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The document was submitted by:

Andrea M. Hricko
Assoc Prof Prev Med
Keck School of Med &
Director, Community Outreach and Education
Southern CA Env Health Sciences Ctr
1540 Alcazar Street CHP 236
L.A. CA 90033
323-442-3077

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The Effect of Air Pollution on Lung Development from 10 to 18 Years of Age

W. James Gauderman, Ph.D., Edward Avol, M.S., Frank Gilliland, M.D., Ph.D., Hita Vora, M.S., Duncan Thomas, Ph.D., Kiros Berhane, Ph.D., Rob McConnell, M.D., Nino Kuenzli, M.D., Fred Lurmann, M.S., Edward Rappaport, M.S., Helene Margolis, Ph.D., David Bates, M.D., and John Peters, M.D.

ABSTRACT

BACKGROUND

Whether exposure to air pollution adversely affects the growth of lung function during the period of rapid lung development that occurs between the ages of 10 and 18 years is unknown.

METHODS

In this prospective study, we recruited 1759 children (average age, 10 years) from schools in 12 southern California communities and measured lung function annually for eight years. The rate of attrition was approximately 10 percent per year. The communities represented a wide range of ambient exposures to ozone, acid vapor, nitrogen dioxide, and particulate matter. Linear regression was used to examine the relationship of air pollution to the forced expiratory volume in one second (FEV_1) and other spirometric measures.

RESULTS

Over the eight-year period, deficits in the growth of FEV_1 were associated with exposure to nitrogen dioxide (P=0.005), acid vapor (P=0.004), particulate matter with an aerodynamic diameter of less than 2.5 μm ($PM_{2.5}$) (P=0.04), and elemental carbon (P=0.007), even after adjustment for several potential confounders and effect modifiers. Associations were also observed for other spirometric measures. Exposure to pollutants was associated with clinically and statistically significant deficits in the FEV_1 attained at the age of 18 years. For example, the estimated proportion of 18-year-old subjects with a low FEV_1 (defined as a ratio of observed to expected FEV_1 of less than 80 percent) was 4.9 times as great at the highest level of exposure to $PM_{2.5}$ as at the lowest level of exposure (7.9 percent vs. 1.6 percent, P=0.002).

CONCLUSIONS

The results of this study indicate that current levels of air pollution have chronic, adverse effects on lung development in children from the age of 10 to 18 years, leading to clinically significant deficits in attained FEV_1 as children reach adulthood.

From the Department of Preventive Medicine, University of Southern California, Los Angeles (W.J.G., E.A., F.G., H.V., D.T., K.B., R.M., N.K., E.R., J.P.); Sonoma Technology, Petaluma, Calif. (F.L.); Air Resources Board, State of California, Sacramento (H.M.); and the University of British Columbia, Vancouver, B.C., Canada (D.B.). Address reprint requests to Dr. Gauderman at the Department of Preventive Medicine, University of Southern California, 1540 Alcazar St., Suite 220, Los Angeles, CA 90089, or at jimg@usc.edu.

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There is mounting evidence that air pollution has chronic, adverse effects on pulmonary development in children. Longitudinal studies conducted in Europe[1-3] and the United States[4-6] have demonstrated that exposure to air pollution is associated with reductions in the growth of lung function, strengthening earlier evidence[7-12] based on cross-sectional data. However, previous longitudinal studies have followed young children for relatively short periods (two to four years), leaving unresolved the question of whether the effects of air pollution persist from adolescence into adulthood. The Children's Health Study[13] enrolled children from 12 southern California communities representing a wide range of exposures to ambient air pollution. We documented the children's respiratory growth from the ages of 10 to 18 years. Over this eight-year period, children have substantial increases in lung function. By the age of 18 years, girls' lungs have nearly matured, and the growth in lung function in boys has slowed considerably, as compared with the rate in earlier adolescence.[14] We analyzed the association between long-term exposure to ambient air pollution and the growth in lung function over the eight-year period from the ages of 10 to 18 years. We also examined whether any observed effect of air pollution on this eight-year growth period results in clinically significant deficits in attained lung function at the age of 18 years.

METHODS

STUDY SUBJECTS

In 1993, the Children's Health Study recruited 1759 fourth-grade children (average age, 10 years) from elementary schools in 12 southern California communities as part of an investigation of the long-term effects of air pollution on children's respiratory health.[6,12,13] Data on pulmonary function were obtained by trained field technicians, who traveled to study schools annually from the spring of 1993 through the spring of 2001 to perform maximal-effort spirometric testing of the children. Details of the testing protocol have been published previously.[12] We analyzed three measures of pulmonary function: forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), and maximal midexpiratory flow rate (MMEF). Pulmonary-function tests were not performed on any child who was absent from school on the day of testing, but such a child was still eligible for testing in subsequent years. Children who moved away from their recruitment community were classified as lost to follow-up and were not tested further. From the initial sample of the 1759 children in 1993, the number of children available for follow-up was 1414 in 1995, 1252 in 1997, 1031 in 1999, and 747 in 2001, reflecting the attrition of approximately 10 percent of subjects per year.

