 μm in diameter.

* $p < 0.01$.

† $p < 0.05$.

for $PM_{10-2.5}$, inorganic or organic acid. The effect of OC (β = 0.345/μg/m^3) remained significant, except after adjusting for $PM_{2.5}$ (which reduced the estimate modestly to 0.335/μg/m^3; p = 0.08) or NO_2 (which reduced the effect to 0.237/μg/m^3; p = 0.11). The effect of NO_2 (β = 0.071/ppb) was reduced and was no longer significant after adjusting for O_3 (to 0.057/ppb; p = 0.05) or $PM_{2.5}$ (to 0.054; p = 0.07) and was markedly reduced after adjusting for OC (to β = 0.039; p = 0.22). The effects of $PM_{2.5}$ and of O_3 were markedly reduced after adjusting for NO_2 or OC and were no longer significant after adjusting for most other pollutants. After adjusting for OC, the effect estimates for some highly correlated pollutants became negative (for EC, organic acid, and inorganic acid, for which the negative effect estimate was significant; p = 0.03). The ORs associated with the within-community variability in OC and NO_2, which were fairly consistently significant in models adjusting for other pollutants, are shown graphically in Figure E1 in the online supplement.

The between-community effect estimates for the pollutants examined were, in general, not significant in the presence of other pollutants in two-pollutant models (*see* Table E2 in the online supplement).

DISCUSSION

In summary, among children with asthma there were associations of bronchitic symptoms with yearly within-community variability in particulate $PM_{2.5}$ and OC, and gaseous NO_2 and O_3. Across communities, symptoms were associated with the 4-year average concentrations of $PM_{2.5}$ and EC, and of gaseous NO_2. The within-community associations were stronger in magnitude (and, in most cases, in significance) than the between-community associations, and in two-pollutant models there were no consistently significant between-community effects. In contrast, the associations of symptoms with the yearly variability of OC and NO_2 were, in general, not confounded by other pollutants, and no other pollutants were significantly associated with an increase in symptoms in models that included OC or NO_2. In addition, playing team sports modified the effect of yearly variability in

TABLE 4. BRONCHITIC SYMPTOMS AS A FUNCTION OF THE 4-YEAR AVERAGE AIR POLLUTANT CONCENTRATIONS (BETWEEN COMMUNITIES) AND AS A FUNCTION OF THE DIFFERENCE BETWEEN ANNUAL AIR POLLUTANT CONCENTRATION AND 4-YEAR AVERAGE CONCENTRATIONS (WITHIN COMMUNITIES) AMONG CHILDREN WITH ASTHMA

	Between Community		Within Community
Pollutant*	OR†/Range* (95% CI)	OR†/Unit* (95% CI)	OR†/Unit* (95% CI)
NO_2	1.77 (1.11–2.81)‡	1.02 (1.00–1.03)‡	1.07 (1.02–1.13)§
O_3	0.80 (0.42–1.54)	0.99 (0.98–1.01)	1.06 (1.00–1.12)‡
PM_{10}	1.72 (0.93–3.20)	1.01 (1.00–1.02)	1.04 (0.99–1.10)
$PM_{2.5}$	1.81 (1.14–2.88)‡	1.03 (1.01–1.05)‡	1.09 (1.01–1.17)‡
$PM_{10-2.5}$	1.38 (0.65–2.92)	1.01 (0.98–1.04)	1.02 (0.95–1.10)
Inorganic acid	1.46 (0.88–2.44)	1.10 (0.97–1.26)	1.20 (0.70–2.06)
Organic acid	1.55 (0.94–2.55)	1.07 (0.99–1.16)	1.19 (0.83–1.70)
EC	1.64 (1.06–2.54)‡	1.55 (1.05–2.30)‡	2.63 (0.83–8.33)
OC	1.74 (0.89–3.40)	1.06 (0.99–1.13)	1.41 (1.12–1.78)§

Definition of abbreviations: CI = confidence interval; EC = elemental carbon; NO_2 = nitrogen dioxide; O_3 = ozone; OC= organic carbon; OR = odds ratio; $PM_{2.5}$ = particulate mass less than 2.5 μm in diameter; PM_{10} = particulate mass less than 10 μm in diameter; $PM_{10-2.5}$ = particulate mass between 10 and 2.5 μm in diameter.

* Between-community ORs are for the range across the 12 communities (33.8, 37.5, 4.0, and 6.4 ppb for NO_2, O_3, and inorganic and organic acid, respectively; and 47.8, 23.0, 24.8, 1.1, and 10.2 μg/m^3 for PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, EC, and OC, respectively). Between-community ORs are also per unit of pollutant (ppb or μg/m^3) for comparison with the within-community OR.

