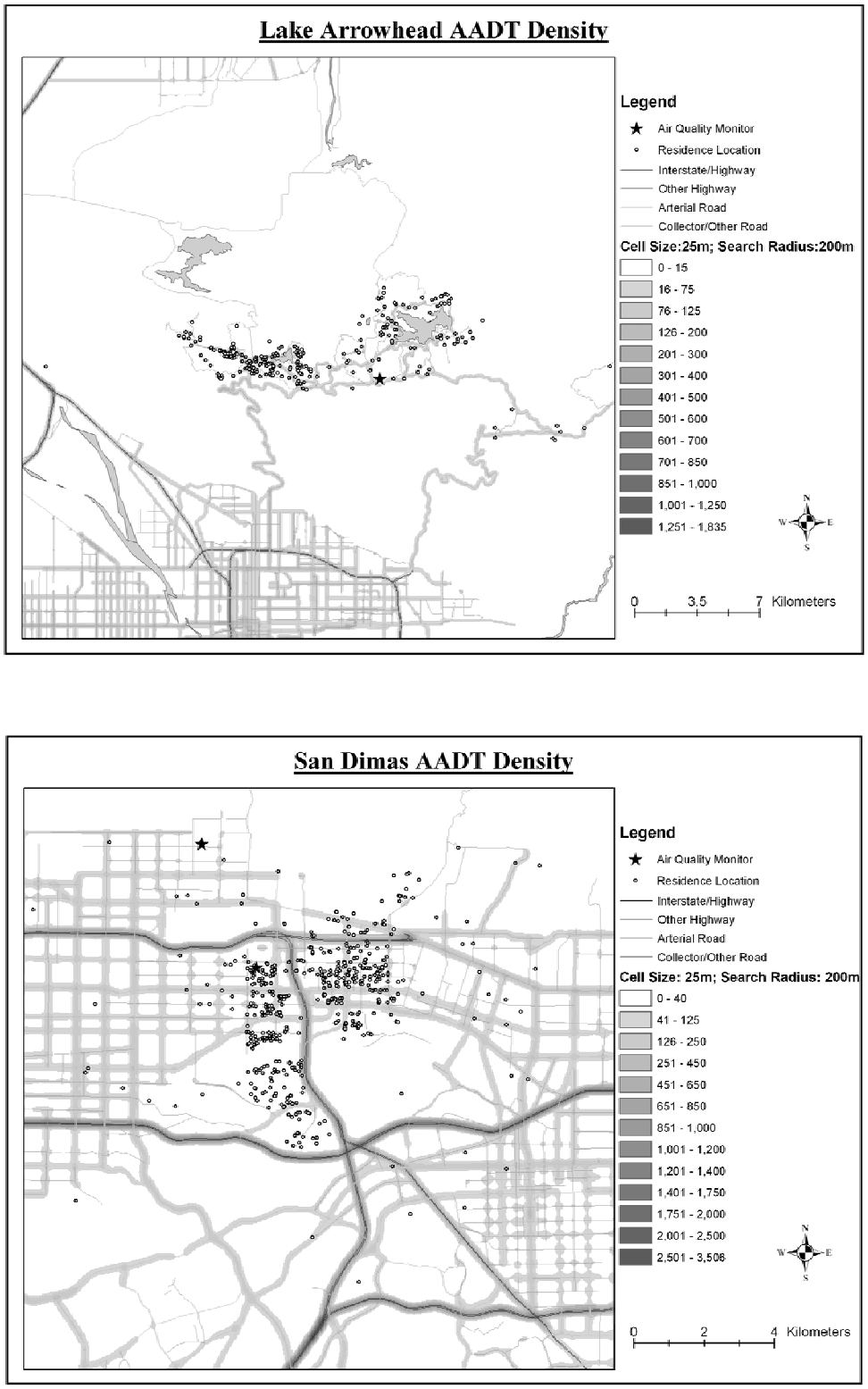


Figure 4.1-44. Spatially mapped traffic density in Lake Arrowhead and San Dimas.

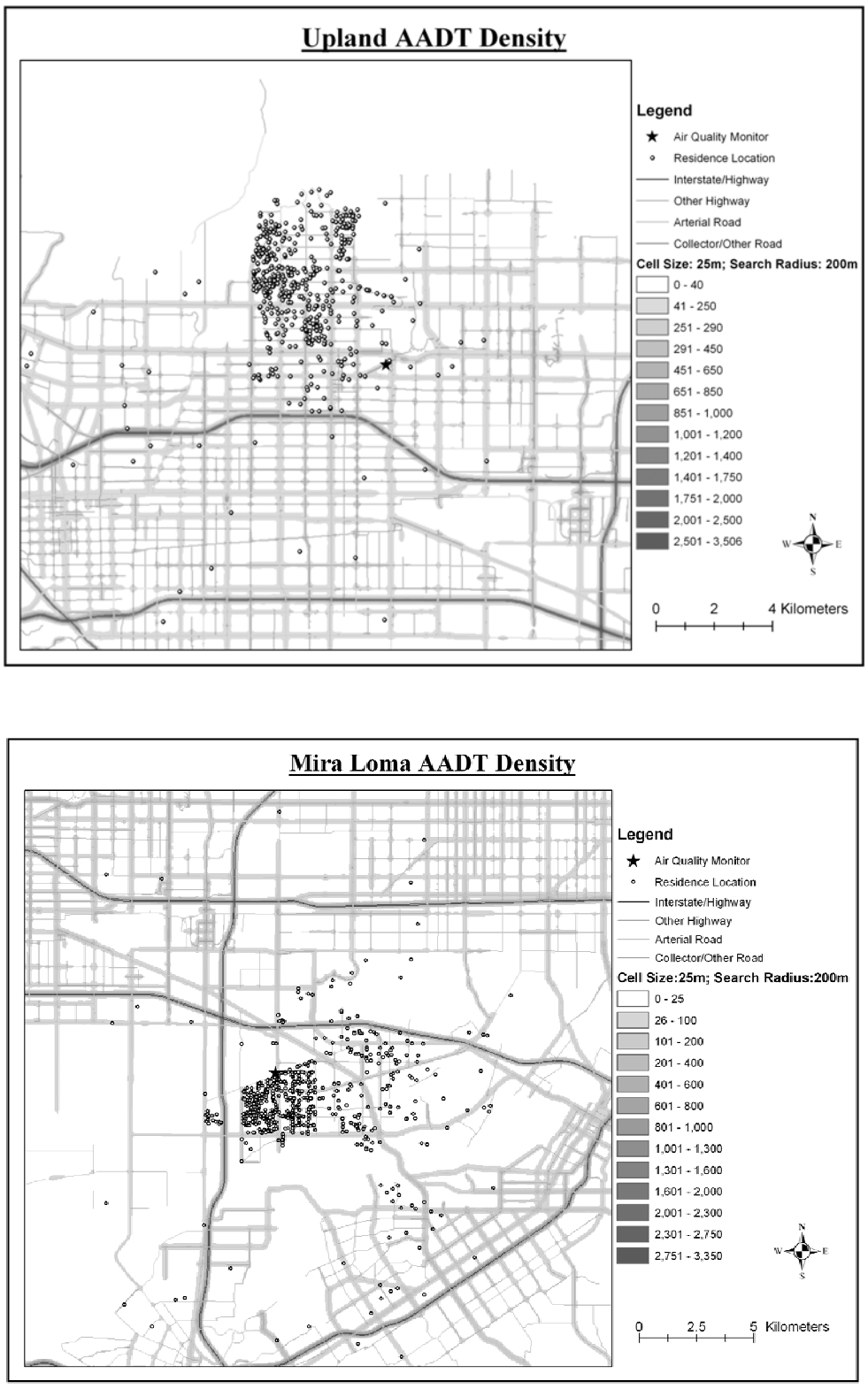
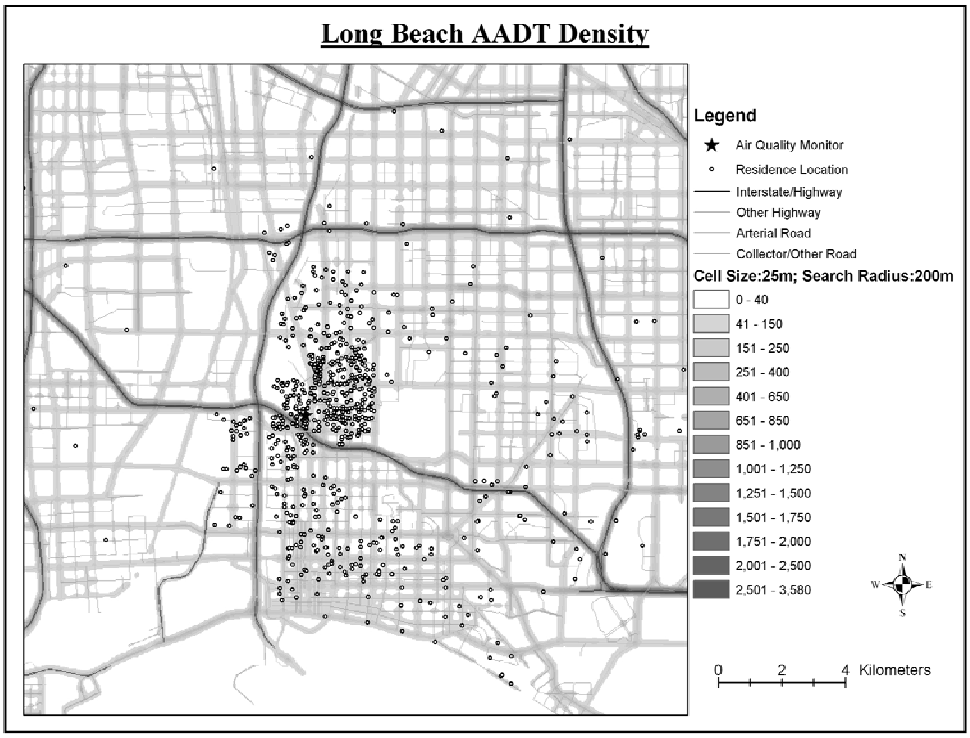


Figure 4.1-45. Spatially mapped traffic density in Upland and Mira Loma.



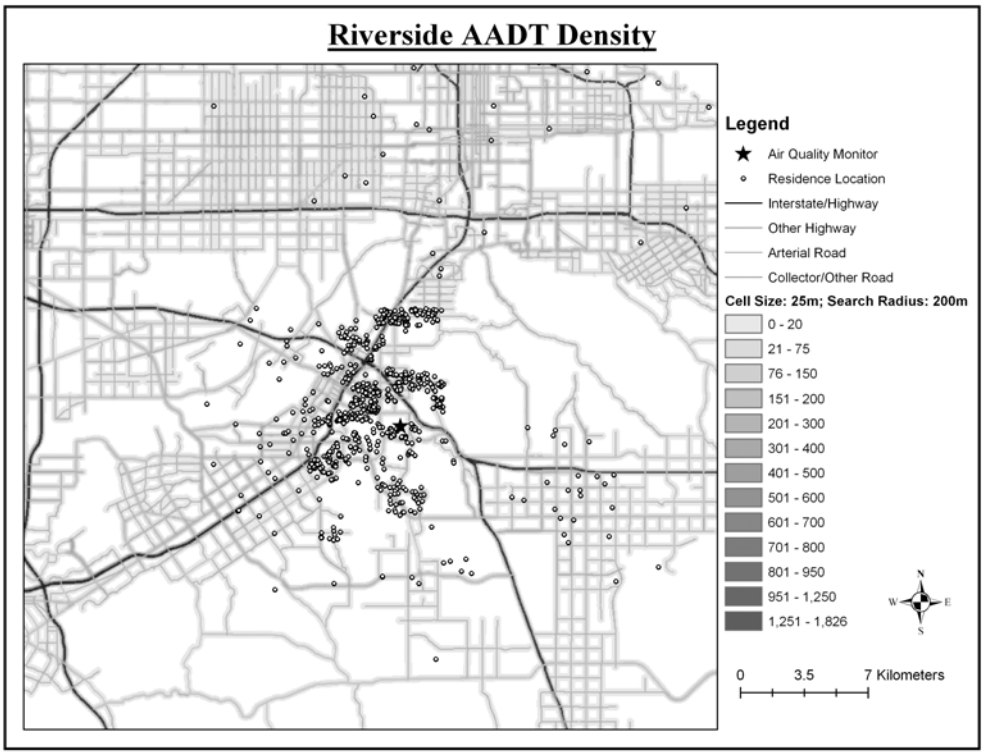
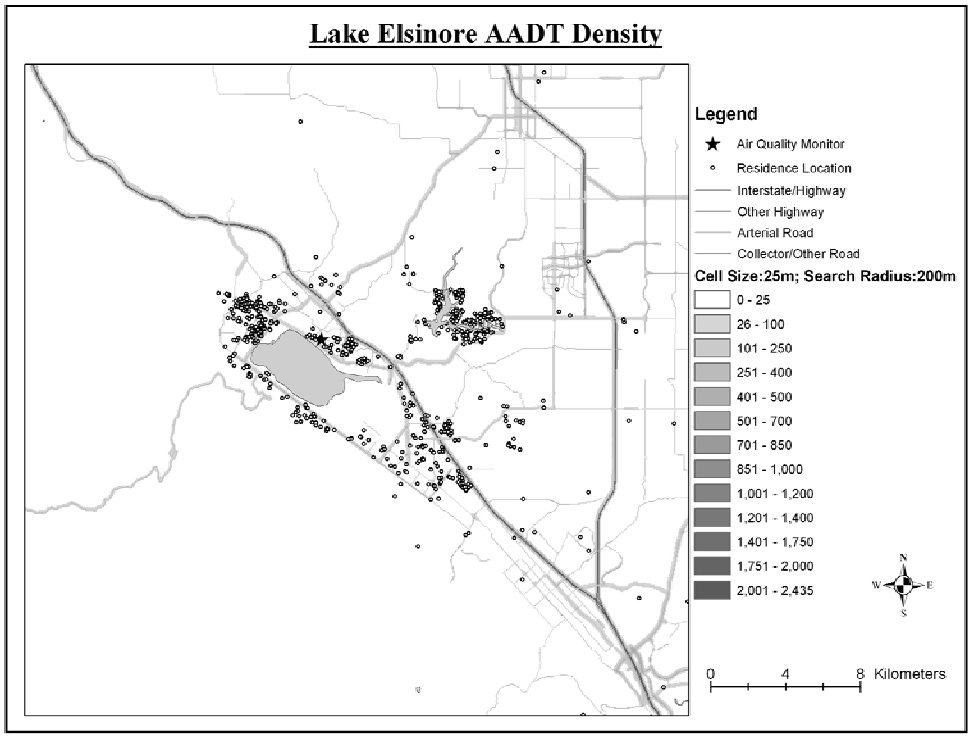


Figure 4.1-46. Spatially mapped traffic density in Long Beach and Riverside.



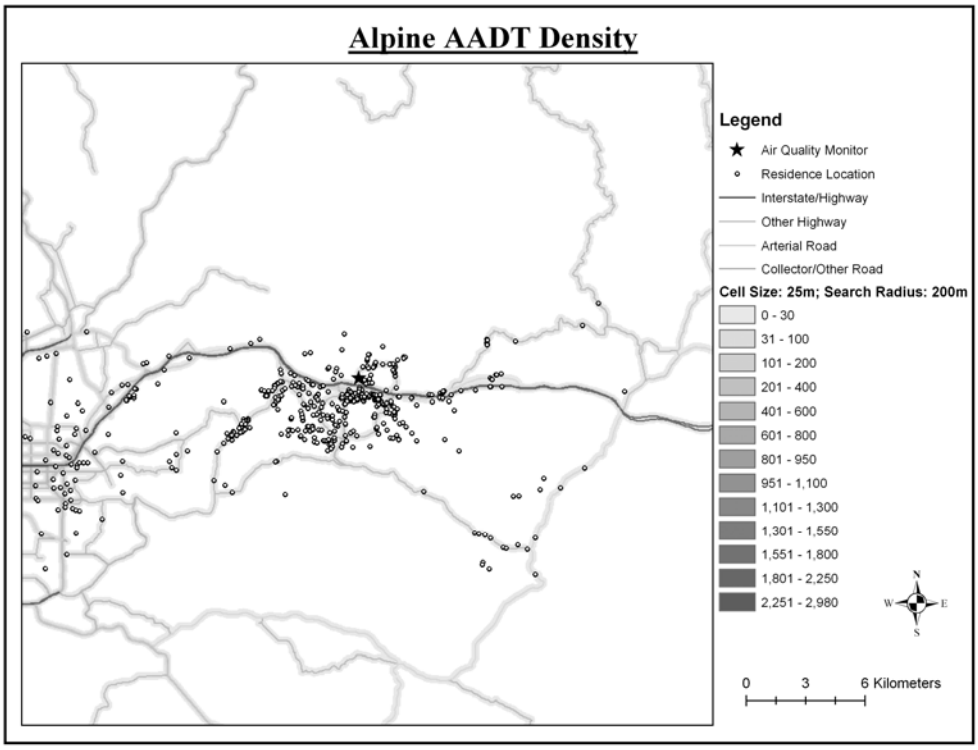


Figure 4.1-47. Spatially mapped traffic density in Lake Elsinore and Alpine.

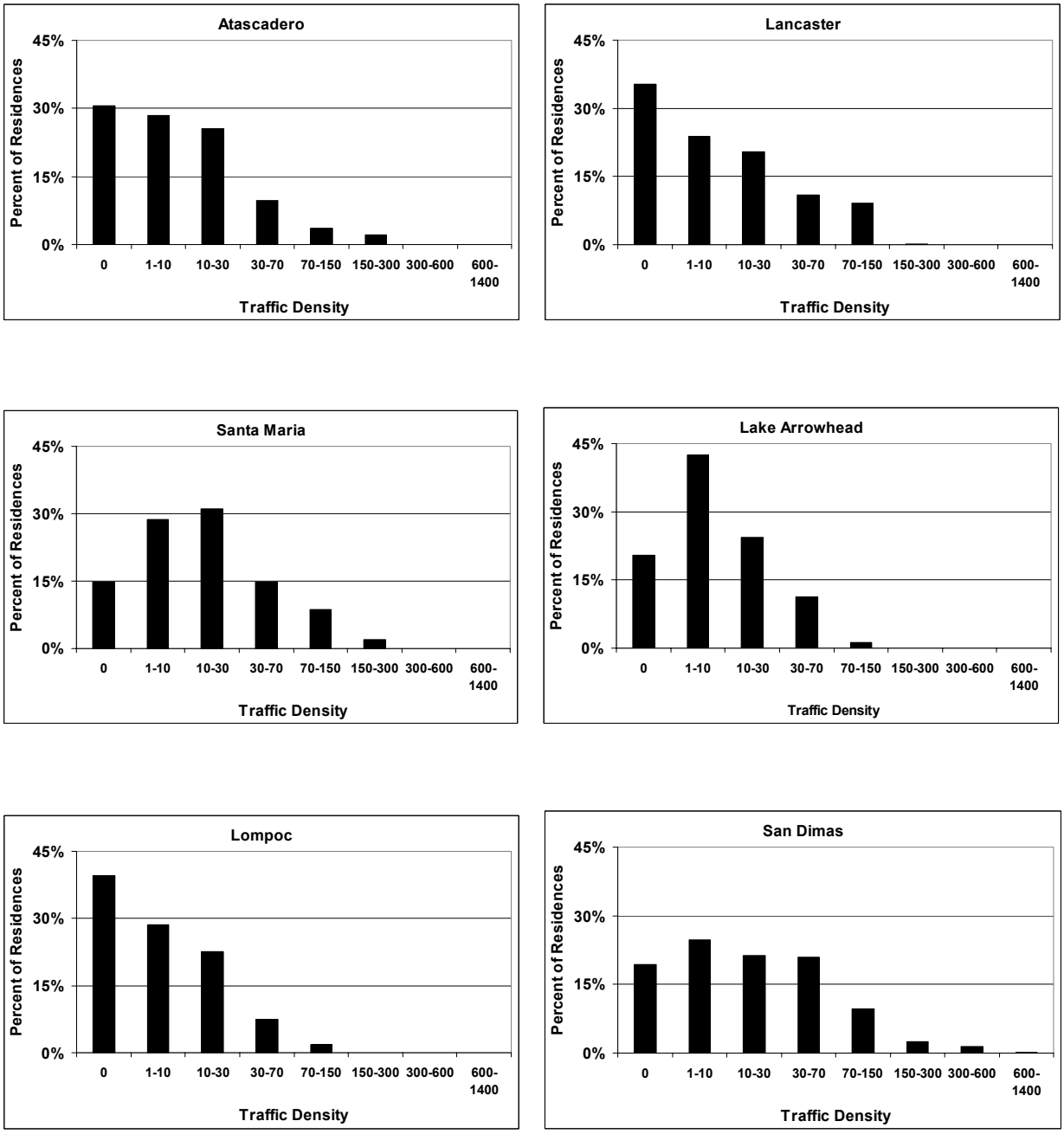


Figure 4.1-48. Distribution of estimated traffic density (arbitrary scale) in Atascadero, Santa Maria, Lompoc, Lancaster, Lake Arrowhead, and San Dimas.