A baseline questionnaire, completed at study entry by each child's parents or legal guardian, was used to obtain information on the children's characteristics, including race, presence or absence of Hispanic ethnic background, level of parental education, presence or absence of a history of asthma diagnosed by a doctor, exposure to maternal smoking in utero, and household exposure to gas stoves, pets, and environmental tobacco smoke. Questions administered at the time of annual pulmonary-function testing were used to update information on asthma status, personal smoking status, and exposure to environmental tobacco smoke. The distribution of baseline characteristics of all study subjects and of two subgroups defined according to the length of follow-up (all eight years or less than eight years) is shown in the Supplementary Appendix (available with the full text of this article at www.nejm.org). The length of follow-up was significantly associated with factors related to the mobility of the population, including race, presence or absence of Hispanic ethnic background, presence or absence of exposure to environmental tobacco smoke, and parents' level of education. However, the length of follow-up was not significantly associated with baseline lung function or the level of exposure to air pollution, suggesting that the loss to follow-up did not differ with respect to the primary variables of interest.

The study protocol was approved by the institutional review board for human studies at the University of Southern California, and written informed consent was provided by a parent or legal guardian for all study subjects. We did not obtain assent from minor children, since this was not standard practice when the study was initiated.

AIR-POLLUTION DATA

Air-pollution–monitoring stations were established in each of the 12 study communities and provided continuous data, beginning in 1994. Each station measured average hourly levels of ozone, nitrogen

dioxide, and particulate matter with an aerodynamic diameter of less than 10 μm (PM_{10}). Stations also collected two-week integrated-filter samples for measuring acid vapor and the mass and chemical makeup of particulate matter with an aerodynamic diameter of less than 2.5 μm ($PM_{2.5}$). Acid vapor included both inorganic acids (nitric and hydrochloric) and organic acids (formic and acetic). For statistical analysis, we used total acid, computed as the sum of nitric, formic, and acetic acid levels. Hydrochloric acid was excluded from this sum, since levels were very low and close to the limit of detection. In addition to measuring $PM_{2.5}$, we determined the levels of elemental carbon and organic carbon, using method 5040 of the National Institute for Occupational Safety and Health.[15] We computed annual averages on the basis of average levels in a 24-hour period in the case of PM_{10} and nitrogen dioxide, and a two-week period in the case of $PM_{2.5}$, elemental carbon, organic carbon, and acid vapor. For ozone, we computed the annual average of the levels obtained from 10 a.m. to 6 p.m. (the eight-hour daytime average) and of the one-hour maximal levels. We also calculated long-term mean pollutant levels (from 1994 through 2000) for use in the statistical analysis of the lung-function outcomes.

STATISTICAL ANALYSIS

The outcome data consisted of the results of 5454 pulmonary-function tests of 876 girls and 5300 tests of 883 boys over the eight-year period. We adopted a two-stage regression approach to relate the longitudinal pulmonary-function data for each child to the average air-pollution levels in each study community.

The first-stage model was a regression of each pulmonary-function measure (values were log-transformed) on age to obtain separate, community-specific average growth curves for girls and boys. To account for the growth pattern during this period, we used a linear spline model[14] that consisted of four straight lines over the age intervals of younger than 12 years, 12 to 14 years, 14 to 16 years, and older than 16 years, constrained to be connected at the three "knot" points. The model included adjustments for log values for height; body-mass index (the weight in kilograms divided by the square of the height in meters); the square of the body-mass index; race; the presence or absence of Hispanic ethnic background, doctor-diagnosed asthma, any tobacco smoking by the child in the preceding year, exposure to environmental tobacco smoke, and exercise or respiratory tract illness on the day of the test; and indicator variables for the field technician and the spirometer. In addition to these covariates, random effects were included to account for the multiple measurements contributed by each subject. An analysis of residual values confirmed that the assumptions of the model had been satisfied. The first-stage model was used to estimate the mean and variance of the growth in lung function over the eight-year period in each of the 12 communities, separately for girls and boys.

The second-stage model was a linear regression of the 24 sex- and community-specific estimates of the growth in lung function over the eight-year period on the corresponding average levels of each air pollutant in each community. Inverses of the first-stage variances were incorporated as weights, and a community-specific random effect was included to account for residual variation between communities. A sex-by-pollutant interaction was included in the model to evaluate whether there was a difference in the effect of a given pollutant between the sexes, and when this value was nonsignificant, the model was refitted to estimate the sex-averaged effect of the pollutant. Pollutant effects are reported as the difference in the growth in lung function over the eight-year period from the least to the most polluted community, with negative differences indicative of growth deficits with increasing exposure. We also considered two-pollutant models obtained by simultaneously regressing the growth in lung function over the eight-year period on pairs of pollutants.