† OR adjusted for age, maternal and child's smoking history, sex, and race; within-community estimates were adjusted for between-community effects of the pollutant, and vice versa.

‡ $p < 0.05$.

§ $p < 0.01$.

TABLE 5. TWO-POLLUTANT MODELS OF WITHIN-COMMUNITY EFFECTS (DIFFERENCE BETWEEN ANNUAL AIR POLLUTANT CONCENTRATION AND 4-YEAR AVERAGE CONCENTRATIONS; n = 48) AMONG CHILDREN WITH ASTHMA

	Adjustment Pollutants								
Main Pollutant	NO_2	O_3	PM_{10}	$PM_{2.5}$	$PM_{10-2.5}$	Inorganic Acid	Organic Acid	EC	OC
NO_2	**0.071***	0.057	0.065†	0.054	0.079*	0.085*	0.071†	0.062†	0.039
O_3	0.028	**0.055**†	**0.039**	**0.029**	**0.054**†	**0.067**	**0.065**	**0.043**	**−0.003**
PM_{10}	0.034	0.026	**0.044**	0.010	0.080†	0.056	0.043	0.033	−0.011
$PM_{2.5}$	0.046	0.062	0.070	**0.085**†	0.080†	0.117†	0.091†	0.084	0.003
$PM_{10-2.5}$	0.046	0.005	−0.070	0.010	**0.023**	0.019	0.017	0.013	−0.013
Inorganic Acid	−0.295	−0.180	−0.221	−0.333	0.110	**0.182**	−0.035	−0.299	−0.876†
Organic Acid	−0.025	−0.080	0.019	−0.048	0.150	0.180	**0.171**	−0.012	−0.253
EC	0.350	0.507	0.503	0.010	0.919	1.463	0.995	**0.966**	−1.307
OC	0.237	0.356†	0.380†	0.335	0.356*	0.653*	0.479*	0.585*	**0.345***

Definition of abbreviations: CI = confidence interval; EC = elemental carbon; NO_2 = nitrogen dioxide; O_3 = ozone; OC= organic carbon; $PM_{2.5}$ = particulate mass less than 2.5 μm in diameter; PM_{10} = particulate mass less than 10 μm in diameter; $PM_{10-2.5}$ = particulate mass between 10 and 2.5 μm in diameter.

Each row gives estimates (β) for the indicated pollutant, adjusted for age, maternal and child's smoking history, sex, and race, the within-community effect of that pollutant and for both the between- and within-community effect of the adjustment pollutant listed at the top of each column. The estimate for each pollutant in a single pollutant model is presented along the diagonal (in bold). Estimates are expressed per ppb for NO_2, O_3, acid; per μg/m^3 for PM, EC, and OC.

* $p < 0.01$.

† $p < 0.05$.

NO_2, which affected only children playing team sports. These results suggest that both NO_2 and the OC fraction of respirable PM deserve greater attention as potential causes of the bronchitic symptoms associated with air pollution in children with asthma.

Particulate air pollution has been associated with both acute and chronic exacerbation of childhood asthma. More chronic symptoms of bronchitis have been observed in previous cross-sectional studies of children with asthma exposed to PM (1–6). Time series and panel studies have shown acute increases in ambient PM to be associated with increases in emergency room visits (19) and hospital admissions for asthma (20, 21), acute symptoms (22–26) and medication use (22, 24), and with decline in PEF rates (22, 23, 25). However, there has been little previous investigation of the relative effect of fine ($PM_{2.5}$) and coarse ($PM_{10-2.5}$) PM, or of the components of PM that may be responsible for acute and chronic asthma exacerbation in children.

In our study, only $PM_{2.5}$ (of the particulate measurements) was associated with bronchitic symptoms both for the 4-year average and for the yearly variation in concentration. In addition, the yearly variability of $PM_{2.5}$ was relatively robust in two-pollutant models. There were no significant associations of symptoms with $PM_{10-2.5}$. Yearly variabilities in particulate OC within communities and in EC variability across communities were associated with symptoms. However, the effect of yearly variation in OC persisted in two-pollutant models with other pollutants. In addition, a distinct advantage of the within-community contrast is that there could be no confounding by unmeasured differences between communities, a generic limitation to ecologic comparisons across communities. Because we examined the within-person change in symptoms over time (for which a paired comparison would be the simplest example), there could be no confounding by individual or community level risk factors that were unlikely to change over the course of the study, for example by atopy, socioeconomic, or other social factors, which may be associated with symptoms among children with asthma and may not have been well measured in this study.