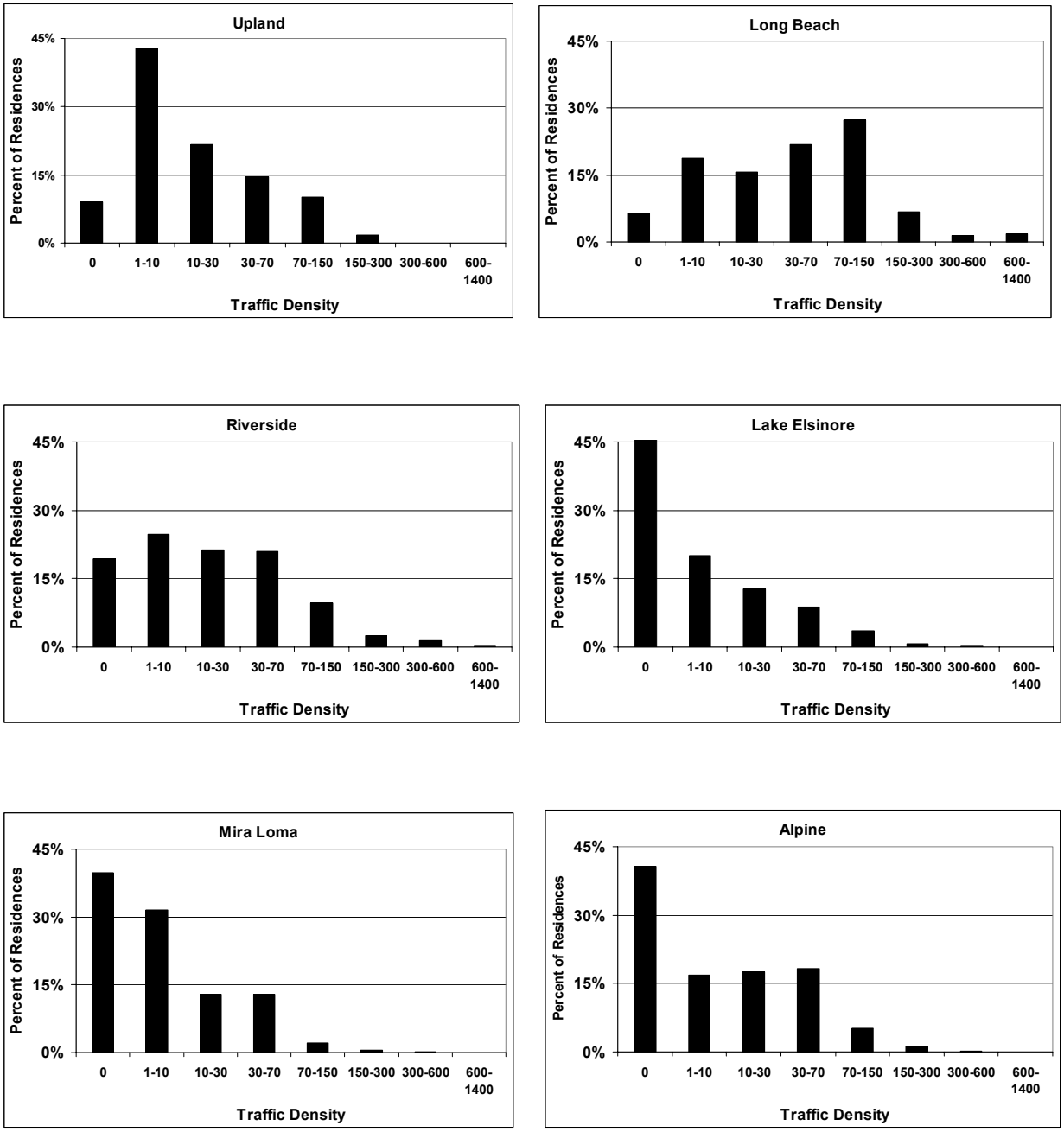


Figure 4.1-49. Distribution of estimated traffic density (arbitrary scale) in Upland, Mira Loma, Riverside, Long Beach, Lake Elsinore, and Alpine.

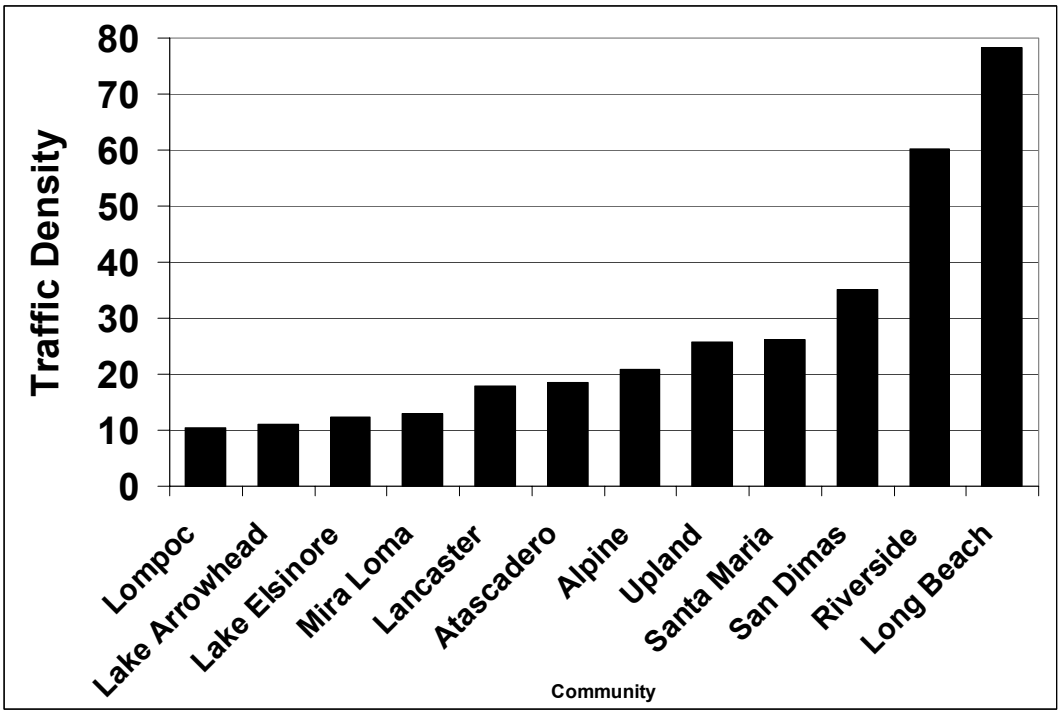


Figure 4.1-50. Average estimated traffic density at CHS participant residences by community.

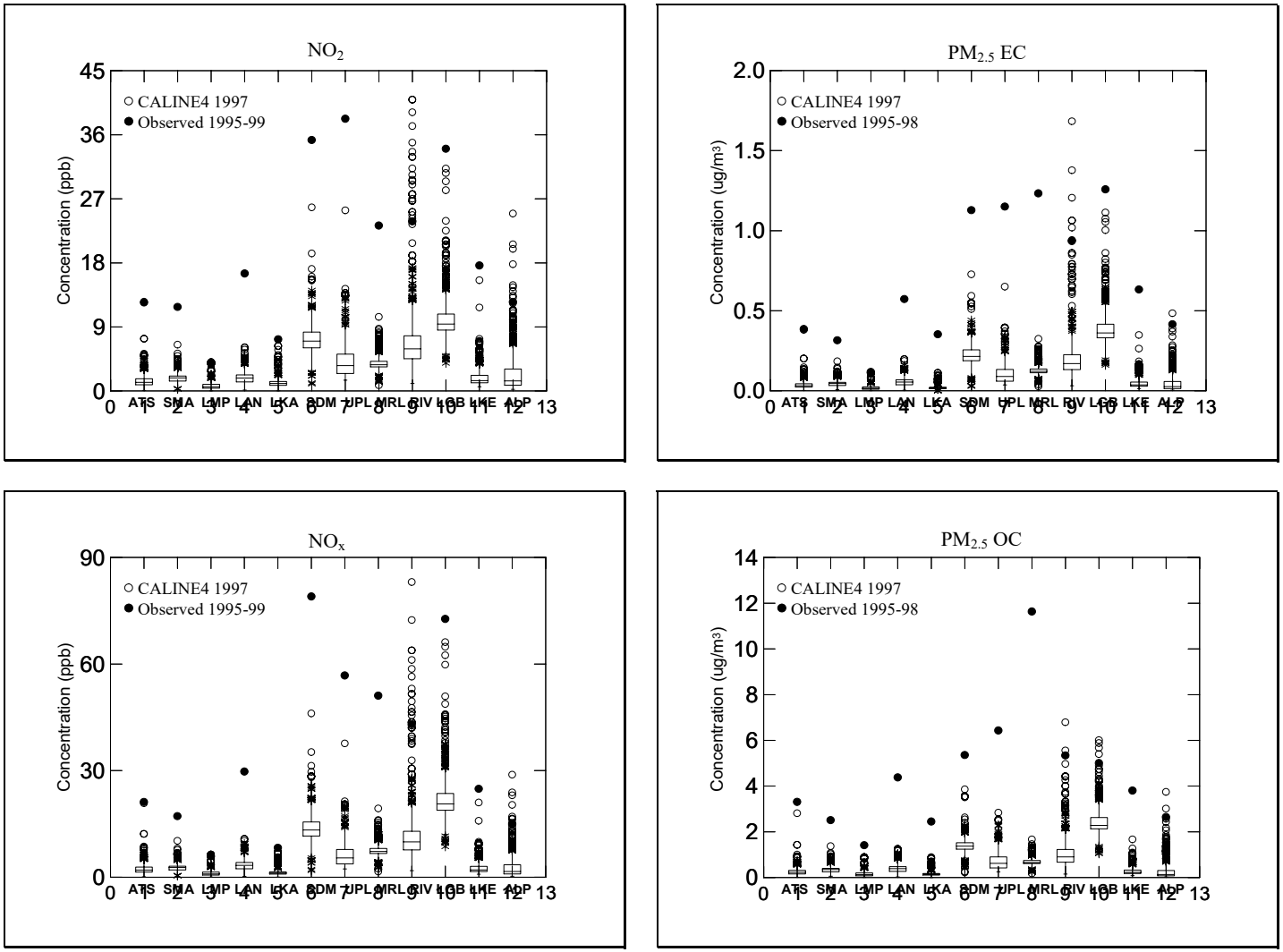


Figure 4.1-51. Box-whisker plots of annual average NO_2, NO_x, $PM_{2.5}$ EC, and $PM_{2.5}$ OC concentrations at CHS residences estimated by the CALINE4 model. The box shows the 25th, 50th, and 75th percentiles, while the whisker shows the high and low values. The station abbreviations are given in Table 4.1-13.

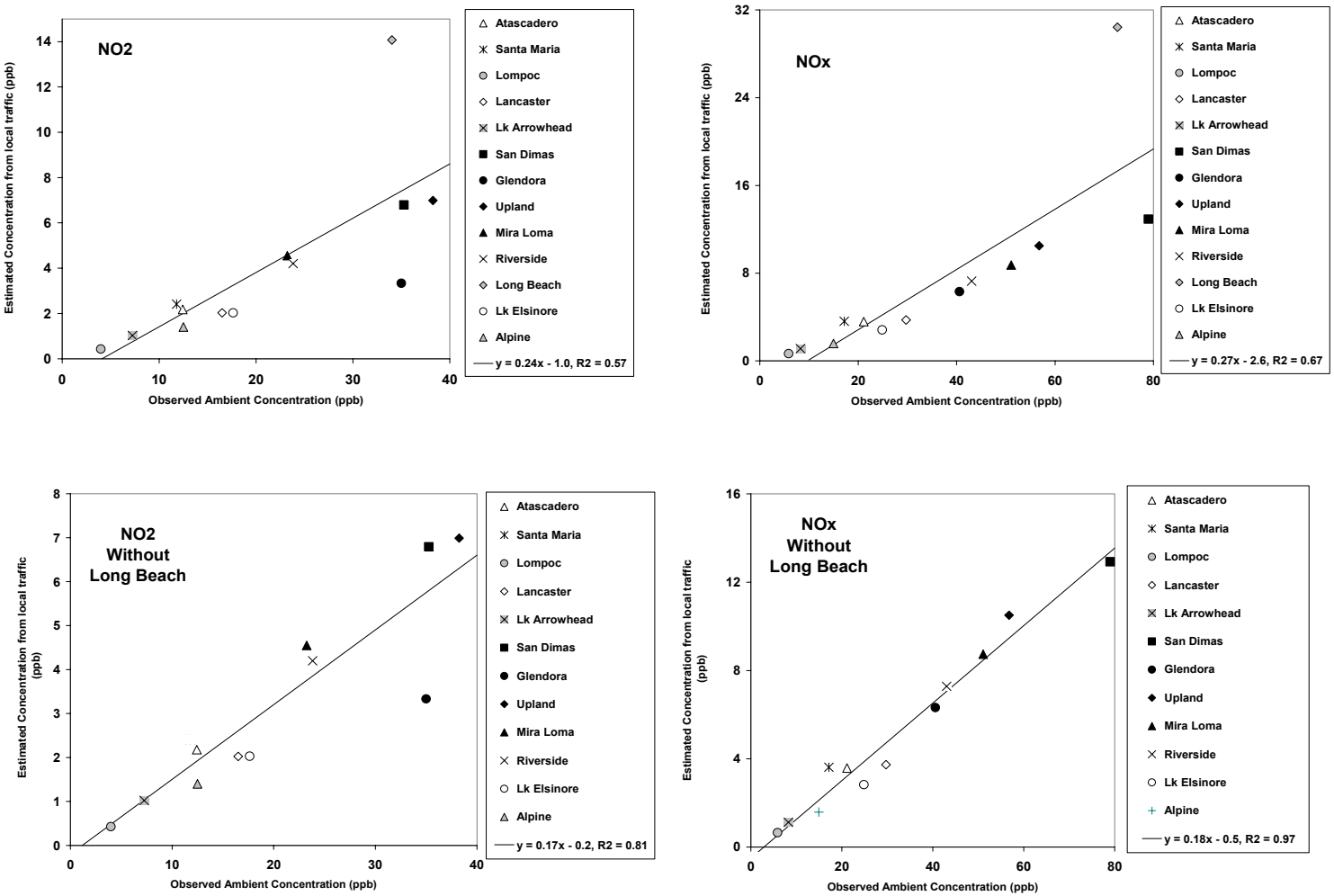


Figure 4.1-52. Comparison of annual average NO_2 and NO_x concentrations estimated by the CALINE4 model for the central air monitoring station locations and the four-year average observed ambient concentrations at the stations. Note, the observations for San Dimas are based on only two years of data.

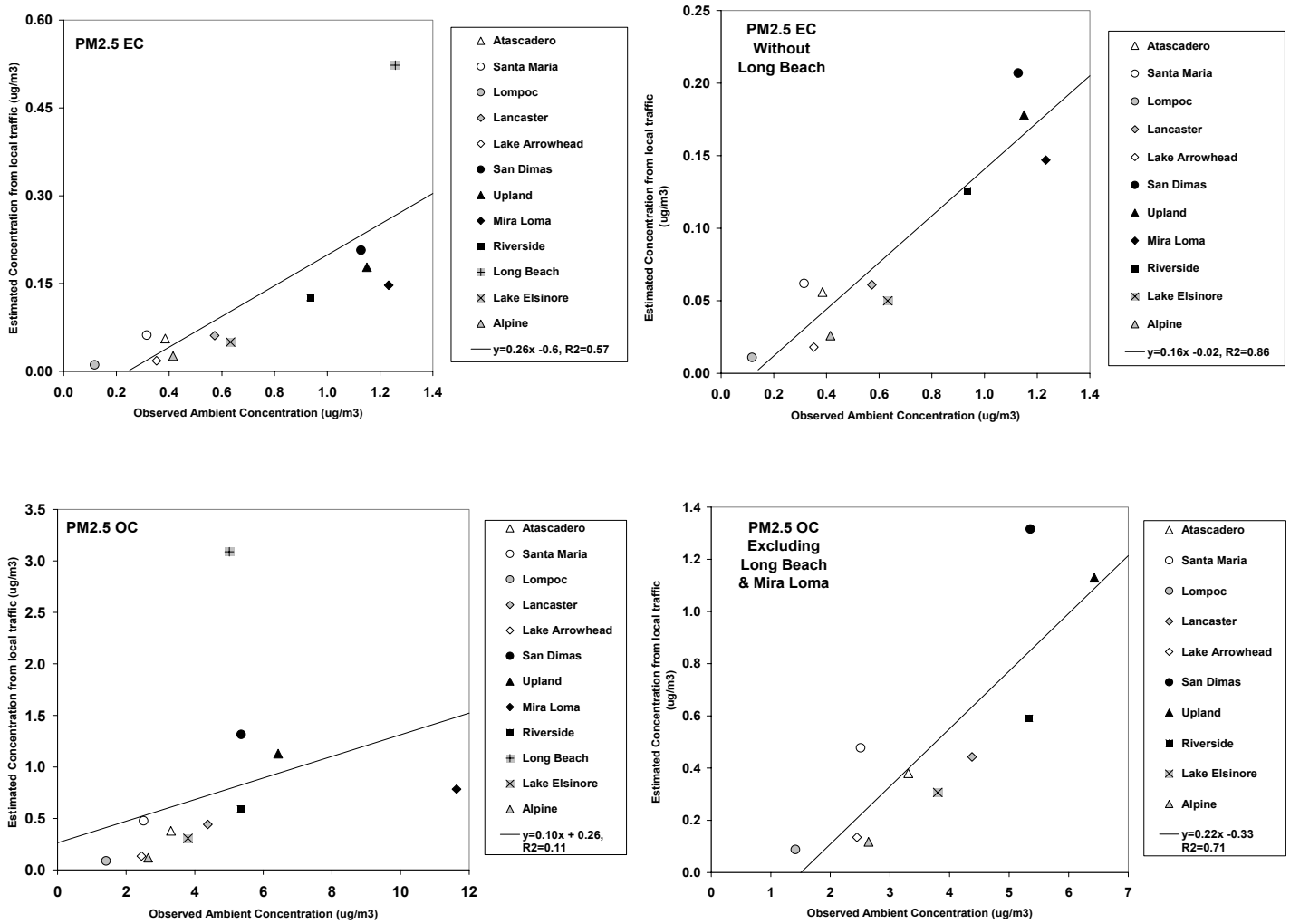


Figure 4.1-53. Comparison of annual average $PM_{2.5}$ EC and OC concentrations estimated by the CALINE4 model for the central air monitoring station locations and the four-year average observed ambient concentrations at the stations. Note, the observations for San Dimas and Glendora are based on only two years of data.