In addition to examining the growth in lung function over the eight-year period, we analyzed the FEV_1 measurements obtained in 746 subjects during the last year of follow-up (average age, 17.9 years) to determine whether exposure to air pollution was associated with clinically significant deficits in attained FEV_1. We defined a low FEV_1 as an attained FEV_1 below 80 percent of the predicted value, a criterion commonly used in clinical settings to identify persons who are at increased risk for adverse respiratory conditions. To determine the predicted FEV_1, we first fitted a regression model for observed FEV_1 (using log-transformed values) with the following predictors: log-transformed height, body-mass index, the square of the body-mass index, sex, race or ethnic group, asthma status, field technician, and interactions between sex and log-transformed height, sex and asthma, and sex and

race or ethnic group. This model explained 71 percent of the variance in the attained FEV_1 level. For each subject, we then computed the predicted FEV_1 from the model and considered subjects to have a low FEV_1 if the ratio of observed to predicted FEV_1 was less than 80 percent. Linear regression was then used to examine the correlation between the community-specific proportion of subjects with a low FEV_1 and the average level of each pollutant from 1994 through 2000. This model included a community-specific random effect to account for residual variation. Regression procedures in SAS software[16] were used to fit all models. Associations denoted as statistically significant were those that yielded a P value of less than 0.05, assuming a two-sided alternative hypothesis.

RESULTS

From 1994 through 2000, there was substantial variation in the average levels of study pollutants across the 12 communities, with relatively little year-to-year variation in the annual levels within each community (Fig. 1). From 1994 through 2000, the

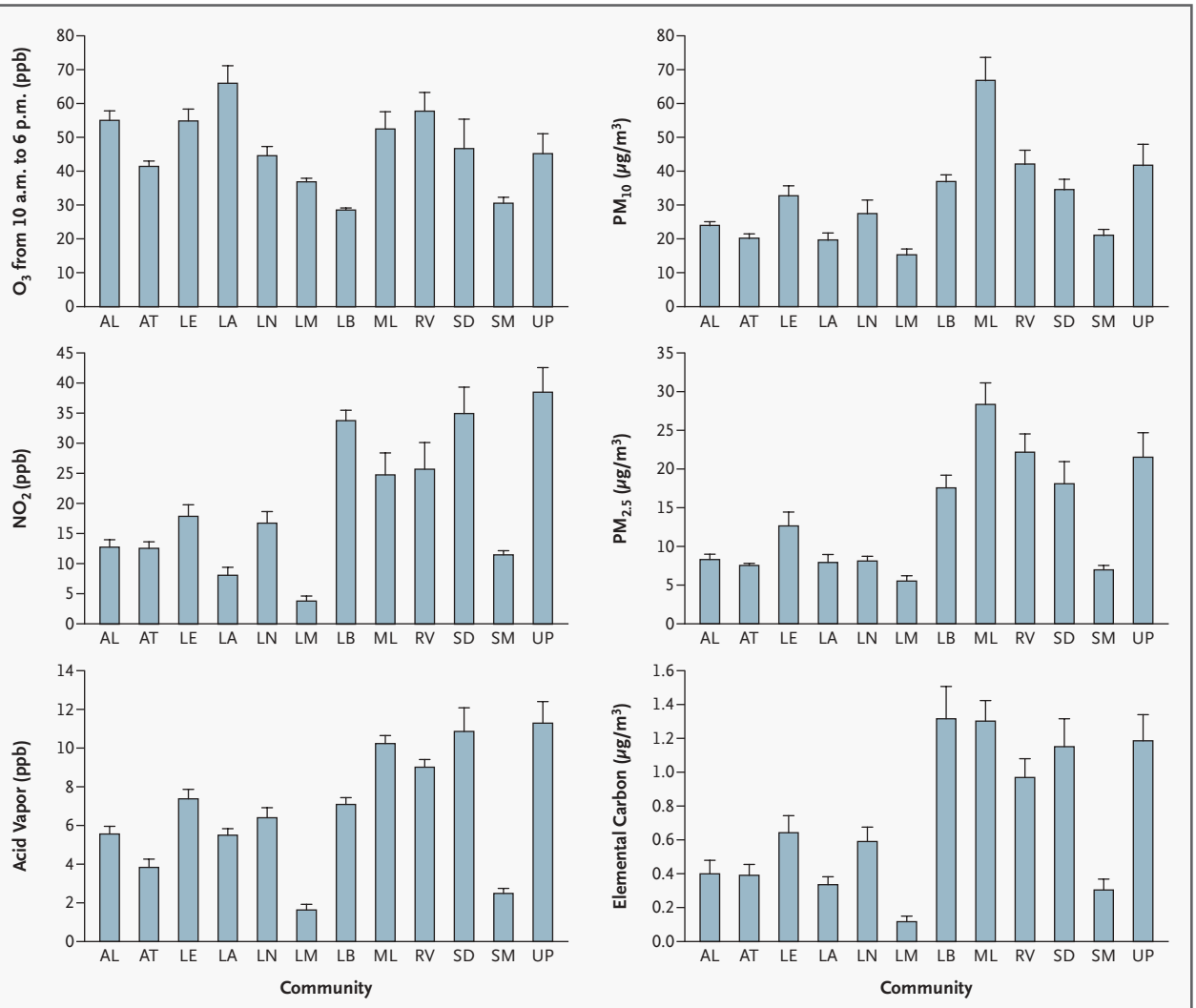

Figure 1. Mean (+SD) Annual Average Levels of Pollutants from 1994 through 2000 in the 12 Study Communities in Southern California.