We measured PM_{10} OC. However, because there was no effect of $PM_{10-2.5}$, and OC accounts for almost half of $PM_{2.5}$ mass in the Los Angeles air basin (8), it is possible that the association observed for yearly variability in $PM_{2.5}$ (which disappeared after adjusting for OC) was due to OC. OC is largely due to emissions from gasoline and diesel vehicle exhaust in Southern California (27). Other primary sources, including wood combustion, charbroiling of meat, and natural gas combustion, as well as vegetative detritus or tire wear debris also contribute to OC. Formation of secondary organic aerosols from gaseous emissions of volatile organic compounds also contribute to ambient concentration, especially in inland sites in the air basin (28–30).

There has been relatively little human experimental or epidemiologic study of the effects of organic compounds in ambient PM. However, OC has been shown to be biologically active in pathways relevant for asthma exacerbation. In a study in Los Angeles, the OC and polycyclic aromatic hydrocarbon content of fine concentrated particles were shown to elicit oxidative stress responses in several experimental biological systems, and fine particulate was more active than coarse particulate (8). Because an important emission source of ambient particulate OC is diesel exhaust, and the responses to ambient particulate were similar to those of diesel exhaustive particulate, the investigators speculated that diesel is responsible for the biologic activity of OC in ambient air. Diesel exhaust particulate enhances allergen-induced Th2-type (allergic) responses in animal models and in human volunteers with allergy, and common indoor and outdoor allergens have been shown to bind specifically to diesel particles (9). In addition, diesel exhaust particles may have direct toxic effects, resulting in an inflammatory response observed in bronchoalveolar lavage and in sputum. The organic extract of diesel exhaust particulate has been demonstrated to be the biologically active fraction in *in vitro* studies (31, 32). This organic fraction contains polycyclic aromatic hydrocarbons, halogenated aromatic hydrocarbons, and quinones, including reactive oxygen species that produce a strong oxidative stress response (32, 33).

Although there is toxicologic evidence for a role for diesel exhaust in effects of OC, the symptom associations with yearly variation in EC were not significant in our study, and EC is also a marker for diesel exhaust in Southern California (34). It is possible that the robust effects of OC were related to secondary organic aerosol formed in inland locations from distant diesel or other primary sources, or to other sources of OC, for example smaller pollen grains or fungal spores or fragments, which have been associated with acute asthma exacerbation in children (35, 36).

The effect of NO_2 on respiratory illness has been extensively studied in epidemiologic studies of exposure from indoor sources, and the observed associations have not been consistent

(37–40). Therefore, it was somewhat unexpected that the most consistent associations with symptoms in our study were for NO_2. Effects were observed both for the 4-year average concentration and for the yearly variation. In addition, playing team sports, which might be expected to increase ventilation rate and, therefore, the dose of pollutant to the lung (41), increased the effect of the yearly variation in NO_2. Unfortunately, most previous studies of air pollution and bronchitis have not examined the effect of NO_2 (1–3, 6), although our results are consistent with a cross-sectional evaluation of bronchitis in children with asthma in this cohort at study entry (5) and in a study of children in Dresden, Germany (42). In a study of Swiss school children, symptoms were associated both with PM_{10} and NO_2, but associations with NO_2 were not statistically significant (4). A plausible mechanism for an effect of NO_2 is the impairment of respiratory response to infection observed in toxicologic, and in limited clinical studies, which could result in increased reporting of bronchitic symptoms (39). In communities with air pollution, especially NO_2, more persistent respiratory symptoms have been reported among children with asthma with viral infections (43).

The within-community variability of OC was relatively strongly correlated with NO_2 (Table 3). This may explain the weaker associations with bronchitic symptoms in children with asthma in the two-pollutant model with OC and NO_2. Although the robust effects in two-pollutant models suggest that OC and/or NO_2 may have been responsible for the associations of air pollution with bronchitic symptoms, inorganic acid and EC were positively associated with symptoms in single-pollutant models but were protective in two-pollutant models with OC (significantly so in the case of inorganic acid; *see* Table 5). These results may reflect the strong correlation of OC with inorganic acid and EC and make the results of these two-pollutant models difficult to interpret. Furthermore, if there was less error in the measurement of OC or NO_2 than of other pollutants highly correlated with these two pollutants, it is possible that the more robust associations with bronchitis could be an artifact of better measurement of these surrogates for a pollutant that was really responsible for the effect. Therefore, a causal role for other pollutants cannot be excluded.