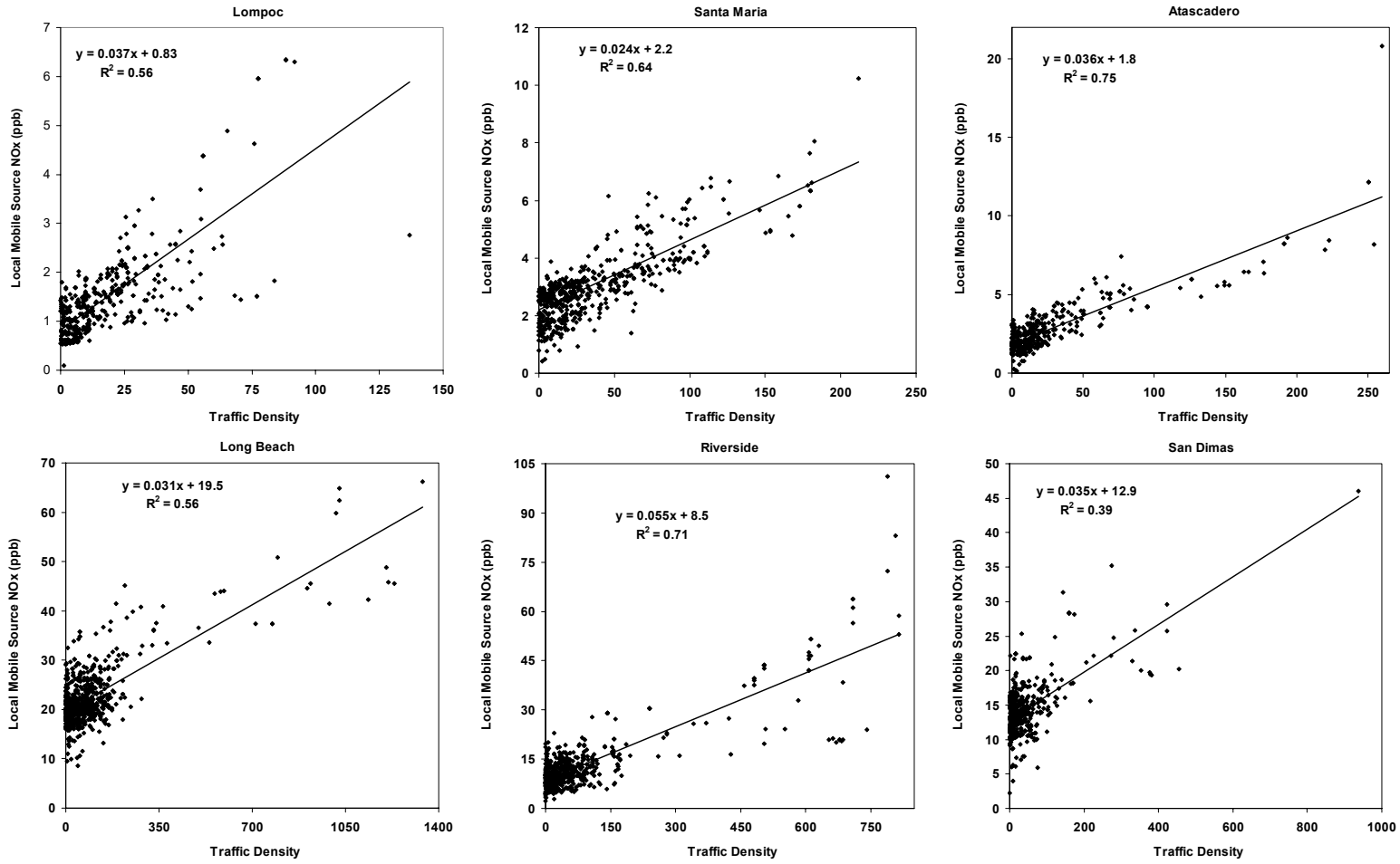


Figure 4.1-54. Comparison of local mobile source NO_x concentrations estimates from the CALINE4 model with estimated traffic density in representative communities.

Table 4.1-16. Mean and standard deviation[#] of estimated annual average personal exposure by community in 1997.

Community**	NO_2 (ppb)*	Ozone (ppb)*	PM_{10} ($\mu g/m^3$)*	$PM_{2.5}$ ($\mu g/m^3$)*	$PM_{2.5}$ EC ($\mu g/m^3$)*	$PM_{2.5}$ OC ($\mu g/m^3$)*
Atascadero	8.2 ±1.3	9.0 ±1.4	11.6 ±1.1	5.8 ±0.5	0.47 ±0.07	2.8 ±0.3
Santa Maria	8.3 ±1.2	8.8 ±1.2	12.6 ±1.2	4.9 ±0.5	0.41 ±0.06	2.2 ±0.3
Lompoc	2.6 ±0.5	10.2 ±1.5	8.9 ±0.8	3.6 ±0.3	0.24 ±0.05	1.3 ±0.2
Lancaster	4.9 ±1.2	11.2 ±1.9	13.0 ±1.6	5.3 ±0.6	0.42 ±0.07	2.8 ±0.4
San Dimas	24.9 ±3.6	9.1 ±1.7	29.6 ±3.2	14.8 ±1.5	1.27 ±0.16	5.7 ±0.6
Upland	20.5 ±3.0	8.4 ±1.4	23.4 ±2.4	14.7 ±1.3	1 ±0.13	6.0 ±0.7
Mira Loma	13.4 ±1.8	11.1 ±1.9	40.7 ±3.7	18.5 ±1.4	1.06 ±0.11	8.3 ±0.6
Riverside	22.6 ±6.3	12.7 ±2.1	30.5 ±4.8	17.9 ±2.5	1.23 ±0.22	6.5 ±1.0
Long Beach	27.7 ±4.4	7.1 ±1.1	29.0 ±3.6	17.4 ±1.8	1.45 ±0.17	7.5 ±0.9
Lake Elsinore	6.1 ±1.3	11.9 ±1.8	17.4 ±1.7	8.5 ±0.7	0.53 ±0.06	2.6 ±0.3
Alpine	6.9 ±2.9	13.8 ±2.1	15.4 ±2.0	6.0 ±0.9	0.43 ±0.11	2.2 ±0.7

* Exposure metrics are for all hours of the day for all pollutants.

[#] The standard deviation reflects the variance in the annual average exposure concentration among subjects within the community.

** Exposure model was not applied to Lake Arrowhead due to uncertainties in residence locations (i.e., poor geocoding quality due to post office box addresses).

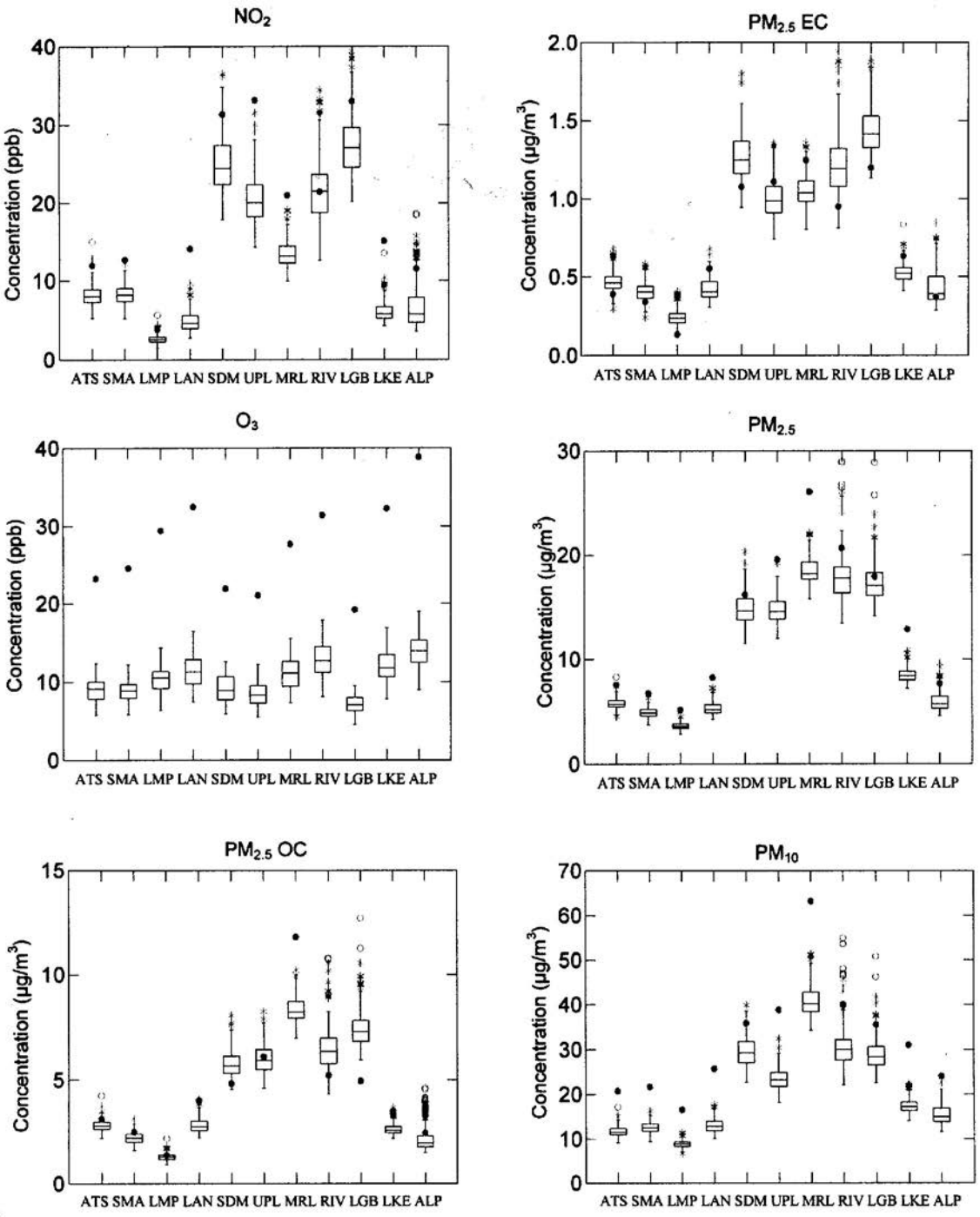


Figure 4.1-55. Box-whisker plots of the estimated annual average personal exposure by community in 1997.

Lower, middle, and top of box are the 25th, 50th, and 75th percentile values. Solid dots are the mean observed ambient pollutant concentration in 1997.

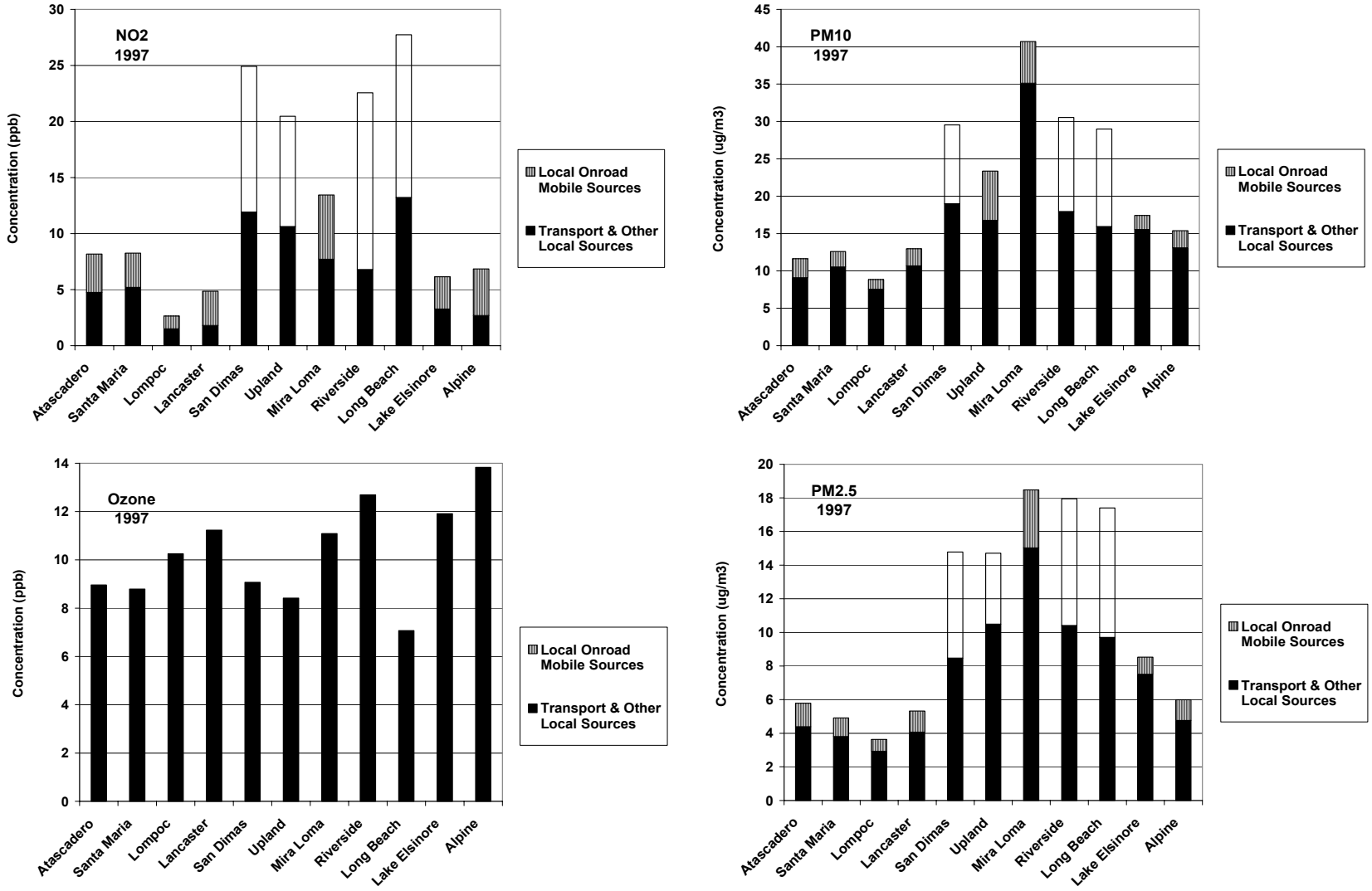


Figure 4.1-56. Estimated personal exposure to NO_2, ozone, PM_{10}, and $PM_{2.5}$ from outdoor local on-road mobile sources and from regional transport and other outdoor local sources in the CHS communities.

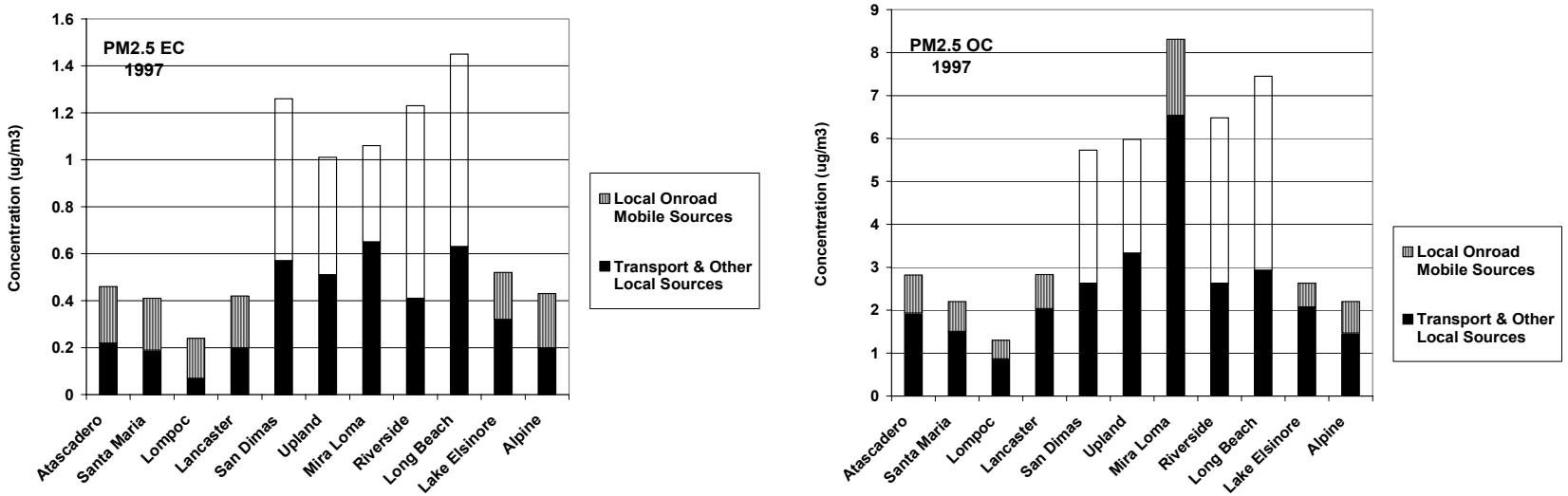


Figure 4.1-57. Estimated personal exposure to ozone and $PM_{2.5}$ EC and $PM_{2.5}$ OC from outdoor local on-road mobile sources and from regional transport and other outdoor local sources in the CHS communities.