AL denotes Alpine, AT Atascadero, LE Lake Elsinore, LA Lake Arrowhead, LN Lancaster, LM Lompoc, LB Long Beach, ML Mira Loma, RV Riverside, SD San Dimas, SM Santa Maria, and UP Upland. O_3 denotes ozone, NO_2 nitrogen dioxide, and PM_{10} and $PM_{2.5}$ particulate matter with an aerodynamic diameter of less than 10 μm and less than 2.5 μm, respectively.

average levels of ozone were not significantly correlated across communities with any other study pollutant (Table 1). However, correlations between other pairs of pollutants were all significant, ranging from an R of 0.64 (P<0.05) for nitrogen dioxide and organic carbon, to an R of 0.97 (P<0.001) for PM_{10} and organic carbon. Thus, nitrogen dioxide, acid vapor, and the particulate-matter pollutants can be regarded as a correlated "package" of pollutants with a similar pattern relative to each other across the 12 communities.

Among the girls, the average FEV_1 increased from 1988 ml at the age of 10 years to 3332 ml at the age of 18 years, yielding an average growth in FEV_1 of 1344 ml over the eight-year period (Table 2). The corresponding averages in boys were 2082 ml and 4464 ml, yielding an average growth in FEV_1 of 2382 ml over the eight-year period. Similar patterns of growth over the eight-year period were observed for FVC and MMEF (Table 2).

Although the average growth in FEV_1 was larger in boys than in girls, the correlations of growth with air pollution did not differ significantly between the sexes, as shown for nitrogen dioxide in Figure 2. The sex-averaged analysis, depicted by the regression line in Figure 2, demonstrated a significant negative correlation between the growth in FEV_1 over the eight-year period and the average nitrogen dioxide level (P=0.005). The estimated difference in the average growth in FEV_1 over the eight-year period from the community with the lowest nitrogen dioxide level to the community with the highest nitrogen dioxide level, represented by the slope of the plotted regression line in Figure 2, was −101.4 ml.

Estimated differences in the growth of FEV_1, FVC, and MMEF during the eight-year period with respect to all pollutants are summarized in Table 3. Deficits in the growth of FEV_1 and FVC were observed for all pollutants, and deficits in the growth of MMEF were observed for all but ozone, with several combinations of outcome variables and pollutants attaining statistical significance. Specifically, for FEV_1 we observed significant negative correlations between the growth in this variable over the eight-year period and exposure to acid vapor (P=0.004), $PM_{2.5}$ (P=0.04), and elemental carbon (P=0.007), in addition to the above-mentioned correlation with nitrogen dioxide. As with FEV_1, the effects of the various pollutants on FVC and MMEF did not differ significantly between boys and girls. Significant deficits in FVC were associated with exposure to nitrogen dioxide (P=0.05) and acid vapor (P=0.03), whereas deficits in MMEF were associated with exposure to nitrogen dioxide (P=0.02) and elemental carbon (P=0.04). There was no significant evidence that ozone, either the average value obtained from 10 a.m. to 6 p.m. or the one-hour maximal level, was associated with any measure of lung function. In two-pollutant models for any of the measures of pulmonary function, adjustment for ozone did not substantially alter the effect estimates or significance levels of any other pollutant (data not shown). In general, two-pollutant models for any pair of pollutants did not provide a significantly better fit to the data than the corre-

Table 1. Correlation of Mean Air-Pollution Levels from 1994 through 2000 across the 12 Study Communities.*

Pollutant	O_3 (10 a.m.–6 p.m.)	NO_2	Acid Vapor†	PM_{10}	$PM_{2.5}$	Elemental Carbon	Organic Carbon
			R value				
O_3							
1-Hour maximal level	0.98	0.10	0.53	0.31	0.33	0.17	0.25
10 a.m.–6 p.m.		−0.11	0.35	0.18	0.18	−0.03	0.13
NO_2			0.87	0.67	0.79	0.94	0.64
Acid vapor†				0.79	0.87	0.88	0.76
PM_{10}					0.95	0.85	0.97
$PM_{2.5}$						0.91	0.91
Elemental carbon							0.82

* Unless otherwise noted, values are the 24-hour average pollution levels. O_3 denotes ozone, NO_2 nitrogen dioxide, and PM_{10} and $PM_{2.5}$ particulate matter with an aerodynamic diameter of less than 10 μm and less than 2.5 μm, respectively.
† Acid vapor is the sum of nitric, formic, and acetic acid levels.