The within-community ORs for the effect of pollution were, in general, considerably larger than the between-community effects (Table 4). If the within-community estimates of effects are correct, then other cross-sectional (between-community) studies in the literature may have underestimated the true effect of air pollution on bronchitic symptoms in children. One explanation for these differences is confounding by poorly measured or unmeasured risk factors that varied between communities. These would tend to reduce the observed effect of pollution in between-community comparisons. As discussed previously, in the within-community analysis there could be no confounding by individual or community risk factors that did not change over the course of the study.

Possible, but less likely, alternative explanations for the larger within-community effects include within-community confounding by yearly changes in infectious respiratory illnesses or other unmeasured risk factors such as indoor allergens, ambient pollen, or mold that might have covaried with air pollutants from year-to-year. The effect of personal smoking and secondhand tobacco smoke exposure, which may have varied over the time of the study, was assessed by questionnaires, and was controlled in the analysis. It is also possible that the between-community effect could have been biased downward if the variances of the random effects were functions of subject-level covariates. This is an observation that has been discussed by Heagerty and Zeger (44). In our sensitivity analyses, we found that the between-community effects in purely marginal models such as those based on the generalized estimating equations approach gave virtually identical results. This gives further assurance that the relatively lower between-community effects, compared with the within-community effects, were not due to incorrect modeling assumptions. Finally, the within-community effects were not likely to be due to any artifactual relationship between observed temporal trends in air pollution levels during this period and a possible downward trend in symptoms. Our models included a random effect for year to account for such a possibility.

Limitations to this study include the relatively imprecise assessment of outcomes based on symptom reporting. However, these outcomes have been widely used in epidemiologic studies of children. Cough of 3 or more months duration, chronic phlegm, and a report of bronchitis in this study are suggestive of chronic, indolent asthma exacerbation, which would likely be remembered well. Symptoms reporting might also reflect repeated acute exacerbation, but acute bronchitis has been reported to have a marked impact on the quality of life, at least in adults, and to persist for several weeks, so such episodes also would be likely to be remembered well (45). In additional analyses (not presented), there were no significant positive associations between pollutants and bronchitic symptoms among children without asthma. Therefore, false-positive misclassification of asthma might have resulted in an underestimation of the effect of air pollution, given that individuals with asthma were more sensitive than individuals without asthma. The misclassification of personal exposure based on community monitors may also have resulted in some underestimation of a true association. Because the range of yearly variability in pollution within communities was small, another threat to the validity of the study is that measurement error could have biased the observed effects. Random measurement error would have been likely to result in underestimation of the true effect of pollution. For a systematic error, for example an upward shift in the measurement of OC or NO_2 in one or more years, to explain the large within-community effects of pollution, the error would have had to occur in years that symptoms also increased. However, a systematic error in measurement from year to year would not have explained the consistency of the within- and between-community effects of NO_2, nor would systematic error explain the NO_2 effect modification by team sports in the direction expected. In addition, the rigorous quality control of measurements at the air monitoring stations established for this study make such an explanation unlikely (46). Finally, reporting bias is an unlikely explanation for the observed within-community associations, both because children were not aware of the specific focus of the study on air pollution and because they were unlikely to have been aware of whether air quality within any community was better or worse in different years.

There are several public health implications of these results. We have previously observed that team sports and time spent outside modify the effect of air pollution on several respiratory outcomes in children (13, 47, 48). These results suggest that regulatory standards should be stringent enough to protect exercising children from the increased dose of pollution to the lung associated with outside physical activity. In addition, previous cross-sectional studies of chronic symptoms may have underestimated the effect of pollutants, if the true effects are reflected by the much larger within-community estimates observed in this study. Furthermore, the yearly variability in bronchitic symptoms in association with changes in air pollution provides indirect evidence that even modest reductions in air pollution could result in improved respiratory health in children. Few studies have evaluated the reduction in chronic symptoms that might be expected from a reduction of air pollution. In the former East Germany, a within-community reduction in total suspended par-

ticulates of between 10 and 20 $\mu g/m^3$ was associated with a 20% reduction of total bronchitis prevalence (1). Although the sources of particulate pollution were different in Germany, that study, and the many studies showing variations in acute symptoms with short-term changes in air pollution, provide supportive evidence that major reductions in bronchitis and corresponding improvement in impaired quality of life associated with symptoms of bronchitis could be anticipated from reductions in air pollution in Southern California. Finally, because the effect of particulate air pollution appears to be largely attributable to the OC fraction, additional research efforts are warranted to examine the effect of this fraction on bronchitis and other outcomes. Efforts to identify specific organic compounds in PM, and the sources of these constituents, might result in better approaches to intervention.

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