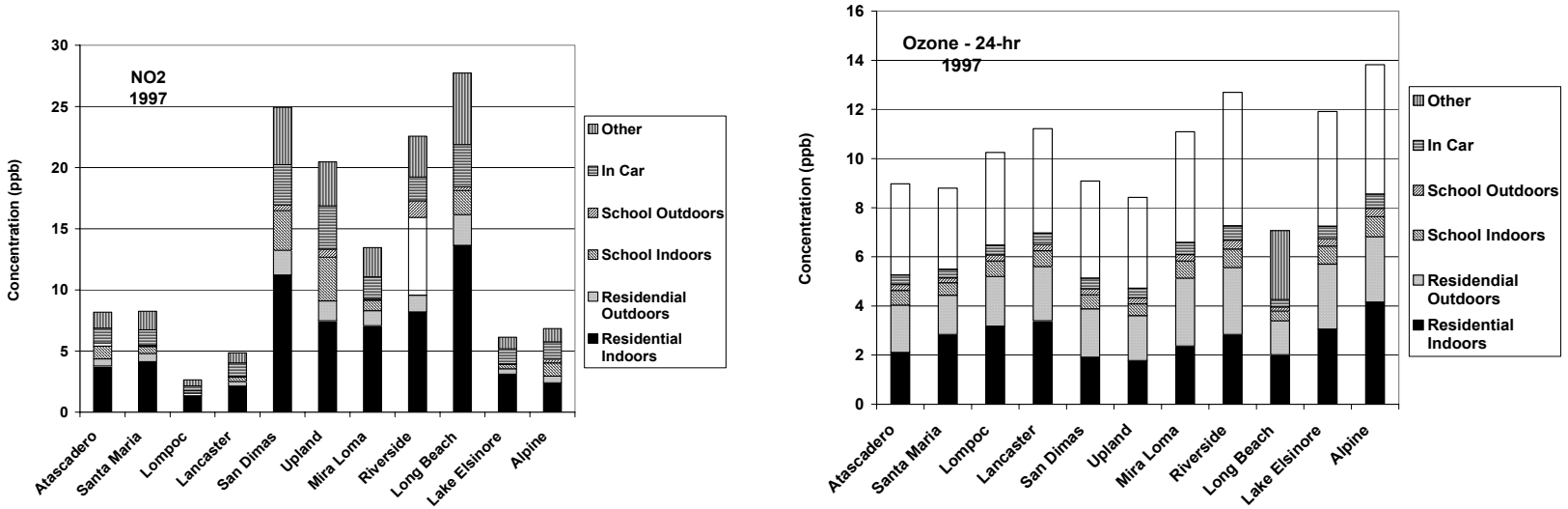


Figure 4.1-58. Estimated personal exposure to NO_2 and ozone of outdoor origin occurring while subjects were indoors and outdoors at residences and schools, in vehicles, and in other microenvironments.

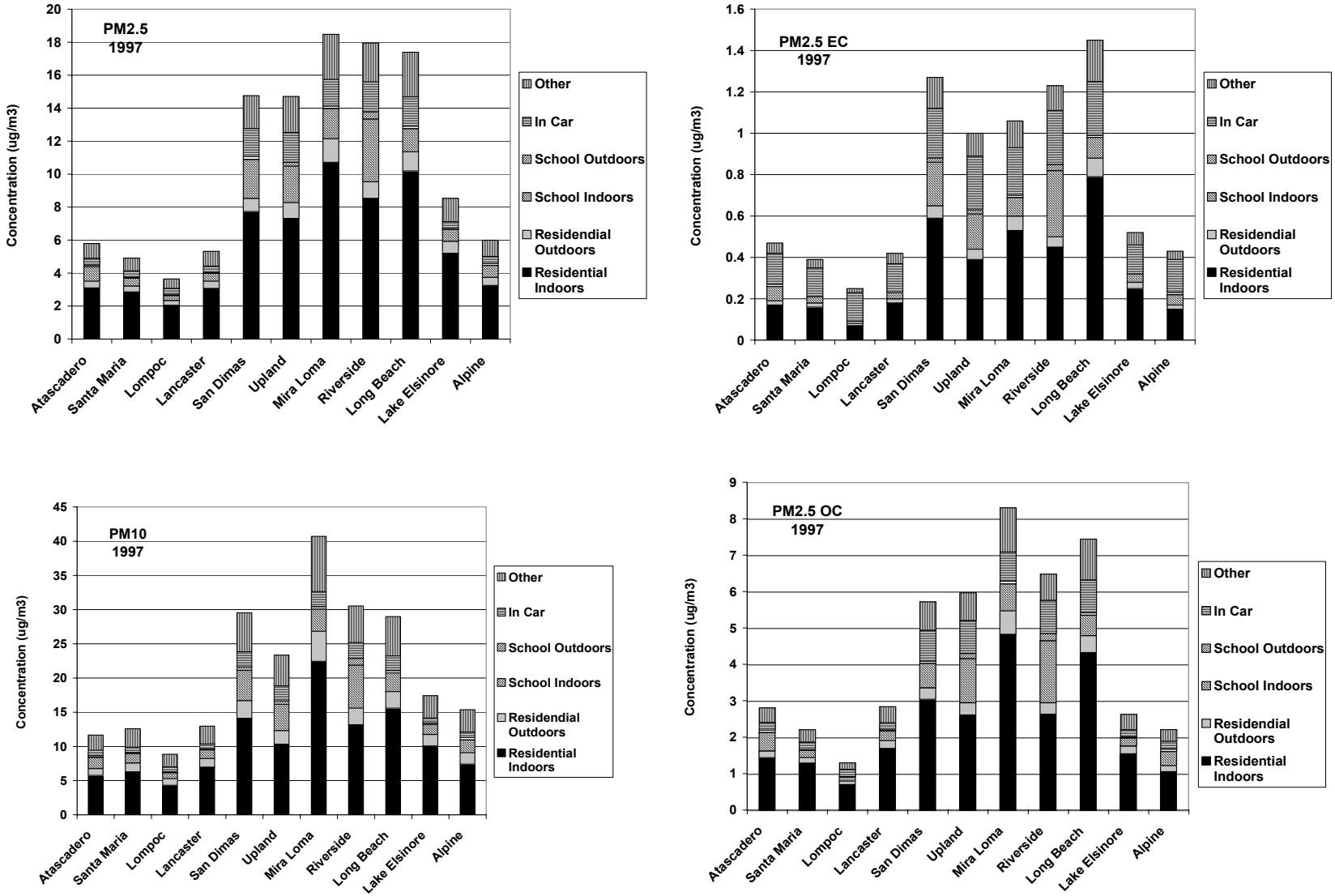


Figure 4.1-59. Estimated personal exposure to $PM_{2.5}$, $PM_{2.5}$ EC, PM_{10}, and $PM_{2.5}$ OC of outdoor origin occurring while subjects were indoors and outdoors at residences and schools, in vehicles, and in other microenvironments.

4.2. Pollution-Related Health Outcomes

4.2.1. Lung Function Level and Growth

The CHS was designed to investigate the long-term, chronic effects of air pollution on children's respiratory health. One of the primary outcomes that the CHS has utilized in this investigation is lung function. Lung function was assessed using a pulmonary function test (PFT), during which each child was encouraged to take a deep breath and expire all of the air from their lungs as quickly as possible. An instrument called a spirometer was used to determine several measures of lung function. These are described below.

- FVC, Forced Vital Capacity: The total volume of air expired from the lung (in milliliters, ml).

- FEV_1, Forced Expiratory Volume in the first second: The volume of air expired during the first second of the PFT (in ml).

- MMEF, Maximal Mid-Expiratory Flow rate: The flow at which air was being expired during the middle 50% of the PFT, i.e. over the portion of the PFT after 25% of FVC had been expired but before 75% of FVC had been expired (in ml/second).

- FEF_{75}, Forced Expiratory Flow at 75% of FVC: The flow at which air was being expired at the point when 75% of the FVC had already been expired (in ml/sec).

- PEFR, Peak Expiratory Flow Rate: The maximum flow at which air was being expired during the PFT (in ml/sec).

FVC is our best measure of lung capacity, although it should be noted that total lung capacity is larger than FVC, since there is some air that remains in the lung after a forced expiration. MMEF and FEF_{75} are commonly considered measures of health of the small airways of the lung, while PEFR is more sensitive to the status of the larger airways. FEV_1 is often considered the best single measure of lung function, as it captures information about both lung volume and flow rate. CHS participants were tested each year until graduation from high school, allowing us to track the development of their lungs during adolescence.

Some of the different measures of pulmonary function described above are not totally independent. The total lung capacity (volume) cannot be easily measured in population studies and was not measured in this study because of exposure and logistics. FVC comes closest to assessing total lung capacity but after a full expiration after a full inspiration, air is left in the lung (called the residual volume). All of the other measurements of pulmonary function in our study are to varying degrees dependent on the FVC. In general, the bigger the FVC, the bigger the FEV_1, MMEF, FEF_{75}, and PEFR will be. But each of the measurements represents a slightly different location in the lung where abnormalities may be occurring. FVC is the best measure of lung volume, FEV_1 is the best integrator of volume and flow, PEFR measures large airway

function and MMEF and FEF_{75} measure small airway function. Different disease processes give different patterns of abnormality and in most cases more than one measure of PFT is affected.

All of these lung function measures increase rapidly as a child grows through the adolescent period. For example, Table 4.2-1 shows the mean levels of each PFT measure at ages 10, 14, and 18 years for children enrolled in 1993 in our 4th grade cohort (Cohort C). There is a high rate of growth from age 10 to 14 for both girls and boys. In girls, lung function growth is slower after age 14 and by age 18, lungs in girls are almost fully developed. Boys, however, continue to grow rapidly after age 14 and are still growing (although at a much reduced rate) at age 18. On average, children are able to expire between 80% and 90% of the air from their lungs in the first second of their PFT (based on the ratio of FEV_1 to FVC).

A primary focus of the CHS has been to determine whether exposure to air pollution affects the growth and development of children's lungs during adolescence. The next section summarizes our results on this topic.

4.2.1.1. Summary of Results

In this section, we describe the results of several analyses that address the question of whether air pollution is related to lung function in children. We have investigated associations with both lung function level (i.e. average at some time point) and growth (i.e. change in lung function over time). As described above, the study was initiated in 1993 with the enrollment of approximately 3,600 children from three grade cohorts, specifically 10th (Cohort A), 7th (Cohort B), and 4th (Cohort C) grades. Section 4.2.1.1.1 summarizes our findings on the relationship between air pollution and the children's lung function level, based on the cross-section of lung function data collected from these three cohorts in the first year of the study. Section 4.2.1.1.2 describes our investigation of air pollution and lung function growth in these cohorts, based on data collected over the first four years of the study.

In 1996, we enrolled a second cohort of approximately 2,000 4th grade children (Cohort D) and began tracking their lung function annually according to the same protocols used for Cohorts A, B, and C. The availability of this second cohort has provided the CHS an opportunity to attempt replication of the findings from the first cohorts. The relationship between air pollution and lung function growth over the first four years in Cohort D is described in Section 4.2.1.1.3. During the course of the study, we have investigated associations between lung function and several other pollutant metric, including traffic density and specific elements of particulate matter. Results of these analyses are summarized in Section 4.2.1.1.4. In 1998, we conducted a sub-study to follow children from Cohorts C and D who had moved away from the community they lived in at study entry. The goals of this sub-study were two-fold: 1) to determine whether children who left our study were different than children who did not move away in terms of their exposure or respiratory health status, and 2) to determine whether the lung function growth that occurred after moving was associated with the change in air quality between the original and new community. Our findings from this sub-study are described in Section 4.2.1.1.5.

The design of the CHS called for following Cohort C participants from 4th grade (average age 10 year) until graduation from high school (average age 18 years). Section 4.2.1.1.6 reports on the

relationship between air pollution and the overall growth in lung function over this 8-year period, and on whether air pollution exposure is related to the attained lung function level at age 18. Section 4.2.1.1.7 describes an analysis of these 8-year data aimed at determining whether the maximum rate of growth during this interval was related to air pollution exposure.

In all results presented below, associations denoted as statistically significant are those that yielded a p-value less than 0.05, assuming a two-sided alternative hypothesis.

4.2.1.1.1. Initial cross-sectional analyses

This section summarizes our analysis of whether initial lung function level, based on measurements obtained in the first year of the CHS, were associated with air pollution. The paper describing this investigation may be found in the Appendix (Peters et al. 1999a). The data for this analysis consisted of PFT's on 3,293 subjects from Cohorts A, B, and C. Air pollution exposures were assessed using air quality data collected in 1986-1990 by existing monitoring stations, and using data collected by our study team in 1994. Expected relationships were seen between lung function and demographic, physical, and other environmental factors. For example, age, sex, race, height, weight, body mass, asthma status, active smoking, and the presence or absence in the home of a gas stove or a cat were all significantly associated with FEV_1. After adjusting for these personal factors, we observed an association between pollution levels and lower lung function in female subjects. For example, based on 1994 pollution data, an increase of 25 ppb in exposure to NO_2 was correlated with a decrease of 44.1 ml in average FEV_1 for females ($p<0.05$). Deficits in FEV_1 in females were also significantly associated with exposure to PM_{10}, $PM_{2.5}$, and strong acid (nitric + hydrochloric). The pollutants NO_2, PM_{10}, and acid were also associated with significant deficits in FVC, MMEF, and peak expiratory flow rate (PEFR) in females. Significant deficits in average PEFR were also related to O_3 exposure in females, and although O_3-effect estimates in females were also negative for the other lung function outcomes, none achieved statistical significance. No statistically significant pollutant associations were observed overall in males for any of the lung function measures.

In a second analysis, we stratified children into two groups based on the amount of time they reported spending outdoors. At entry to the study, subjects were asked how many hours they spent outdoors over the previous 2-week period. Responses to this question were used to stratify subjects into either the "more outdoors" or "less outdoors" group based on whether they were above or below the median for their respective community, sex, and grade cohort. For both males and females, pollutant related deficits in average lung function were generally larger in those subjects who spent more time outdoors. For example, an increase of 25 ppb in NO_2 was associated with a decrease of 75.9 ml in average FEV_1 in more-outdoors females, but a decrease of only 17.8 ml in less-outdoors females. For boys, those spending more time outdoors had statistically significant deficits in average FVC and FEV_1 associated with exposure to O_3.

We included the three grade levels (Cohorts A, B, and C) in this cross-sectional study to determine whether older children, because of their longer exposure, had greater pollutant-related effects on their lung function. Although we found no significant or consistent patterns across lung function measures, the pollutant effects on FEV_1 for females were more negative in the 10^{th} grade cohort.

These analyses suggested that exposure to air pollution may have chronic effects on children's lung function. The strongest associations were observed with NO_2, PM_{10}, $PM_{2.5}$ and strong acid (nitric + hydrochloric). The high correlation in levels of these pollutants across communities prevented our determination of which, if any, of these pollutants might be most important. Somewhat surprisingly, O_3 was not generally associated with deficits in lung function. Although we had measures of physical size in these subjects, we did not know the rates of growth based on these cross-sectional data. On the assumption that air pollution may have its greatest effect as the lung develops, we now turn our attention to the longitudinal data to assess the role of air quality on lung function growth.

4.2.1.1.2. Four-year follow-up, Cohorts A, B, and C

We examined longitudinal lung function data from the first 4 years of follow-up to determine whether air pollution affected lung function growth. The paper describing this investigation may be found in the Appendix (Gauderman et al. 2000). The outcome data for this evaluation included lung function measurements from 1993 to 1997 for Cohorts B and C, and from 1993 to 1995 (through 12th grade) for Cohort A. A total of 11,536 lung function measurements conducted on 3,035 children were included in this analysis. Approximately 50% of these children were from Cohort C, with 25% in Cohort A and 25% in Cohort B. The exposures of interest were the 3-year mean levels of each pollutant, based on air quality data collected at CHS community stations over the period 1994 to 1996. The 3-year mean levels of NO_2, inorganic acid (nitric + hydrochloric), PM_{10}, $PM_{2.5}$, and the coarse particle fraction $PM_{10} - PM_{2.5}$ were significantly correlated with one another, but none of these pollutants was correlated with mean levels of O_3.

The 3-stage model described in Section 3.6 was used to determine whether the average lung function growth rates of the children in each community were associated with the corresponding average pollutant levels in these communities. Because lung function increases nonlinearly from childhood through adolescence, all analyses were conducted separately by grade cohort. The growth parameter of interest was the annual average percent growth in lung function. As an example, FEV_1 increased at an average rate of 11.8% per year in both boys and girls from cohort C over this 4 year period. Across the 12 communities, FEV_1 growth rates in Cohort C ranged from 11.1% (San Dimas) to 12.5% (Lompoc). The average lung function growth rates in the 12 communities were compared graphically with the community mean concentrations of each pollutant. We reported pollutant effects as the difference in estimated percent growth rate per year from the lowest to highest observed mean pollutant concentrations. Negative differences indicated reduced growth with increased exposure.

Figure 4.2-1 shows the adjusted community average FEV_1 growth rates in Cohort C, plotted against mean concentrations of six pollutants. Deficits in FEV_1 growth were significantly correlated with NO_2 ($p=0.02$), inorganic acid ($p=0.04$), PM_{10} ($p=0.02$), $PM_{2.5}$ ($p=0.05$) and $PM_{10} - PM_{2.5}$ ($p=0.03$). For example, the estimated FEV_1 growth rate (represented by the straight line on the graph) at the lowest NO_2 concentration was 12.14% while it was 11.37% at the highest NO_2 concentration, yielding a pollutant effect of –0.77%. This absolute difference of 0.77% translates into relative reduction of 6.3% (0.77/12.14) in growth rate for those exposed to the highest NO_2 levels compared to those exposed to the lowest levels. In Cohort C, deficits in growth of FVC, MMEF, and FEF_{75} were also associated with exposure to NO_2, PM_{10}, and

inorganic acid. In Cohorts A and B, almost all pollutant effect estimates for NO_2, inorganic acid, PM_{10}, $PM_{2.5}$, and $PM_{10} - PM_{2.5}$ were negative, but none of them achieved statistical significance. This lack of statistical signficance in Cohorts A and B may be due to their lower sample size, relative to the size of Cohort C. Lung function growth was not associated with O_3 exposure in any of the Cohorts.

The observed associations between FEV_1 growth and pollution in Cohort C remained significant with adjustment for various indoor sources of air pollution, including a gas stove, passive tobacco smoke, and pets. Additionally, the pollutant effects were of similar magnitude in subsets of asthmatic and non-asthmatic children. The effects in asthmatics were not by themselves, statistically significant, but the sample size in this group was quite small (about 14% of the study sample). There were no significant differences in air pollution effects between boys and girls. Stratification of Cohort C by time spent outdoors revealed that the magnitudes of pollutant effects were generally larger in those who reported spending more time outdoors, compared to the less-outdoors group. For example, the estimated NO_2 effect on FEV_1 growth was –1.00% in the more-outdoors group, and was –0.57% in the less-outdoors group.

In a series of 2-pollutant models for FEV_1 growth in Cohort C, adjustment for O_3 had little impact on the effect estimates or statistical significance of any of the other pollutants. For example, the univariate effect estimates for NO_2 (–0.77%) and PM_{10} (–0.85%) became –0.76% and –0.86%, respectively, with adjustment for O_3. However, in the 2-pollutant model with NO_2 and PM_{10}, their corresponding effect estimates were both reduced (–0.50% and –0.48%, respectively), and both were not statistically significant. A similar pattern of 2-pollutant versus univariate effect estimates was observed for any pair of the pollutants NO_2, inorganic acid, or the PM metrics. This reduction of effect in 2-pollutant models is expected given the positive correlation among these pollutants, and underscores the difficulty in identifying the independent effects of any single pollutant.

4.2.1.1.3. Four-year follow-up, Cohort D

The availability of Cohort D provided us an opportunity to replicate our own findings. The paper describing this investigation may be found in the Appendix (Gauderman et al. 2002). The data for this investigation included 7,106 PFT measurements made on 2,081 children from Cohort D over the period 1996 – 2000. The communities and data collection protocols were the same as those used for Cohort C. Mean pollutant levels in each community were computed using air quality data collected over the period 1996-1999. In addition to the pollutants investigated for Cohort C, we also obtained data for elemental carbon (EC) and organic carbon (OC) based on analysis of the $PM_{2.5}$ filters. Mean levels of O_3 were not significantly correlated across communities with any other pollutant, but all remaining pollutants were correlated with one another. The statistical approach to modeling the relationship between pollutants and lung function growth was the same as that described above for Cohort C.