Table 2. Mean Levels of Growth in Pulmonary Function during the Eight-Year Study Period, from 1993 to 2001.*

Pulmonary-Function Measure	Girls			Boys		
	Age of 10 yr	Age of 18 yr	Average 8-yr growth	Age of 10 yr	Age of 18 yr	Average 8-yr growth
FVC (ml)	2262	3790	1528	2427	5202	2775
FEV_1 (ml)	1988	3332	1344	2082	4464	2382
MMEF (ml/sec)	2311	3739	1428	2287	4709	2422

* Levels at the ages of 10 and 18 years are derived from the growth model described in the Methods section. FVC denotes forced vital capacity, FEV_1 forced expiratory volume in one second, and MMEF maximal midexpiratory flow rate.

sponding single-pollutant models; this was not surprising, given the strong correlation between most pollutants.

The association between pollution and the growth in FEV_1 over the eight-year period remained significant in a variety of sensitivity analyses (Table 4). For example, estimates of the effect of acid vapor and elemental carbon (model 1 in Table 4) changed little with adjustment for in-utero exposure to maternal smoking (model 2), presence in the home of a gas stove (model 3) or pets (model 4), or parental level of education (model 5). To account for possible confounding by short-term effects of air pollution, we fitted a model that adjusted for the average ozone, nitrogen dioxide, and PM_{10} levels on the three days before each child's pulmonary-function test. This adjustment also had little effect on the estimates of the long-term effects of air pollution (model 6). Table 4 also shows that the effects of pollutants remained large and significant in the subgroups of children with no history of asthma (model 7) and those with no history of smoking (model 8). The effects of pollutants were not significant among the 457 children who had a history of asthma or among the 483 children who had ever smoked (data not shown), although the sample sizes in these subgroups were small. Model 9 demonstrates that the extremes in pollutant levels did not drive the observed associations; in other words, we found similar effect estimates after eliminating the two communities with the highest and lowest levels of each pollutant. Finally, model 10 shows the effects of pollutants in the subgroup of subjects who underwent pulmonary-function testing in both 1993 and 2001 (i.e., subjects who participated in both the first and last year of the study). The magnitudes of effects in this subgroup were similar to those in the entire sample (model 1), suggesting that observed effects of pollutants in the entire sample cannot be attributed to biased losses to follow-up across communities. These sensitivity analyses were also applied to the other pollutants and to FVC and MMEF, with similar results.

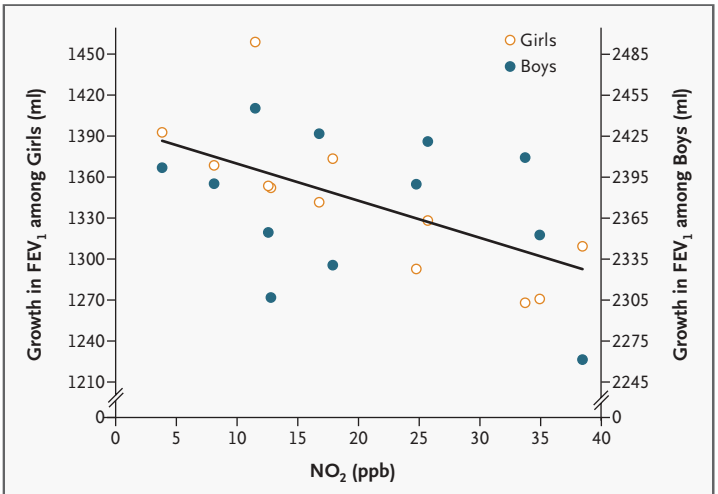

Figure 2. Community-Specific Average Growth in FEV_1 among Girls and Boys During the Eight-Year Period from 1993 to 2001 Plotted against Average Nitrogen Dioxide (NO_2) Levels from 1994 through 2000.

Pollution-related deficits in the average growth in lung function over the eight-year period resulted in clinically important deficits in attained lung function at the age of 18 years (Fig. 3). Across the 12 communities, a clinically low FEV_1 was positively correlated with the level of exposure to nitrogen dioxide ($P=0.005$), acid vapor ($P=0.01$), PM_{10} ($P=0.02$), $PM_{2.5}$ ($P=0.002$), and elemental carbon ($P=0.006$). For example, the estimated proportion of children with a low FEV_1 (represented by the regression line in Fig. 3) was 1.6 percent at the lowest level of exposure to $PM_{2.5}$ and was 4.9 times as great (7.9 percent) at the highest level of exposure to $PM_{2.5}$

Table 3. Difference in Average Growth in Lung Function over the Eight-Year Study Period from the Least to the Most Polluted Community.*