Over this 4-year study period, FEV_1 increased at an average of 11.8% per year in both boys and girls, ranging across communities from 11.0% (San Dimas) to 12.4% (Santa Maria and Lancaster). FEV_1 growth rates were negatively correlated with mean levels of acid (nitric + formic + acetic) ($p=0.03$), with a pollutant effect of –0.6% across the range of acid exposure. (Hydrochloric acid values were excluded from these analyses because they were typically very low or at the level of analytical detection). This absolute difference of 0.6% translated into a

relative reduction of 5% in the FEV_1 growth rate from lowest to highest mean acid levels. Negative correlations were also observed between FEV_1 growth and the other pollutants, but none achieved statistical significance. We observed larger pollutant-related deficits in MMEF in this Cohort (Figure 4.2-2). MMEF growth rates were negatively correlated with NO_2 (p=0.02), acid (p=0.005), $PM_{2.5}$ (p=0.05), and EC (p=0.04). Across the range of mean acid levels, the MMEF growth rate declined from 11.6% to 10.3% (pollutant effect = –1.3%), corresponding to a relative reduction of 11% (1.3/11.6) in MMEF growth. Additional analysis also revealed significant associations between the ratio MMEF/FVC and NO_2 and acid, and between PEFR and O_3.

Two-pollutant models for both FEV_1 and MMEF revealed the most consistent associations with acid. Specifically, the univariate effect estimates for acid remained negative and of similar or larger magnitude in a model that included any of the other pollutants. On the other hand, adjustment for acid substantially changed the univariate effect estimates of all other pollutants. Although these analyses might suggest that acid is most strongly related to lung function deficits, the high correlation among pollutants makes it difficult to identify the independent effects of any one pollutant.

The pollutant effects observed in Cohort D were generally comparable to those observed for Cohort C (Table 4.2-2). To facilitate direct comparisons between Cohorts, the effect estimates for Cohort C in this Table are scaled to the same range as those used for Cohort D, i.e. to the difference from least to most polluted community over the Cohort D study period. As an example, for FEV_1, the acid effect estimate was –0.82% (p=0.01) in Cohort C and –0.63% (p=0.03) in Cohort D, while for MMEF, the corresponding acid effects were –1.16% (p=0.02) and –1.28% (p=0.005). For all combinations of pollutants and lung function measures, there were no significant differences in pollutant effects between cohorts. As in Cohort C, the pollutant effects were generally larger in Cohort D for children who reported spending more time outdoors. For example, the effect of acid on FEV_1 growth was –1.01% (p=0.002) in the more-outdoors subgroup, but only –0.3% (p=0.45) in the less-outdoors subgroup.

Although it was difficult to identify specific pollutants that were most associated with lung function deficits, some trends emerged from the analysis of these two Cohorts. For example, associations of lung function growth with PM_{10} and $PM_{10} - PM_{2.5}$ observed in Cohort C were not replicated in Cohort D. On the other hand, fine particles ($PM_{2.5}$) and the EC portion of $PM_{2.5}$ were correlated with growth deficits in both Cohorts. Of the gaseous pollutants, NO_2 and acid showed consistent associations across Cohorts, but the correlation between PEFR and O_3 observed in Cohort D was not seen in Cohort C.

In summary, the replication in Cohort D of our earlier Cohort C findings adds significant strength to the evidence that air pollution causes deficits in lung function development in children from 4^{th} to 8^{th} grade (average ages 10 to 14 years). In Section 4.2.1.1.6, we will revisit Cohort C to determine how air pollution exposure affected lung function development over the entire adolescent period, from 4^{th} to 12^{th} grade.

4.2.1.1.4. Four-year follow-up, associations with other pollutant measures

In our published work on lung function, we have focused on the pollutants described above. These were the pollutants that formed the basis for our selection of communities and that were monitored continuously during the study period. However, during the course of the study, we have investigated associations between lung function and various other pollutant metrics. Results from these analyses are summarized below.

Lung function growth and revised estimates of community-average NO_2

In 2000, we conducted a pilot study (supported through our Southern California Environmental Health Sciences Center), to measure NO_2 levels at the homes and schools of a sub-sample of our CHS participants. Homes were randomly sampled for NO_2 monitoring within strata defined by community, neighborhood, and traffic density (TD). Neighborhood was defined as the set of homes of children that attended the same elementary school. Within each neighborhood, the median of distance-weighted TD was computed, and homes were further stratified as 'above' or 'below' the median TD. Within each community/neighborhood/TD stratum, we randomly sampled between 4 and 8 homes for monitoring. Passive NO_2 monitors were deployed for two 2-week periods, one in the summer and one in the winter of 2000. In addition to the homes, samplers were deployed at elementary schools and at the central site monitoring location. All sampling within a given community was conducted over the same 2-week period to facilitate spatial comparisons among sites.

We computed the average of all NO_2 levels recorded at homes and compared this average to the corresponding levels recorded at the central site monitor. In 10 of the 12 communities, the home-based average was less than the level recorded at the central site. The ratio of home-average to central site value in these 10 communities ranged from 0.63 (Lancaster) to 0.95 (Riverside). In the remaining 2 communities (Lake Arrowhead and Lompoc), these ratios were both 1.10. These results indicated that the NO_2 levels in the neighborhoods where children spend most of their time are typically lower than levels recorded at the community central site monitoring location.

We applied our observed ratios of home-average to central-site levels to the long-term NO_2 averages recorded at central sites, i.e. to the NO_2 levels used in our growth analyses reported above. In an analysis of 4-year growth in cohorts C and D combined, the estimated NO_2 effect using central site data was –0.66% (p=0.03), i.e. a reduction of 0.66% in the annual-average growth rate of FEV_1. Using the ratio-adjusted central site data, this effect estimate was larger in magnitude (–0.92%) and more significant (p=0.006). In general, non-differential exposure measurement error will produce effect estimates that are biased toward the null (i.e. toward an effect size of zero). Thus, the increased NO_2 effect size we observed is what we would expect if the ratio-adjustment served to reduce measurement error in children's assigned NO_2 exposures.

Lung function growth and constituents of PM

The filters used to measure $PM_{2.5}$ mass were also analyzed to determine levels of various constituents of the $PM_{2.5}$, including nitrate, sulfate, and ammonium. In general, long-term average levels of these constituents were very highly correlated with $PM_{2.5}$ mass across communities (see Table 4.2-3). Not surprisingly, estimated effects of these constituents on 4-year lung function growth were nearly identical to those shown for $PM_{2.5}$ in Table 4.2-2.

Some studies have used surrogates for air pollution that are thought to reflect more specific sources of ambient particulate exposure than what is captured in the community-mean level of PM_{10} or $PM_{2.5}$. For example, mortality time-series of the Harvard Six Cities Study have been undertaken to investigate the association with daily $PM_{2.5}$ mass concentration, as well as the silicon (Si), lead (Pb), and selenium (Se) content of $PM_{2.5}$ (Laden et al. 2000). Silicon was considered as a measure of $PM_{2.5}$ from non-combustion sources, lead reflected $PM_{2.5}$ from gasoline combustion (1979-88), and selenium was used as a marker for coal combustion-related PM. The strongest association with daily mortality rates was observed for lead. Se and $PM_{2.5}$ mass were also significantly associated with death rates whereas silicon showed no association, supporting the hypothesis that PM from combustion sources is more important than PM from non-combustion sources.

The CHS team, thus, decided to investigate associations between more source specific indicators of ambient pollution and health. In 2001, chemical elements were analyzed in bi-weekly samples of $PM_{2.5}$, collected in all 12 communities. We analyzed this exposure data to determine the association between lung function growth and pollution from specific sources. To accomplish this goal in a valid manner, we first asked whether the 2001 annual mean value would be an appropriate surrogate for the long-term (1994-2001) average conditions. Given the lack of older data for chemicals, we compared the 2001 community mean values of PM_{10}, $PM_{2.5}$, NO_2, acid, and various metrics of ozone with the 1994-2000 mean. For all these pollutants, cross-community correlations were very high ($r > 0.96$). Assuming that there was little change in the PM composition across these years, we believe that the elemental data of 2001 provide a reasonable surrogate for investigating the association with pulmonary function growth over the previous years. The models were restricted to the maximum mid-expiratory flows (MMEF). Effects on MMEF were strongest and most consistent, thus ideal to test the specific contributions of various exposure surrogates. Note that the single pollutants need to be primarily considered indicators of mixtures from specific sources, thus, we do not investigate hypotheses of specific effects of a single constituent on one specific measure of pulmonary function. Our approaches to determine exposure are not sufficient to investigate effects on such level of detail. The analysis is based on the same population (i.e. the 4-year cohort data) and statistical framework used in other analyses (Gauderman et al. 2000) and described in this report.

The elements aluminum (Al), silicon (Si), sulfur (S), chlorine (Cl), potassium (K), calcium (Ca), titanium (Ti), manganese (Mn), iron (Fe), nickel (Ni), copper (Cu), zinc (Zn), bromine (Br), strontium (Sr), and lead (Pb) all showed community mean values above the detection limit (XRF). A crustal factor (CF) was derived as the sum of (Fe+Ca+Si+Al+K).

To overcome multiple testing problems, we first investigated the bivariate associations of the chemical elements, including CF, and the exposure terms used in the previous models (Gauderman et al. 2000; Gauderman et al. 2002). Factors with correlations >0.8 with any of the primary surrogates (PM_{10}, $PM_{2.5}$, NO_2, or acid) were not further considered. Unfortunately, almost all constituents of PM were highly correlated with at least one or often several of the other measures. For example, the Pearson correlation of CF and PM_{10} reached 0.94. However, silicon and aluminum (both highly correlated) and chlorine were less correlated with the primary surrogates. The MMEF analyses revealed no association between Si (Al) and Cl with the MMEF

growth. Figure 4.2-3 shows the result for silicon. Given the high correlation between Si and Al, the associations between Al and MMEF are very similar to the ones shown for Si.

The high correlation between all combustion related pollutants precludes a clear allocation of effects to specific sources with this approach. However, the analysis is in line with the interpretation that the $PM_{2.5}$ fraction(s), which do not originate from combustion, may not impose adverse effects on children's lungs. It is an inherent limitation of the elemental measurements that the compounds are not known. Silicon is ubiquitous in ambient aerosols with contributions from various crustal material in the form of aluminosilicates, or as crystalline or amorphous Si. Thus, the Si-signal would also be a marker for the contributions from silica, a known occupational risk factor for pulmonary silicosis. However, lack of association with the Si content should not be interpreted as incompatible with these known effects (Hertzberg et al. 2002). The ambient silica exposures are much lower - even if all Si measured on $PM_{2.5}$ were to originate from silica.

We have used the fraction of Si in $PM_{2.5}$, thus our results cannot directly contribute to the debate about the health relevance of the coarse fraction (Schwartz et al. 1996; Ostro et al. 1999; Laden et al. 2000).

Lung function growth and pollutant measures of fresh exhaust
The central site monitors of the CHS have determined levels of three pollutants thought to be good indicators of fresh vehicle exhaust, including nitric oxide (NO), carbon monoxide (CO), and ultrafine particles. Data for NO were available from all study years, while data for CO and ultrafine particles have only been collected more recently. As described in Sections 4.1.1.4.3 and 4.1.1.4.4, CO and ultrafine particle data were not available for all 12-study communities, and thus we await more complete exposure data for these pollutants before assessing their effects on lung function. NO data, on the other hand, was available from all study years, as was total oxides of nitrogen ($NOx = NO_2 + NO$). Across communities, the annual average levels of NO_2, NO, and NOx were highly correlated. Specifically, the correlations in averages based on data from 1994-2001 were R=0.97 between NO_2 and NOx, R=0.85 between NO_2 and NO, and R=0.95 between NOx and NO. We have analyzed the associations between these three pollutants and 8-year growth in FEV_1 and MMEF. Statistically significant associations between 8-year growth of FEV_1 and MMEF were observed with all three pollutants. However, the magnitudes of the effects were larger and more statistically significant for NO_2 than for NOx, and larger for NOx than for NO.

A marker of fresh exhaust such as NO is likely to exhibit substantial variation in levels within a given community. Specifically, levels should be high near sources (e.g. roadways) and much lower at only modest distances from the sources. Thus, the use of a single community-average level of NO (or any other marker of fresh exhaust) to characterize the exposure of all children in the study likely introduces substantial measurement error. The effect of exposure measurement error is often to reduce effect estimates and statistical significance. It is therefore not surprising that the associations we observed with NO were not as large as that of NO_2, which has a more regional character.

Lung function growth and traffic density (TD)
As described in Section 4.1.3.1, the residences of all CHS participants were geocoded. A variety of traffic-related measures (e.g. distance to the nearest freeway, traffic-weighed distance, CALINE model-based estimates of traffic-derived pollution) were then computed and assigned to each location. TD estimates were computed separately for freeways and surface roads. We analyze both of these metrics, as well as the sum of freeway and surface road TD. We let TD_{csi} denote the CALINE estimate of traffic density (freeway, surface road, or total) at home *i* in neighborhood *s* and community *c*. Neighborhood was defined as the set of homes of children that attended the same elementary school. For each TD metric, we computed the average TD in each neighborhood (TD_{cs}) and in each community (TD_c). Finally, we computed the deviation of TD at each home from the corresponding neighborhood average ($\Delta TD_{csi} = TD_{csi} - TD_{cs}$), and the deviation of the neighborhood average from the community average ($\Delta TD_{cs} = TD_{cs} - TD_c$). The three variables TD_c, ΔTD_{cs}, and ΔTD_{csi} define orthogonal (independent) variables that can be used to assess health effects at the town, neighborhood, and individual (home) levels, respectively. Focusing on the 4-year growth data from cohorts C and D combined, we modified the multi-stage model described in Section 3.6 to test for association between lung function development and TD at each of these three levels. We also fit a separate model that included only TD_{csi}. The estimate of TD effect from this 'combined' model represents a weighted average of the estimates from the town, neighborhood, and home levels.

Community-mean traffic density (TD_c) ranged from 0.14 (Lompoc) to 2.18 (Long Beach). Even within the Los Angeles basin, there was a wide range in TD_c, from 0.31 in Upland to 2.18 in Long Beach. Correlations (R) between-community-mean traffic density (TD_c) and community mean of annual average pollutant levels were R= –0.35 for 10am-6pm O_3, R=0.32 for PM_{10}, R=0.42 for $PM_{2.5}$ R=0.67 for NO_2, R=0.44 for inorganic acid (HNO_3 + HCl), and R=0.62 for EC. Only the correlations of average TD with NO_2 and EC were significant at $p<0.05$. Table 4.2-4 shows the effects of the various TD metrics on growth of FVC, FEV_1, and MMEF. Based on total (freeway+surface road) TD, no significant associations with growth of any lung function measure were observed at the town, neighborhood, or home levels. The combined effect of TD, averaging across these three levels, was close to zero and not significant. Freeway-based TD showed similar nonsignificant associations with all three lung function growth measures. For surface-road TD, variation in average traffic from neighborhood to neighborhood was associated with deficits in FVC and FEV_1 growth. However, consistent associations with surface-road TD were not observed at the town and home levels, and the overall combined surface-road TD effect was not significant. Models that included both combined TD and community-average NO_2 showed a statistically significant association of growth with NO_2, but again no evidence of a TD effect (data not shown). Additional models with TD and inorganic acid, or TD and EC, showed similar trends, i.e. an effect of the pollutant but not TD.

The availability of TD estimates at each home allows investigation of effects within each community. In the above analyses, we considered two types of within-community effects: neighborhood-to-neighborhood and home-to-home. There was some evidence that deficits in lung function growth were associated with surface-road TD based on neighborhood comparisons, but consistent effects were not observed in home-to-home comparisons or with freeway-based TD. It is possible that a neighborhood average TD value better characterizes a child's actual exposure than the estimated TD at his home, as the child spends much of his/her day at school, in

transit from home to school, and possibly at after-school activities in his/her neighborhood. If this is the case, however, it is not clear why we did not also see associations with freeway TD at the neighborhood level. The correlation of community average TD with measured pollutant levels at the central site monitors were relatively weak compared to the correlations we have observed among pollutants. This opened the door to identify an effect of TD at the community level that was independent of the effects we reported above with measured air pollutants. The lack of association with TD at the community level may indicate that transported pollutants have a larger impact on lung function health than local, fresh emissions. Additional measurements of air pollutants within each community (e.g. at homes and schools) are needed to validate traffic density models in our study communities and to investigate within-community associations between air pollution and lung function.

4.2.1.1.5. Movers study, Cohorts C and D

Long-term studies of free-living populations can be complicated by practical limitations such as subject withdrawal or re-location (Detels et al. 1987). Subject withdrawal or relocation may inadvertently introduce bias through the loss of specific sub-groups within the general study population, such as sensitive individuals who perceive themselves as being at increased risk if they remain in the study area. Subjects who relocate to other communities can also experience substantial changes in ambient pollution exposure by moving from an area of higher pollution to one characterized by lower ambient pollutant levels or vice versa.

As the CHS longitudinal study progressed year by year, a number of subjects moved away from study communities due to changes in family status, parents' change of job, or other considerations. To assess (a) the potential for systematic bias caused by out-migration of portions of the study cohort, and (b) whether re-location to another community of differing pollution profile had a measurable effect on subjects' lung function growth rates, an investigation was undertaken to locate and study former study subjects who had moved away from study areas. Although this "movers" project was funded separately by another agency (U.S. EPA), the relevance of its findings to the CHS makes it appropriate for inclusion in the discussion. The paper describing this investigation may be found in the Appendix (Avol et al. 2001).

Our previous findings (Gauderman et al. 2000) reporting observed decrements in several annual lung function growth rate indices (FEV_1, FEF_{75}, MMEF) in subjects living in areas of higher pollution (PM_{10}, NO_2, or inorganic acid) led us to wonder whether a change in community pollution levels (caused by relocation to a different community) could lead to measurable changes in lung function performance. To test this hypothesis, we identified a pool of subjects in 1998 who had begun their testing in the CHS in 1993 or 1994, who had one or more years of acceptable lung function data, and who had moved away from CHS communities at least one year prior to "mover" study follow-up (in 1998). Ambient pollution data had to be obtainable for the subject's residential location at the time of follow-up, and subjects had to have moved no farther away than California, Arizona, Nevada, Oregon, Washington, or Utah. On the basis of these criteria, 164 subjects were eligible for study, 149 responded to telephone or mail contact, and 110 subjects were tested.

Subjects were assigned pollution scores on the basis of annual average 24hr NO_2, daily average PM_{10} mass, and average daytime (10am to 6pm) O_3 levels in their current and former

communities. Differences between current and former community O_3, NO_2, and PM_{10} levels were calculated and used in pollutant-specific analyses representing subject-specific changes in ambient exposure. Negative pollution scores reflected moves to areas of lower pollution (in other words, the current community of residence had lower ambient levels of O_3, NO_2, or PM_{10} than did the former community). Positive pollution scores represented moves to communities with higher ambient air pollution levels.

Subjects participated in the follow-up study by completing a written questionnaire and performing maximal effort spirometry, in an identical protocol to that performed by the subjects as students in participating schools in prior years. Testing involved 59 boys (age 10.2$\pm$0.5 [mean$\pm$SD] yr at baseline and 15.1$\pm$0.4 yr at follow-up) and 51 girls (age 9.9$\pm$0.4 yr at baseline and 14.9$\pm$0.4 yr at follow-up). Annual average changes in lung function were individually determined by subtracting subjects' baseline values from their follow-up values and dividing by the difference in the age at testing. Linear regression was used to determine whether annual average changes in lung function correlated with average changes in pollution. Models were adjusted for sex, race, CHS entry year, annual average change in height, weight and body mass index, and the interaction of sex with annual average change in height.

As depicted in Figure 4.2-4, increased exposure to PM_{10} was associated with decreased rates of annual growth in MMEF ($p=0.04$), PEFR ($p=0.007$), and with marginally decreased rates of annual growth in FEV_1 ($p=0.06$). Effect estimates for changes in pollution levels for PM_{10}, NO_2, and O_3 are shown in Table 4.2-5. For each 10ug/m^3 increase in annual average 24hr PM_{10}, annual lung function growth was estimated to decrease by 6.6ml for FEV1, 16.7ml/s for MMEF, and 34.9ml/s for PEFR. In other words, subjects moving to communities with higher daily PM_{10} had lower annual lung function growth rates, while subjects moving to communities with lower daily PM_{10} levels had higher annual rates of lung function growth. Increases in NO_2 and O_3 were also estimated to reduce lung function growth rates, but none of these effects were statistically significant at the 5% level.

To address issues of bias due to loss of follow-up, annual lung function growth rates and responses to health questionnaires of the "movers" were compared to those of their 1993 peers (who remained in study communities through Spring 1998, and were denoted as "stayers" [n=1002] for the purposes of this analysis). No statistically significant differences were observed in the baseline questionnaire data for movers and stayers with regard to anthropomorphic characteristics, respiratory health status, or residential exposure indices. Overall, movers and stayers were generally comparable in terms of physical co-variates and lung function, with only a few exceptions. More movers than stayers were non-Hispanic whites, and the average annual lung function changes in movers and stayers were comparable except for peak flow rates, which were slightly lower [~69ml/yr] in movers.

Based on the results of this investigation, it seems unlikely that any systematic study bias was introduced by subjects moving away from CHS communities. However, the differences in ambient pollution levels between current and former communities of residence were sufficient to measurably alter annual lung function growth rates in subjects who relocated. On average, lung growth rates for subjects who moved to communities of lower PM_{10} accelerated, while lung growth rates for subjects who moved to communities of higher PM_{10} slowed down.

4.2.1.1.6. Eight-year follow-up, Cohort C: 8-year growth and attained level

Note: The manuscript describing this analysis is currently in review. These results should therefore not be quoted or cited.

The manuscript describing this investigation may be found in the Appendix (Gauderman et al. in review). The focus of this analysis is on determining whether the 8-year growth in lung function (from 4^{th} to 12^{th} grade, average ages 10 to 18) is related to air pollution exposure. The outcome data consisted of 5,301 PFT measurements recorded from 846 girls, and 5,305 measurements recorded from 863 boys. Community-average pollution levels were computed using on-study air monitoring data over the 7-year period from 1994 to 2000. We adopted a 2-stage modeling approach to relate 8-year lung function growth to community-average air pollution.

The first-stage model was a regression of each pulmonary function measure (log-transformed) on age to obtain community-specific average growth curves, separately for girls and boys. To account for the growth pattern during this period, we used a linear spline model (Wang et al. 1993) that consisted of four straight lines over the age-year intervals <12, 12-14, 14-16, and >16, constrained to be connected at the three knot points. The model included adjustments for log height, body mass index (BMI), BMI^2, race, Hispanic ethnicity, a history of doctor-diagnosed asthma, any tobacco smoking by the child in the last year, exposure in the home to environmental tobacco smoke (ETS), exercise or respiratory illness on the day of the test, and indicator variables for field technician and spirometer. Race, Hispanic ethnicity, and history of asthma and ETS exposure at study entry were obtained from a baseline questionnaire. The baseline questionnaire was also used to obtain data on household exposure to gas stoves and pets, exposure to maternal smoking while in utero, and parental education (less than high school, completed high school, some college, college degree, some graduate training). Annual questions administered at the time of the pulmonary function test were used to update asthma status and ETS, and to obtain each child's smoking, exercise, and respiratory illness information. In addition to these covariates, random effects were included to account for the multiple measurements contributed by each subject. Analysis of residuals confirmed that model assumptions were satisfied. The first-stage model was used to estimate the mean and variance of 8-year lung function growth 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 8-year growth estimates on the corresponding community-average levels of each air pollutant. Inverses of the first-stage variances were incorporated as weights, and a community-specific random effect was included to account for residual between-community variation. A sex-by-pollutant interaction was included in the model to test for a difference in pollutant effect by sex, and when non-significant, the model was refitted to estimate the sex-averaged pollutant effect. Pollutant effects are reported as the difference in 8-year growth from the least to most polluted community, with negative differences indicative of growth deficits with increasing exposure. We also considered two-pollutant models obtained by regressing 8-year growth on pairs of pollutants simultaneously.

Significant ($p<0.05$) deficits in FEV_1 growth were associated with NO_2, acid (nitric + formic + acetic), PM_{10}, $PM_{2.5}$, and elemental carbon (EC). Significant deficits in FVC growth were associated with NO_2 and EC, while reduced MMEF growth was associated with NO_2. There was

no significant evidence that O_3 was associated with any of the lung function measures. In a series of 2-pollutant models for FEV_1 growth, no 2-pollutant model fit significantly better than any of the univariate models. Adjustment for O_3 did not substantially alter the univariate effect estimates of any other pollutant, and O_3 was not statistically significant in any of these 2-pollutant models. The NO_2 and acid effect estimates on FEV_1 growth were robust to adjustment for other sources of exposure to air pollution, including environmental tobacco smoke, *in utero* tobacco smoke, and presence in the home of a gas stove. Pollutant effect estimates for NO_2, acid, and EC were also significant and of similar magnitude in the subset of non-asthmatic children, and in the restricted sample of children who had a PFT measurement in 1993 and 2001, i.e. children who were observed over the full 8-year duration of the study.

Based on the cross-sectional data obtained in our last year of follow-up (2001), we calculated the percent-predicted for FEV_1 for each child. This was based on a ratio of their observed FEV_1 to their FEV_1 predicted from a model that included age, ln(height), sex, BMI, BMI^2, race/ethnicity, asthma status, indicator variables for field technician, and sex-by-ln(height), sex-by-asthma, sex-by-race/ethnicity interaction terms. A child was defined to have 'low FEV_1' if their observed/predicted FEV_1 was 80%, a criterion commonly used in clinical settings to identify individuals who are at increased risk for adverse respiratory conditions. Across the 12 communities, low FEV_1 was positively correlated with NO_2 (p=0.005), acid (p=0.01), PM_{10} (p=0.02), $PM_{2.5}$ (p=0.002), and EC (p=0.006). For example, the estimated proportion of children with low FEV_1 (represented by the regression line in Figure 2, see manuscript) was 1.6% at the lowest $PM_{2.5}$ exposure, and was 4.9 times greater (7.9%) at the highest $PM_{2.5}$ exposure. Similar associations between these pollutants and low FEV_1 were observed in the subsets of never-asthmatics and never-smokers (data not shown). Low FEV_1 was not significantly correlated with O_3 in any subject group.

4.2.1.1.7. Eight-year follow-up, Cohort C: Maximum growth rate

Note: Manuscript preparation for these data is ongoing. In this section, we describe the sample, methods, and a brief summary of results to date. These results should be considered preliminary pending peer review, and should not be quoted or cited.

The focus of this section is to examine the effect of air pollution on biologically important aspects of the lung function growth curves of school aged children that were followed from the 4^{th} grade (average age of 10 years) to the 12^{th} grade (average age of 18 years) during 1994-2000. Because it has been shown that lung function growth in children follows a gender-specific nonlinear pattern (Wypij et al. 1993; Berhane et al. 2000), the rates of growth in these nonlinear curves are not constant over the childhood growth period. One may then ask several biologically important questions in examining the effect of air pollution on childhood lung function growth patterns and attained levels. Specifically, one can investigate *(i)* whether the 8-year growth in lung function levels is related to air pollution *(ii)* whether the attained lung function level at any given age is related to air pollution, or *(iii)* whether the growth rate during puberty (a period of the fastest growth period) is related to air pollution. The first two questions have been dealt with in Section 4.2.1.1.6. In this section, we focus on the third question, i.e., on examining whether the maximum growth rate is related to air pollution.

The analyses posed several methodologic challenges. Firstly, the proper estimation of a growth curve with enough detail about the growth pattern during puberty and the subsequent estimation of the maximum rate of growth of the resulting non-linear curves pose methodologic challenges. Secondly, estimation of the variances of the community-specific maximum rate of growth estimates is not straight forward, as it cannot be easily obtained in closed form (a problem that has been well documented in Silverman (1985). Thirdly, inference on the relationship between the maximum rate of lung function growth and air pollution should incorporate the uncertainty estimates in the community-specific predicted maximum rates of growth in a proper way.

To address the above issues, we developed and applied a 2-stage mixed effects model. The estimation algorithm for this model

(i) fits community-specific lung function growth curves with proper adjustments for covariates (confounders and effect-modifiers) and subject-specific random growth parameters that account for inter-child variability in growth patterns,
(ii) uses a Bayesian Markov Chain Monte Carlo (MCMC) method (Zeger and Karim 1991; Carlin and Louis 1996; Hastie and Tibshirani 2000) to obtain variance estimates for the estimated community-specific maximum rates of growth, and
(iii) fits an ecologic regression that takes into account the uncertainty estimates of the estimated community-specific functionals to examine the relationship between maximum lung function growth rates and air pollution. The technical details of the above methodology are summarized in (Berhane 2002; Berhane in preparation-b).

In (i), community-specific lung function growth patterns are modeled by using piecewise cubic polynomials that are smoothly joined at a number of breakpoints known as knots. To make the curves more robust to influences of scarcity of data at both ends of the age range, we also put linearity constraints at two boundary values on both ends of the data. The resulting curves, known as natural splines (DeBoor 1974), enjoy the simplicity of being linear combinations of piecewise cubic polynomial functions. Hence, one can fit them using off-the-shelf software such as procedure PROC MIXED in SAS or the function LME in the S-plus language.

The results we describe below are limited to cohort C. The data consisted of 5,301 PFT measurements recorded from 846 girls, and 5305 measurements recorded from 863 boys. In fitting the first stage model, the PFT data were log transformed to satisfy normality requirements of the model, which was confirmed via model diagnostics. After a careful exploratory analysis to determine appropriate locations of the breakpoints and knots, the most parsimonious fits were found to be the ones that put interior break points at ages 11, 12 and 14 years, and boundary knots at the ages 10 and 18 years. But, because we fit community specific growth curves and the amount of data we have per community is limited, the models that included an additional knot between ages 10 and 12 (at 11 years of age) were relatively unstable for girls and did not converge at all for boys. Hence, the results that we present in this report are based on models that fitted three piecewise cubic polynomials between the ages 10-12, 12-14 and 14-18, and placed linearity constraints outside the range of 10-18 years. This first stage model included adjustments for log-height (as a nonlinear interaction term with age), race/ethnicity, baseline asthma status, respiratory illness during the day of the test, body mass index, room temperature, barometric pressure, and indicator variables for field technician and spirometer. It also included subject-specific random growth effects with an unstructured covariance matrix, to account for inter-child

variations in growth patterns. The resulting curves had five growth parameters, say (β_{1c}, β_{2c}, β_{3c}, β_{4c}, β_{5c}), per community $c=1, ..., 12$.

In an intermediate step, the first derivatives of the community-specific curves (to get age specific rates of growth) were obtained. Using a Bayesian MCMC method (outlined in Zeger et al. (1991) and Berhane et al. (in preparation-b), 10,000 Gibbs sampling realizations of the community-specific curves were obtained (with 1000 burn-in iterations) in order to estimate the full posterior distribution of the growth curve. The community-specific mean maximum rates of growth, say F_c, and their variances, $V_F^{(c)}$, were estimated from these posterior distributions. Figure 4.2-5 gives the growth curves (top two panels) and the rate of growth curves (lower two panels) for log (MMEF), along with 95% Bayesian confidence bands (broken lines) and 100 Gibbs sampling realizations (in gray) from the Markov chain Monte Carlo (MCMC) methodology. The histograms on the y-axis of the lower panels give posterior distributions of the maximum rate of growth of log (MMEF). Growth curves that added an additional knot at age 11 showed a clearer, and higher, maximum rate of growth (results not shown). As noted above, however, the uncertainty in that estimated peak growth rate was much larger than without that additional knot, particularly for the community-specific rates, so we have not used these estimates in the regressions on air pollution.

In the second stage, an ecologic regression was fitted, with appropriate inverse variance weighting based on the variance estimates of the estimates of maximum rates of growth, to examine the effect of multi-year average pollution levels to the community-specific estimates of maximum rate of lung function growth.

Descriptive details about the multi-year pollution levels that we use in this section have been provided in Section 4.2.1.1.6. The pollutants are highly correlated with each other, except for ozone which is not highly correlated with any of the other pollutants. Attempts have been made to look at the effect of two pollutants at a time, but our ability to distinguish between the independent effects of single pollutants is limited due to multicollinearity problems (see Section 4.2.1.1.8 on an approach to deal with the multipollutant issue). The average number of PFT measurements per child was about 7.8 over the follow-up period and did not vary appreciably by gender or community.

Because the lung-function growth trajectories are different, gender-specific first stage models were fitted to log transformed values of FEV_1 using boundary knots at ages 10 and 18 years, and interior knots at ages 12 and 14 years. To test whether the effect of air pollution was different between boys and girls, second stage ecologic models were fitted that included main effects for pollution and gender along with a *Gender X AP* interaction term. The interaction term that tests for gender differences in pollution effects was not significant for any of the air pollutants considered. Comparing the least to worst polluted communities over the range of 1994-2000 average pollution levels, the most significant deficit for FEV_1 was observed for total acid (nitric + formic + acetic), consistent with prior findings. Similar models were also fitted for FVC and MMEF. The results for FVC indicate that there was no significant gender-difference in the effects of air pollution. The most significant effects for MMEF were observed for total acid, PM_{10}, $PM_{2.5}$ and Elemental Carbon (EC) in girls. The effects for boys were smaller with the exception of O_3 (10-6), which showed bigger effects in boys. The estimated O_3 effect on peak growth rate was somewhat larger than that estimated for the four-year average growth rate

described earlier, but consistent with the trend comparing the 4- and 8-year analyses for this cohort. An extensive sensitivity analysis is being conducted on these preliminary results, and the final findings will be reported in upcoming publications.

4.2.1.1.8. Can specific pollutants be associated with health outcomes?

Most of the analyses described above are univariate, one pollutant being considered at a time. For various endpoints, we attempted to fit multipollutant models, but seldom obtained any models in which two or more pollutants both made significant contributions. Nevertheless, when drawing inferences about the effect of a particular pollutant, we still wish to take account of our uncertainty about whether other pollutants should be adjusted for, even if their contributions are not significant in any particular model. This is a well known problem in statistics known as "model selection" and "model averaging." Model selection refers to evaluation of the probabilities associated with each of a whole set of alternative models. Model averaging refers to evaluation of the effect of a particular variable when the form of the true model is unknown. Recent developments in the theory of Bayes model averaging (Raftery et al. 1997; George and Foster 2000) provide an approach to these problems. We have applied these methods to the analysis of 4-year changes in MMEF in cohorts C and D in relation to seven pollutants: O_3, NO_2, PM_{10}, $PM_{2.5}$, OC, EC, and acid (nitric + formic + acetic). Details of the statistical methods are described in Berhane et al. (in press). Basically, we fitted all possible models including 0, 1, 2, …, 7 pollutants and evaluated the posterior probability associated with each model and then used these probabilities to evaluate the contribution of each variable to the outcome, averaging over all models that contained that variable. Table 4.2-6 illustrates the Bayes model selection process on these data. A Beta distribution was used to specify the prior probability for each model, based on the number of variables they contained, with hyperparameters chosen to encourage parsimonious models. The table gives both the prior and posterior probabilities for all well-fitting models, together with the ratio of posterior to prior, a quantity known as the Bayes factor. Kass and Raftery (1995) provide subjective guidelines for interpretation of Bayes factors: less than 1 constitute evidence against a particular model, 1-3, barely worth a mention, 3-20, positive evidence in favor of a model, 20-150, strong evidence; greater than 150, very strong evidence. By these criteria, the best fitting model is that containing only acid (nitric + formic + acetic), but all two-pollutant models that include acid and models containing O_3 together with NO_2 or EC would be positively favored.

Table 4.2-7 provides a summary of the posterior distributions of the regression coefficients for each pollutant, averaging across all possible models. A multivariate normal prior was used for the coefficients, with zero mean and covariance matrix given by a multiple of the Fisher information matrix. The first two rows give the posterior probabilities and Bayes factors for each variable being included in the model; only acid attains a Bayes factor (5.27) in Kass and Raftery's "positive" range. The next two rows give the posterior probability for the sign of the coefficient given that it is in the model; again only the coefficient for acid is negative substantially more than half the time (BF=3.79). The next two rows combine the first two comparisons, providing the marginal probability that each coefficient is negative across all models, not just those in which the variable appears; in this case, the evidence for acid is much stronger (BF = 7.53). The final pair of rows gives the posterior mean and standard deviation of the coefficients, averaging across models which contain that variable. A comparison of the mean to its standard deviation is somewhat misleading here, as the posterior distributions are mixtures

of approximately normal distributions across a number of different high-probability models, and hence are not particularly normally distributed.

Although all variables except O_3 are univariately associated with MMEF growth rates, this analysis suggests that acid is the single best predictor of this outcome and no other variable significantly improves the fit of the model.

4.2.1.1.9. Can thresholds be identified for specific pollutants?

The question of whether it is possible to establish a "threshold" of a pollutant concentration below which there are no demonstrable health effects has important regulatory implications. Before addressing this question for specific pollutants and endpoints, we first explore some of the methodological challenges, illustrated with the effect of NO_2 on 4-year changes in MMEF in cohorts C and D.

One way to think about this question is to fit a model with an unknown threshold to be estimated and compare the fit of the best fitting model with a simple linear model. The model is of the form:

$$Y_c = \alpha + \beta(X_c - \tau)\, I(X_c > \tau)$$

where τ denotes the threshold and $I(.)$ is an indicator function taking the value 1 if the condition is true and 0 if false. One would then test H_0: $\tau = 0$ against H_1: $\tau > 0$ in this model. Figure 4.2-6 shows a plot of the community mean adjusted slope estimates for the 12 communities × 2 cohorts, plotted against the corresponding 4-year mean NO_2 concentrations. Superimposed on the plot are three lines, one representing the best fitting linear relationship (split line), one for the best fitting threshold relationship (dashed line), and one for the threshold relationship corresponding to the upper 95% confidence limit on the threshold (dotted line), derived as described below. We see that the best fitting threshold model, with a threshold at 12 ppb, differs only very slightly from a simple linear relationship; the improvement in the R^2 from 0.259 to 0.273 is completely nonsignificant ($p = 0.45$). Indeed, only a threshold model with a threshold as large as 30 ppb can be rejected compared with the best fitting model.