Pollutant	FVC		FEV_1		MMEF	
	Difference (95% CI)	P Value	Difference (95% CI)	P Value	Difference (95% CI)	P Value
	ml		*ml*		*ml/sec*	
O_3						
10 a.m.–6 p.m.	−50.6 (−171.0 to 69.7)	0.37	−22.8 (−122.3 to 76.6)	0.62	85.6 (−130.0 to 301.1)	0.40
1-Hour maximal level	−70.3 (−183.3 to 42.6)	0.20	−44.5 (−138.9 to 50.0)	0.32	45.7 (−172.3 to 263.6)	0.65
NO_2	−95.0 (−189.4 to −0.6)	0.05	−101.4 (−164.5 to −38.4)	0.005	−211.0 (−377.6 to −44.4)	0.02
Acid vapor	−105.2 (−194.5 to −15.9)	0.03	−105.8 (−168.8 to −42.7)	0.004	−165.0 (−344.8 to 14.7)	0.07
PM_{10}	−60.2 (−190.6 to 70.3)	0.33	−82.1 (−176.9 to 12.8)	0.08	−154.2 (−378.3 to 69.8)	0.16
$PM_{2.5}$	−60.1 (−166.1 to 45.9)	0.24	−79.7 (−153.0 to −6.4)	0.04	−168.9 (−345.5 to 7.8)	0.06
Elemental carbon	−77.7 (−166.7 to 11.3)	0.08	−87.9 (−146.4 to −29.4)	0.007	−165.5 (−323.4 to −7.6)	0.04
Organic carbon	−58.6 (−196.1 to 78.8)	0.37	−86.2 (−185.6 to 13.3)	0.08	−151.2 (−389.4 to 87.1)	0.19

* Values are the differences in the estimated rate of eight-year growth at the lowest and highest observed levels of the indicated pollutant. Differences are scaled to the range across the 12 study communities in the average level of each pollutant from 1994 through 2000 as follows: 37.5 ppb of O_3 (measured from 10 a.m. to 6 p.m.), 46.0 ppb of O_3 (the one-hour maximal level), 34.6 ppb of NO_2, 9.6 ppb of acid vapor, 51.4 μg of PM_{10} per cubic meter, 22.8 μg of $PM_{2.5}$ per cubic meter, 1.2 μg of elemental carbon per cubic meter, and 10.5 μg of organic carbon per cubic meter. CI denotes confidence interval.

(P=0.002). Similar associations between these pollutants and a low FEV_1 were observed in the subgroup of children with no history of asthma and the subgroup with no history of smoking (data not shown). A low FEV_1 was not significantly correlated with exposure to ozone in any group.

DISCUSSION

The results of this study provide robust evidence that lung development, as measured by the growth in FVC, FEV_1, and MMEF from the ages of 10 to 18 years, is reduced in children exposed to higher levels of ambient air pollution. The strongest associations were observed between FEV_1 and a correlated set of pollutants, specifically nitrogen dioxide, acid vapor, and elemental carbon. The effects of these pollutants on FEV_1 were similar in boys and girls and remained significant among children with no history of asthma and among those with no history of smoking, suggesting that most children are susceptible to the chronic respiratory effects of breathing polluted air. The magnitude of the observed effects of air pollution on the growth in lung function during this age interval was similar to those that have been reported for exposure to maternal smoking[17,18] and smaller than those reported for the effects of personal smoking.[17,19]

Cumulative deficits in the growth in lung function during the eight-year study period resulted in a strong association between exposure to air pollution and a clinically low FEV_1 at the age of 18 years. In general, lung development is essentially complete in girls by the age of 18 years, whereas in boys it continues into their early 20s, but at a much reduced rate. It is therefore unlikely that clinically significant deficits in lung function at the age of 18 years will be reversed in either girls or boys as they complete the transition into adulthood. Deficits in lung function during young adulthood may increase the risk of respiratory conditions — for example, episodic wheezing that occurs during a viral infection.[20] However, the greatest effect of pollution-related deficits may occur later in life, since reduced lung function is a strong risk factor for complications and death during adulthood.[21-27]

Deficits in lung function were associated with a correlated set of pollutants that included nitrogen dioxide, acid vapor, fine-particulate matter ($PM_{2.5}$), and elemental carbon. In southern California, the primary source of these pollutants is motor vehicles, either through direct tailpipe emissions or downwind physical and photochemical reactions of vehicular emissions. Both gasoline- and diesel-powered engines contribute to the tons of pollutants exhausted into southern California's air every day, with diesel vehicles responsible for disproportionate amounts of nitrogen dioxide, $PM_{2.5}$, and ele-

Table 4. Sensitivity Analysis of the Effects of Acid Vapor and Elemental Carbon on Growth in FEV_1 over the Eight-Year Study Period.*