A fuller description of the fit of alternative models is provided in Figure 4.2-7, showing the fit of all possible models with thresholds between 0 and 40 ppb, together with the critical value for the F statistic comparing each model with the best fitting one. Thus, all we can conclude from this analysis is if there is a threshold at all, it must be less than 30 ppb. However, the converse is not true. This analysis does not imply that any exposure less than 30 ppb is safe. The reason for this is that with only 24 observations, the test of a threshold has very little power. To demonstrate this, we conducted a simulation experiment in which we generated 20,000 sets of MMEF data each, under a variety of models assuming a true threshold of various magnitudes and corresponding slopes for the high-exposure portion of the exposure-response relationship, holding the distribution of community ambient exposures fixed. Figure 4.2-8 shows the resulting power for the various simulated threshold models. Using the fitted relationship between high-exposure slope and threshold, the power is at best only 27% if the true threshold were as large as 30 ppb (a value at which the estimated slope is quite unstable), and only 14% if the true threshold were 22 ppb under a more stable linear estimate of the relationship between threshold and high-exposure slope. In other words, even if there truly was a relatively large threshold for

long-term average air pollution exposure below which there was no adverse effect, our study would have very little chance of detecting such a phenomenon.

Another way of examining the question of possible threshold effects is to ask whether we can find significant evidence of an exposure-response relationship if we limited our analysis to the subset of communities with exposures *below* some value of interest. Figure 4.2-9 shows the fitted slopes and their 95% confidence limits for analyses restricted in this way to various maximum exposure values. We see that only if communities with up to 30 ppb are included in the analysis is the estimated exposure-response relationship significant at the 5% level. However, there is very little change in the magnitude of the estimated slope down to about 20 ppb. Beyond that point, so few communities remain and the range of exposure values is so small that the confidence limits on the estimate become very large and no conclusions can be drawn. Thus, even though we cannot reject the null hypothesis that there is no effect of exposures below 30 ppb, our study has very little power to detect such an effect if it in fact exists. The apparent linearity of the exposure-response relationship down to 20 ppb further suggests that there is no evidence that any nonlinearity exists, at least down to that point.

Finally, we can get an even better picture of the shape of the low-exposure end of the relationship between MMEF and NO_2 by fitting various continuous exposure-response relationships. Figure 4.2-10 compares the fit of the linear no-threshold model shown in Figure 4.2-6 with a cubic polynomial. Again, despite the apparent threshold behavior, with no appreciable effect below 12 ppb, the improvement in R^2 from 0.259 to 0.280 is completely nonsignificant. Figure 4.2-11 provides two flexible, data driven, estimates of the exposure-response relationship. The top panel of Figure 4.2-11 is based on a smoothing spline fit with 3 degrees of freedom and is a purely data driven depiction of the functional form of the pollution effect. The bottom panel fits two separate lines that are joined smoothly at 12 ppb, a cutoff suggested by the smoothing spline. Neither of these curves fits significantly better than a simple linear relationship, although they both are compatible with an apparent threshold at about 12 ppb.

To summarize this methodological discussion, a variety of methods are available to examine the question of the existence of thresholds, but many more communities (distributed both above and below the postulated threshold) would be required for the study to have sufficient power to detect such a phenomenon if it really existed. *We emphasize that neither the failure to reject a model with thresholds below about 30 ppb nor to demonstrate a significant exposure-response relationship using only the communities below that value provides any evidence that such exposures are "safe."*

Before leaving this discussion, we also want to emphasize that this analysis was based on the community average responses to the long-term average ambient exposures. Two alternative hypotheses are possible:

- first, that even if it were possible to show that the population on average is not affected by exposures below some threshold, some subset of particularly sensitive individuals may be affected by exposures well below that value;
- second, even if it appeared that the effect of the long-term average exposure was linear, some aspects of the temporal variability in exposure might have threshold behavior.

The first of these hypotheses can be tested for identifiable groups of subjects, such as those with asthma, but we can never rule out the possibility that there are other unknown characteristics that are associated with unusual susceptibility (e.g., those with a particular genotype). The results summarized below include subgroup analyses for asthmatics, males and females, and children spending more time outdoors, but since the sample size for these subgroups are small, power for identifying threshold effects is even more limited than for the full cohort. To get an idea of the impact of unobserved variation in susceptibility, we did a further analysis of the MMEF vs. NO_2 data assuming a lognormal distribution of individuals' personal thresholds, fitting a linear relationship between the community mean MMEF and the proportion of individuals with thresholds below the ambient exposure for that community. The model generally showed a best fit for a population mean threshold of about 20 ppb (results not shown), but the results are very sensitive to the assumed variance in personal thresholds, a quantity that cannot be estimated from data in the form of ours. Thus, we do not feel that this line of approach is particularly rewarding.

The second hypothesis can be tested by examining a range of alternative exposure metrics, summarizing the temporal variation in exposure in various ways. In principle, one could compute the percent of time above threshold τ or the average exposure above τ for a range of values of τ, but we were concerned about the proliferation of significance tests and resulting increase in type I error rate. Instead, we chose to look for evidence of nonlinearity in the relationship between continuous exposure levels and concurrent decrements in lung function, integrated over time, by adding components of variance at different time scales to a model that included a linear effect of average exposure.

Table 4.2-8 summarizes the results of such comparisons for FVC and two pollutants. Whereas average NO_2 concentration shows a significant association with FVC, none of the temporal components of variation significantly improve the fit. On the other hand, there is no association with average concentration on O_3, but there is an association with the components of variance on hourly, daily, and (to a lesser extent) weekly scales. Thus, communities with large fluctuations in O_3 levels on these time scales appear to have slower lung function growth than to communities with similar average levels but less variability. This suggests that only relatively high concentrations of O_3, perhaps attained for only a few hours or days, may be the most relevant. Further analysis along these lines is on-going.

As shown in Sections 4.2.1.1.2 and 4.2.1.1.3, associations with the cluster of highly correlated pollutants NO_2, PM_{10}, $PM_{2.5}$, Acid (defined as either the sum of nitric and hydrochloric acids, or the sum of nitric and formic and acetic acids), EC, and OC tend to be very similar, and we would not expect much difference between them in terms of tests of thresholds. Figure 4.2-12 illustrates the exposure-response relationships for MMEF with the other pollutants. None show any evidence of low-exposure thresholds, while for EC and acid, the relationship appears to be linear throughout the range. There is a suggestion of a threshold for O_3, but the association with this pollutant is not significant in either model.

Table 4.2-1. Summary of mean lung function levels as children age from 10 to 18 years.

Lung Function Measure	Females			Males		
	10 years	14 years	18 years	10 years	14 years	18 years
FVC (ml)	2270.0	3460.9	3781.3	2451.1	3886.5	5263.5
FEV1 (ml)	1987.2	3040.8	3318.8	2097.0	3321.0	4507.9
MMEF (ml/sec)	2371.7	3539.1	3806.8	2344.9	3586.1	4802.6
FEF75 (ml/sec)	1494.1	2378.3	2519.8	1448.5	2300.8	3172.1
PEFR (ml/sec)	4771.1	6832.1	7599.8	4897.3	7396.6	10163.2

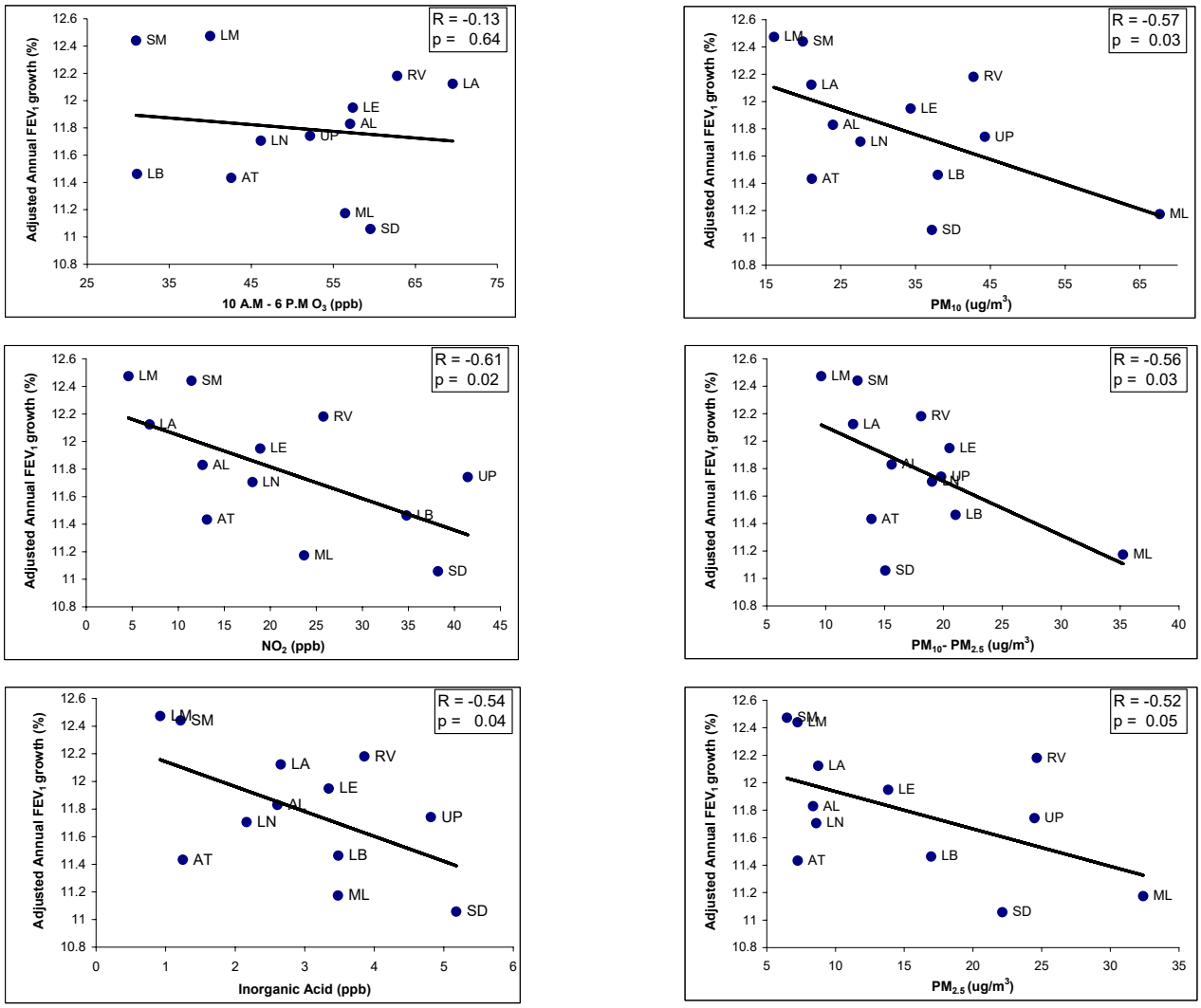


Figure 4.2-1. Adjusted average annual FEV1 growth rates for cohort C in the 12 communities versus the mean pollutant levels over the study period.

(Reprinted with permission from *Amer J Respir Crit Care Med*, Vol. 162, pp. 1383-90)

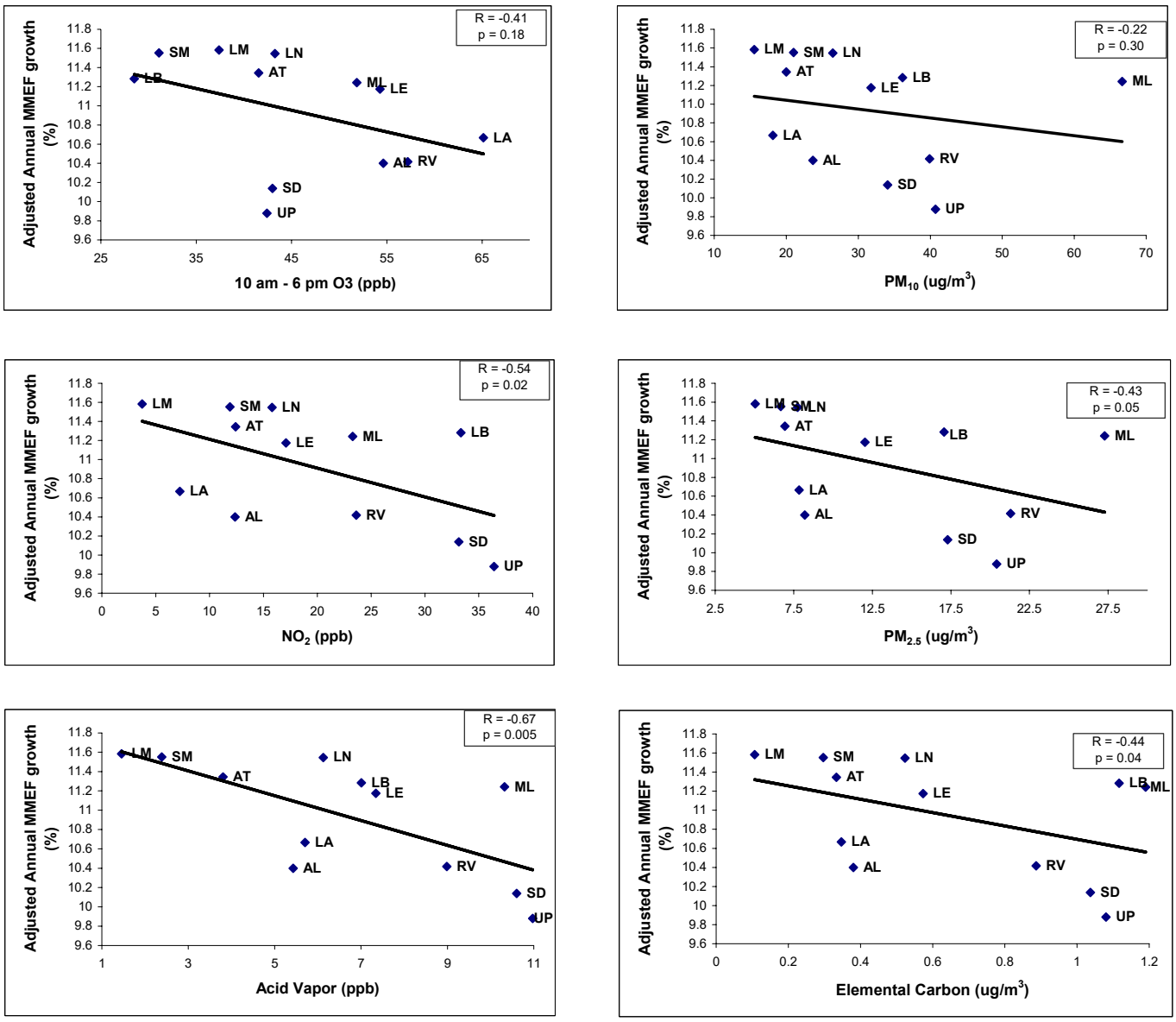


Figure 4.2-2. Adjusted average annual MMEF growth rates for Cohort D in the 12 communities versus the mean pollutant levels over the study period.

(Reprinted with permission from *Amer J Respir Crit Care Med*, Vol 166, pp.76-84)

Table 4.2-2. Difference in annual percent growth rates from the least to the most polluted community: Comparison of cohorts C and D.

PFT	Pollutant[a]	Cohort C (n=1,457)[b] % (95 % CI)	Cohort D (n=1,678)[b] % (95 % CI)
FVC	O_3 (10-6)	-0.22 (-0.77, 0.33)	-0.33 (-0.90, 0.24)
	NO_2	-0.46 (-0.92, 0.00)	-0.23 (-0.76, 0.29)
	Total Acid	-0.55 (-0.97,-0.11) *	-0.33 (-0.82, 0.17)
	PM_{10}	-0.60 (-1.18,-0.01) *	-0.03 (-0.68, 0.62)
	$PM_{2.5}$	-0.42 (-0.86, 0.03)	-0.14 (-0.67, 0.40)
	EC	-0.49 (-0.88,-0.09) *	-0.17 (-0.67, 0.33)
FEV_1	O_3 (10-6)	-0.32 (-1.14, 0.50)	-0.55 (-1.27, 0.16)
	NO_2	-0.66 (-1.34, 0.02)	-0.48 (-1.12, 0.17)
	Total Acid	-0.82 (-1.44,-0.19) *	-0.63 (-1.21,-0.05) *
	PM_{10}	-0.94 (-1.78,-0.10) *	-0.21 (-1.04, 0.64)
	$PM_{2.5}$	-0.63 (-1.28, 0.02)	-0.39 (-1.06, 0.28)
	EC	-0.71 (-1.30,-0.12) *	-0.40 (-1.02,0.23)
MMEF	O_3 (10-6)	-0.43 (-1.64, 0.80)	-0.80 (-1.94, 0.36)
	NO_2	-0.92 (-1.95, 0.12)	-1.10 (-2.00,-0.20) *
	Total Acid	-1.16 (-2.12,-0.19) *	-1.28 (-2.16,-0.40) ***
	PM_{10}	-1.41 (-2.61,-0.21) *	-0.67 (-1.92, 0.59)
	$PM_{2.5}$	-0.94 (-1.88, 0.01)	-0.94 (-1.87, 0.00) *
	EC	-1.07 (-1.94,-0.19) *	-0.92 (-1.78, 0.05) *
PEFR	O_3 (10-6)	-0.36 (-1.34, 0.63)	-1.21 (-2.06,-0.36) **
	NO_2	-0.82 (-1.62,-0.02) *	-0.17 (-1.18, 0.84)
	Total Acid	-1.00 (-1.75,-0.25) **	-0.74 (-1.62, 0.14)
	PM_{10}	-1.27 (-2.15,-0.37) **	-0.42 (-1.60, 0.77)
	$PM_{2.5}$	-0.82 (-1.55,-0.09) *	-0.44 (-1.41, 0.55)
	EC	-0.89 (-1.57,-0.20) *	-0.20 (-1.15, 0.76)

(Reprinted with permission from *Amer J Respir Crit Care Med*, Vol 166, pp.76-84)

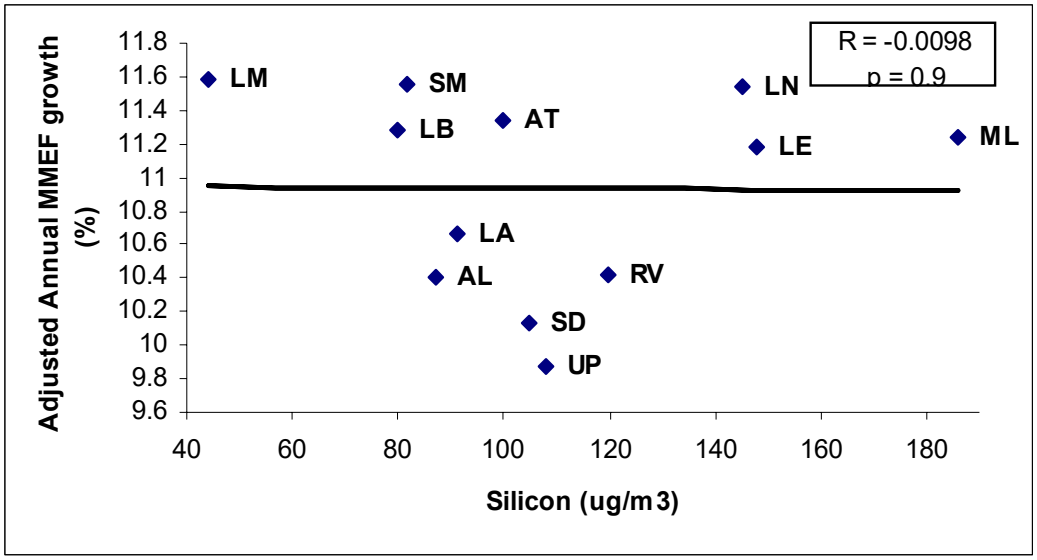


Figure 4.2-3. Association of MMEF with Silicon.

Table 4.2-3. Correlations among community average pollutant levels.