Model	Acid Vapor	Elemental Carbon
	Difference (95% Confidence Interval)	
Main model (model 1)†	−105.8 (−168.8 to −42.7)	−87.9 (−146.4 to −29.4)
Additional covariates‡		
Main model + in-utero exposure to maternal smoking (model 2)	−108.8 (−173.3 to −44.2)	−85.8 (−147.4 to −24.1)
Main model + exposure to gas stove (model 3)	−106.0 (−181.5 to −30.6)	−84.8 (−154.7 to −14.9)
Main model + pets in home (model 4)	−108.4 (−171.6 to −45.2)	−89.8 (−149.1 to −30.6)
Main model + parental level of education (model 5)	−100.7 (−167.2 to −34.2)	−80.9 (−142.7 to −19.0)
Main model + short-term effects of pollution (model 6)§	−112.4 (−201.4 to −23.3)	−103.2 (−181.8 to −24.5)
Subgroup effects		
No history of asthma (model 7)¶	−98.1 (−166.4 to −29.8)	−88.9 (−149.2 to −28.6)
No history of smoking (model 8)‖	−115.6 (−233.7 to 2.5)	−113.3 (−214.9 to −11.6)
After exclusion of communities with lowest and highest levels of pollution (model 9)**	−106.7 (−192.3 to −21.2)	−94.7 (−173.7 to −15.7)
Complete follow-up (model 10)††	−132.4 (−226.2 to −38.7)	−97.4 (−195.6 to 0.9)

* Values are the differences in the estimated rate of eight-year growth at the lowest and highest observed levels of the indicated pollutant. Differences are scaled to the range across the 12 study communities in the average level of each pollutant from 1994 through 2000 as follows: 9.6 ppb of acid vapor and 1.2 μg of elemental carbon per cubic meter.
† Model 1 is equivalent to effect estimates for FEV_1 in Table 3 and is based on data on 1759 children.
‡ The main model was adjusted for each of the covariates listed.
§ Values were adjusted for the average levels of O_3, NO_2, and PM_{10} on the three days before each child's pulmonary-function test.
¶ The analysis includes data on 1302 children with no history of doctor-diagnosed asthma.
‖ The analysis includes data on 1276 children with no history of active tobacco smoking at any time during follow-up.
** The analysis excludes children from the two communities with the lowest and highest levels of each pollutant. This leaves 1507 children (excluding those from Lompoc and Upland) in the analysis of acid vapor and 1484 children (excluding those from Lompoc and Long Beach) in the analysis of elemental carbon.
†† The analysis includes 713 children who underwent pulmonary-function testing in both 1993 and 2001 (i.e., those observed throughout the study).

mental carbon. In the current study, however, we could not discern the independent effects of pollutants because they came from common sources and there was a high degree of intercorrelation among them; similar difficulties have also been encountered in other studies of lung function and air-pollutant mixtures.[1,2,9,28-30] Since ozone is also formed during photochemical reactions involving fuel-combustion products, one might expect ozone to be correlated with the other study pollutants and therefore to show similar associations with lung function. However, the Children's Health Study was specifically designed to minimize the correlation of ozone with other pollutants across the 12 study communities. Thus, although ozone has been convincingly linked to acute health effects in many other studies,[11] our results provide little evidence that ambient ozone at current levels is associated with chronic deficits in the growth of lung function in children. Only a few other studies have addressed the long-term effects of ozone on lung development in children, and results have been inconsistent.[31] Although we found little evidence of an effect of ozone, this result needs to be interpreted with caution given the potential for substantial misclassification of exposure to ozone.[32,33]

The mechanism whereby exposure to pollutants could lead to reduced lung development is unknown, but there are many possibilities. Our observation of associations between air pollution and all three measures of lung function — FVC, FEV_1, and MMEF — suggests that more than one process is involved. FVC is largely a function of the number and size of alveoli, with differences in volume pri-

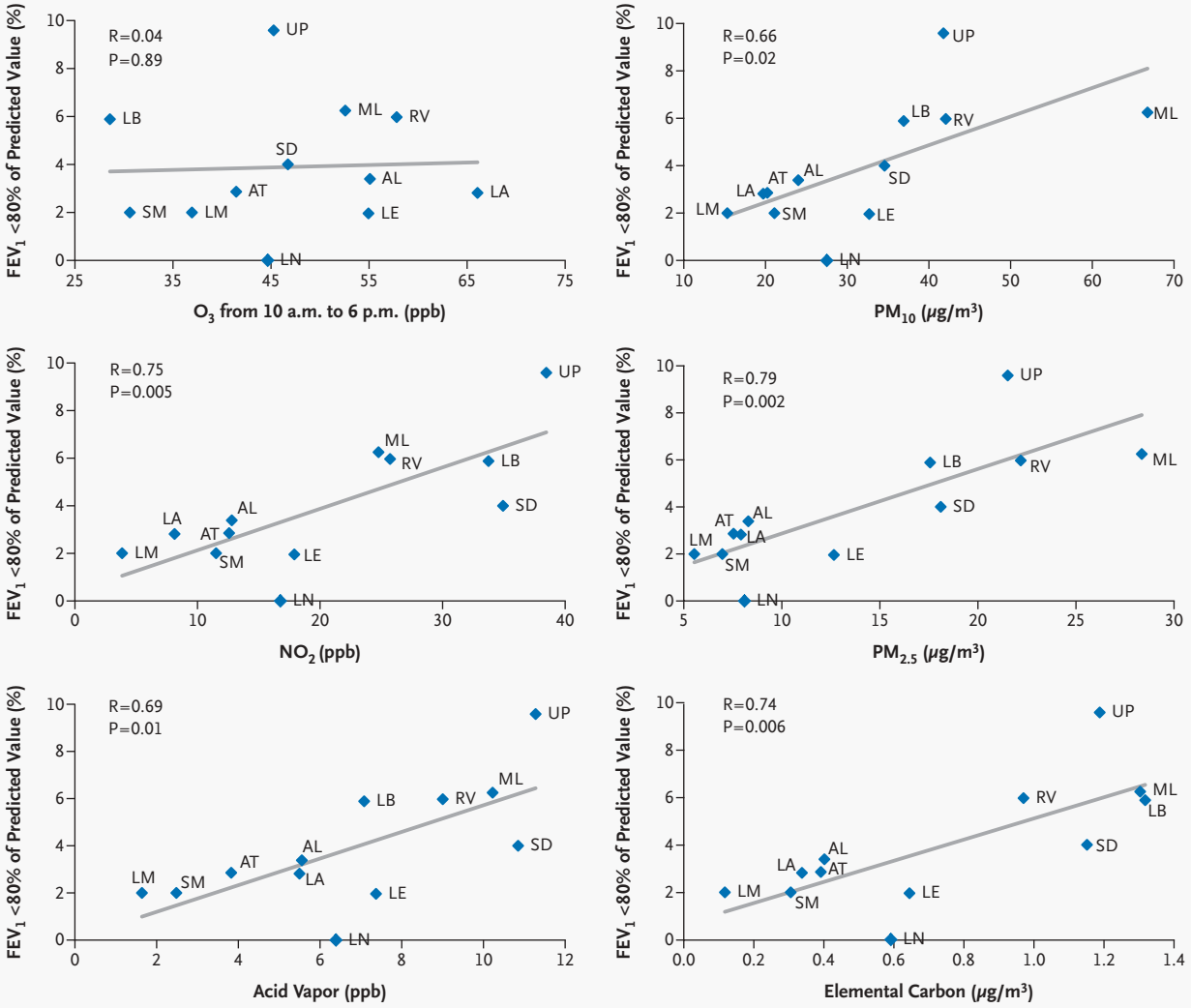

Figure 3. Community-Specific Proportion of 18-Year-Olds with a FEV_1 below 80 Percent of the Predicted Value Plotted against the Average Levels of Pollutants from 1994 through 2000.

The correlation coefficient (R) and P value are shown for each comparison. AL denotes Alpine, AT Atascadero, LE Lake Elsinore, LA Lake Arrowhead, LN Lancaster, LM Lompoc, LB Long Beach, ML Mira Loma, RV Riverside, SD San Dimas, SM Santa Maria, and UP Upland. O_3 denotes ozone, NO_2 nitrogen dioxide, and PM_{10} and $PM_{2.5}$ particulate matter with an aerodynamic diameter of less than 10 μm and less than 2.5 μm, respectively.

marily attributable to differences in the number of alveoli, since their size is relatively constant.[34] However, since the postnatal increase in the number of alveoli is complete by the age of 10 years, pollution-related deficits in the growth of FVC and FEV_1 during adolescence may, in part, reflect a reduction in the growth of alveoli. Another plausible mechanism of the effect of air pollution on lung development is airway inflammation, such as occurs in bronchiolitis; such changes have been observed in the airways of smokers and of subjects who lived in polluted environments.[35,36]

A strength of our study was the long-term, prospective follow-up of a large cohort, with exposure and outcome data collected in a consistent manner throughout the study period. As in any epidemiologic study, however, the observed effects could be biased by underlying associations of the exposure and outcome to some confounding variables. We adjusted for known potential confounders, includ-

ing personal characteristics and other sources of exposure to pollutants, but the possibility of confounding by other factors still exists. Over the eight-year follow-up period, approximately 10 percent of study subjects were lost to follow-up each year. Attrition is a potential source of bias in a cohort study if loss to follow-up is related to both exposure and outcome. However, we did not see evidence that the loss of subjects was related to either baseline lung function or exposure to air pollution. In addition, we observed significant associations between air pollution and lung growth in the subgroup of children who were followed for the full eight years of the study, with effects that were similar in magnitude to those in the group as a whole, thus making loss of subjects an unlikely source of bias.

We have shown that exposure to ambient air pollution is correlated with significant deficits in respiratory growth over an eight-year period, leading to clinically important deficits in lung function at the age of 18 years. The specific pollutants that were associated with these deficits included nitrogen dioxide, acid vapor, $PM_{2.5}$, and elemental carbon. These pollutants are products of primary fuel combustion, and since they are present at similar levels in many other areas,[37,38] we believe that our results can be generalized to children living outside southern California. Given the magnitude of the observed effects and the importance of lung function as a determinant of morbidity and mortality during adulthood, continued emphasis on the identification of strategies for reducing levels of urban air pollutants is warranted.

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