Pollutant[a]	PM_{10}	PM_{10} - $PM_{2.5}$	$PM_{2.5}NH_4$	$PM_{2.5}NO_3$	$PM_{2.5}$other	$PM_{2.5}SO_4$
$PM_{2.5}$	0.94 ***	0.22	0.99 ***	0.99 ***	0.98 ***	0.85 ****
PM_{10}		0.54	0.94 ***	0.94 ***	0.94 ***	0.78 ***
PM_{10} - $PM_{2.5}$			0.24	0.26	0.27	0.13
$PM_{2.5}NH_4$				0.99 ***	0.97 ***	0.85 ****
$PM_{2.5}NO_3$					0.97 ***	0.77 ***
$PM_{2.5}$other						0.77 ***

* p<0.05
** p<0.01
*** p<0.005
**** p<0.0005

Table 4.2-4. Traffic density (TD) and 4-year lung function growth.

			FVC		FEV1		MMEF	
TD Metric	Model	Comparison	% Diff	(p-value)	% Diff	(p-value)	% Diff	(p-value)
Total	1	Towns	-0.06	(0.32)	-0.10	(0.32)	-0.18	(0.32)
		Neighborhoods	-0.17	(0.41)	-0.16	(0.32)	0.05	(0.32)
		Homes	0.15	(0.09)	0.08	(0.32)	-0.19	(0.32)
	2	Combined	0.01	(0.88)	-0.04	(0.32)	-0.17	(0.32)
Freeway	3	Towns	-0.18	(0.25)	-0.28	(0.15)	-0.48	(0.07)
		Neighborhoods	0.18	(0.52)	0.24	(0.48)	0.53	(0.49)
		Homes	0.12	(0.29)	0.02	(0.86)	-0.39	(0.18)
	4	Combined	0.04	(0.65)	-0.04	(0.68)	-0.38	(0.05)
Surface	5	Towns	-0.02	(0.40)	-0.14	(0.29)	-0.26	(0.17)
		Neighborhoods	-0.72	(0.03)	-0.79	(0.05)	-0.73	(0.43)
		Homes	0.22	(0.13)	0.19	(0.28)	0.14	(0.71)
	6	Combined	-0.02	(0.83)	-0.06	(0.56)	-0.20	(0.25)

Notes: Total TD is the sum of freeway and surface road TD.
Effect estimates are the % difference in lung function growth rate per increase of 0.5 units in TD.

Table 4.2-5. Effect of changes in PM_{10}, NO_2 or O_3 on average annual lung function growth rates.

	PM_{10} 24hr avg	NO_2 24hr avg	O_3 10am to 6pm avg
FVC, ml			
mean change[1]	-1.8	-2.7	-1.4
(95% C.I.)	(-9.1, 5.5)	(-12.9, 7.5)	(-10.8, 8.0)
FEV_1, ml			
mean change[1]	-6.6	-8.2	0.1
(95% C.I.)	(-13.5, 0.3)	(-17.8, 1.4)	(-8.7, 8.9)
MMEF, ml/s			
mean change[1]	-16.6*	-10.7	-3.4
(95% C.I.)	(-32.1, -1.1)	(-3.8, 11.4)	(23.6, 16.8)
PEFR, ml/s			
mean change[1]	-34.9**	-23.6	-8.9
(95% C.I.)	(-59.8, -10.0)	(-59.5, 12.3)	(-41.6, 23.8)

[1]changes shown are per 10 units of pollutant, respectively.

* $p < 0.05$

** $p < 0.01$

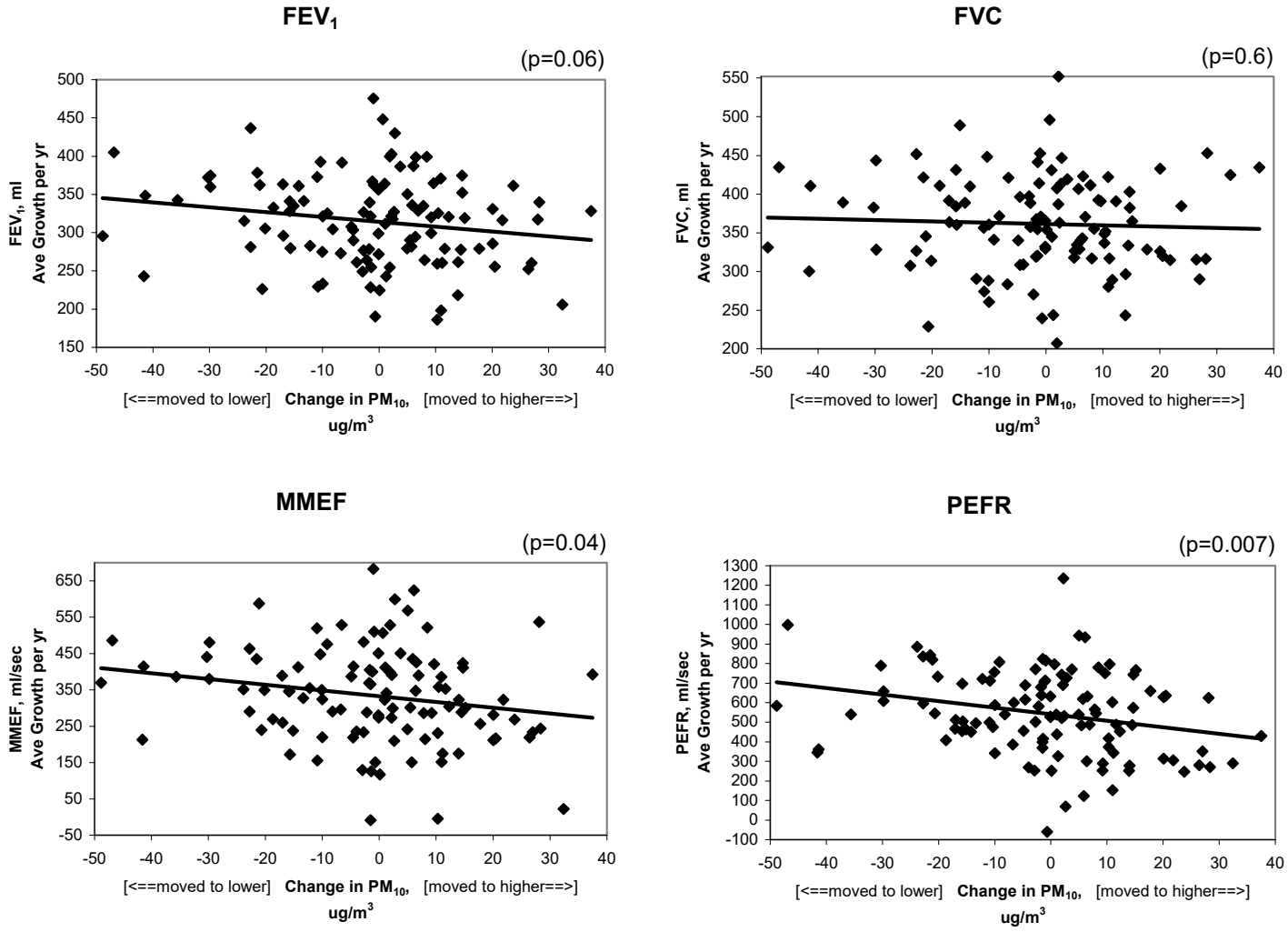


Figure 4.2-4. Effect of incremental changes in PM_{10} on annual lung function development for FEV_1, FVC, MMEF, and PEFR for all moved subjects studied.

Annual lung function variables have been adjusted for sex; race; annual average changes in height, weight, and BMI; baseline year; interaction of sex with height. Movement to the right on the x-axis represents a subject's relocation to an area of higher pollution, while movement to the left reflects relocation to an area of lower pollution.

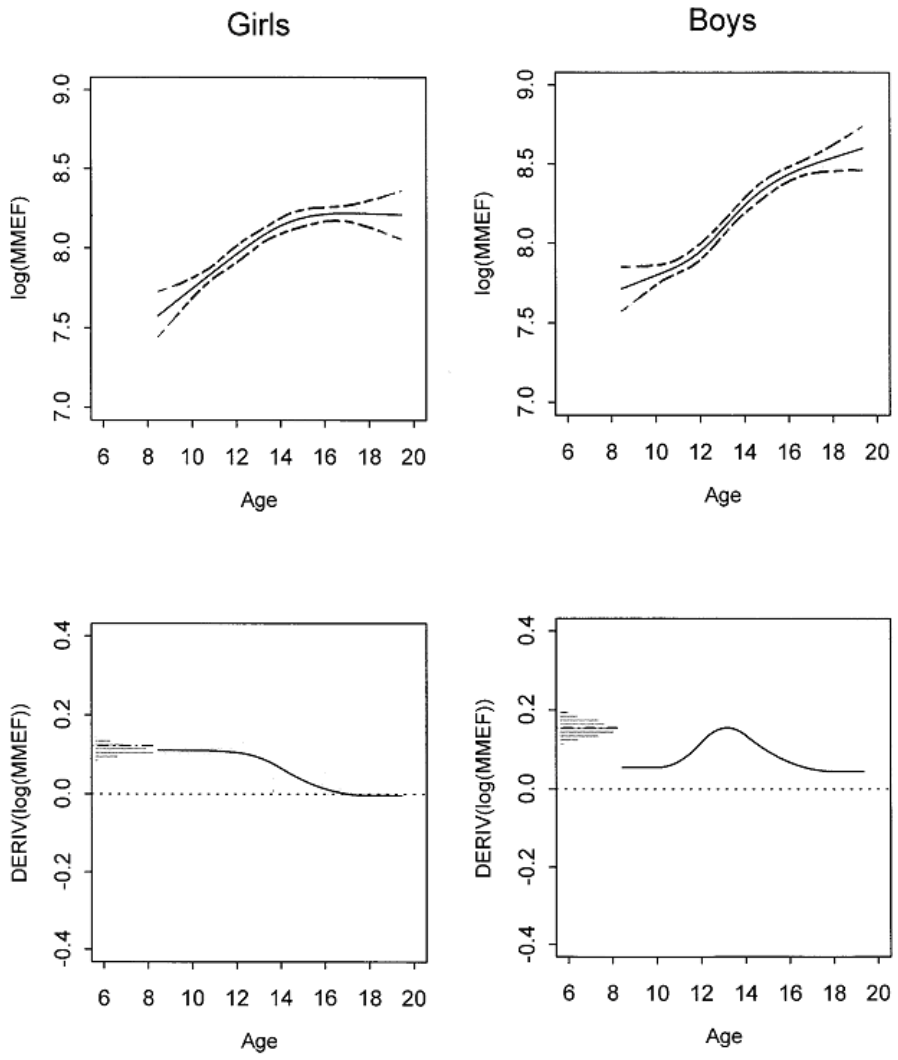


Figure 4.2-5. Gender specific growth curves for log(MMEF).

The top panels give the actual growth trajectories, along with 95% Bayesian confidence limits (broken curves) and 100 realizations from the MCMC process (gray). The lower panels give the rates of growth (as derivatives for the growth trajectories), along with 100 realizations from the MCMC process (gray). The histograms on the lower panels give the posterior distributions of the maximum rate of growth.

Table 4.2-6. Probabilities and Bayes factors for all possible main-effects models for 4-year changes in MMEF in cohorts C and D, based on various combinations of seven pollutants.

Pollutant(s)	Prior Probability	Posterior Probability	Bayes Factor
EC	0.0401	0.0920	2.3
Acid (nitric + formic + acetic)	0.0401	0.3216	8.0
All single pollutant models	0.2804	0.5689	2.0
O_3, NO_2	0.0072	0.0182	5.7
O_3, EC	0.0072	0.0166	5.8
O_3, Acid	0.0072	0.0188	5.7
NO_2, Acid	0.0072	0.0182	5.7
PM_{10}, Acid	0.0072	0.0221	5.6
$PM_{2.5}$, Acid	0.0072	0.0220	5.6
OC, Acid	0.0072	0.0201	5.6
EC, Acid	0.0072	0.0184	5.7
All 2 pollutant models	0.1509	0.2137	1.4
All 3 pollutant models	0.0805	0.0718	0.9
All 4 pollutant models	0.0417	0.0239	0.6
All 5 pollutant models	0.0199	0.0073	0.4
All 6 pollutant models	0.0019	0.0071	0.3
All 7 pollutant models	0.0003	0.0018	0.2

Table 4.2-7. Posterior distributions and Bayes factors for coefficients of each pollutant, averaging across all possible models.

Posterior summary	O_3	NO_2	PM_{10}	$PM_{2.5}$	OC	EC	Acid
Pr(β≠0)	0.1312	0.1653	0.1116	0.1339	0.1051	0.2039	0.5061
BF(β≠0)	0.78	1.02	0.65	0.79	0.60	1.32	5.27
Pr(β<0|β≠0)	0.6280	0.6672	0.5210	0.5926	0.5525	0.7118	0.7911
BF(β<0|β≠0)	1.69	2.00	1.09	1.45	1.23	2.47	3.79
Pr(β<0)	0.0824	0.1103	0.0582	0.0793	0.0580	0.1452	0.4004
BF(β<0)	1.01	1.40	0.70	0.97	0.70	1.92	7.53
E(β|β≠0)	-0.003	-0.005	+0.001	-0.004	-0.006	0.21	-0.034
SD(β|β≠0)	0.012	0.020	0.022	0.034	0.071	0.53	0.054

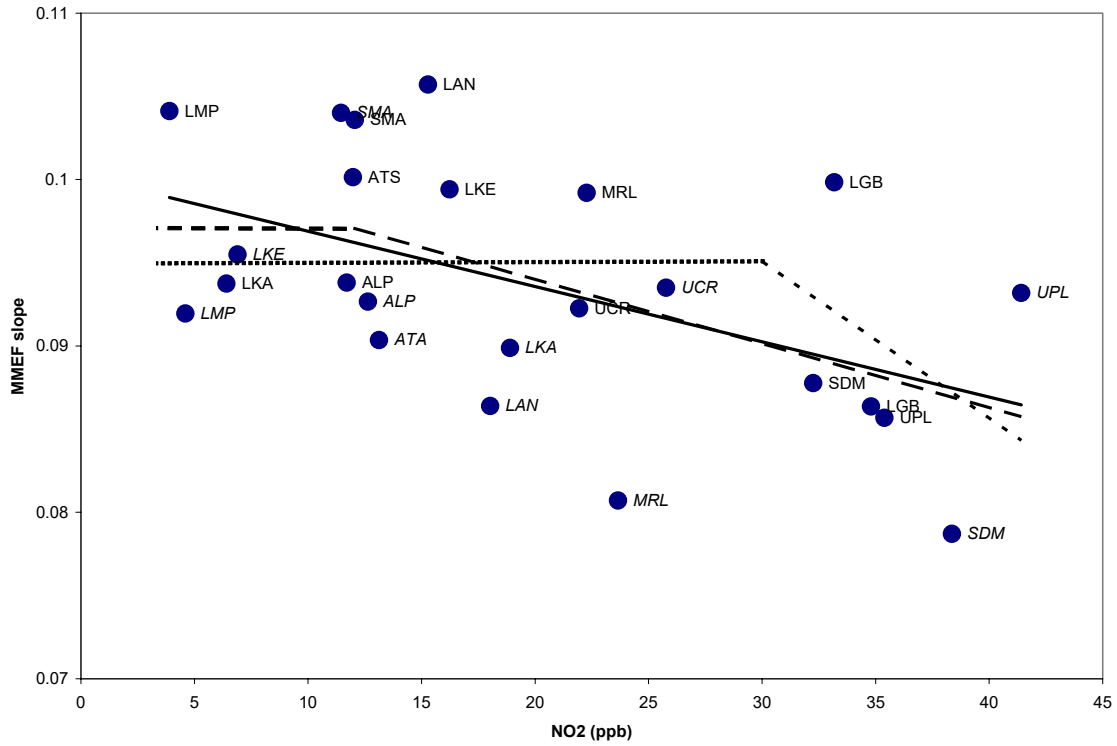


Figure 4.2-6. Exposure-response relationship between four-year rates of change of MMEF and average NO_2 concentrations in cohorts C and D.

(Italicized labels refer to cohort C, roman labels to cohort D). Fitted relationships are superimposed: linear (solid; null hypothesis); threshold at 12 ppb (dashed, maximum likelihood estimate), threshold at 30 ppb (dotted, upper 95% confidence limit).

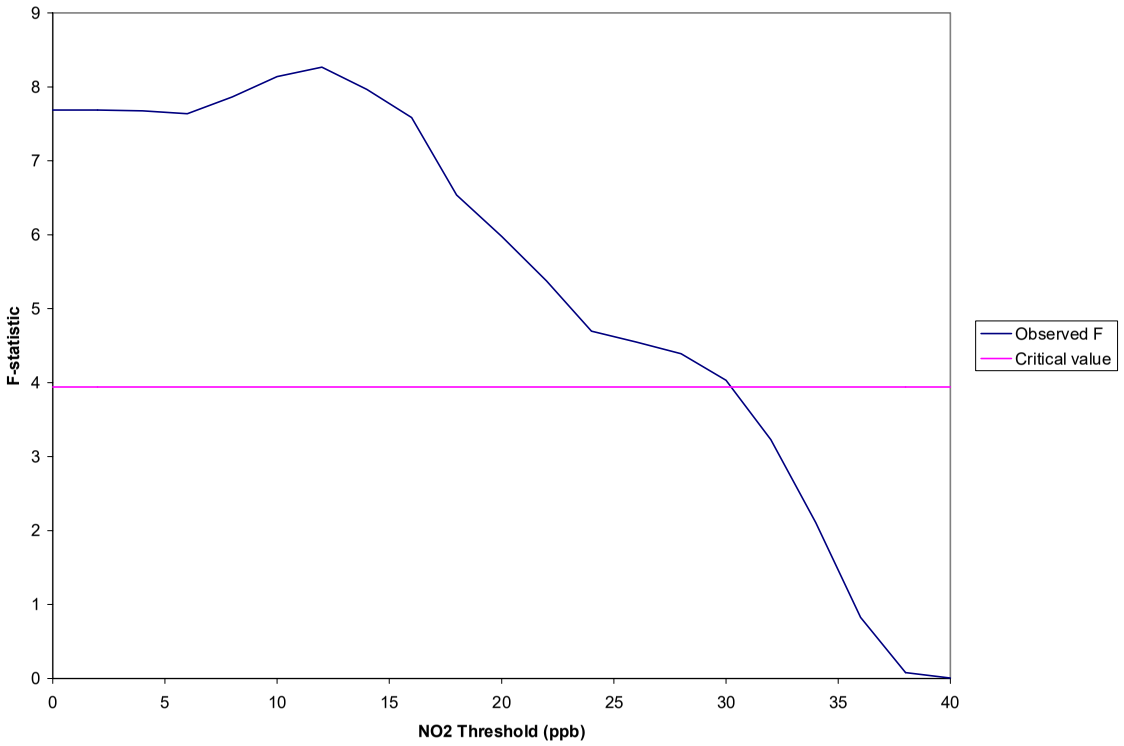


Figure 4.2-7. Comparison of fit of alternative threshold models for the data shown in Figure 4.2-6.

The curve shows the F statistic on 2 and 21 degrees for freedom for the fitted models at each possible threshold value, showing that the fit is maximized at a threshold of 12 ppb, but that that model does not fit significantly better than the simple linear model (threshold = 0). The horizontal line provides the critical value for 5% significance comparing any particular threshold to the best fitting model, showing that thresholds in excess of 30 ppb would be significantly rejected.

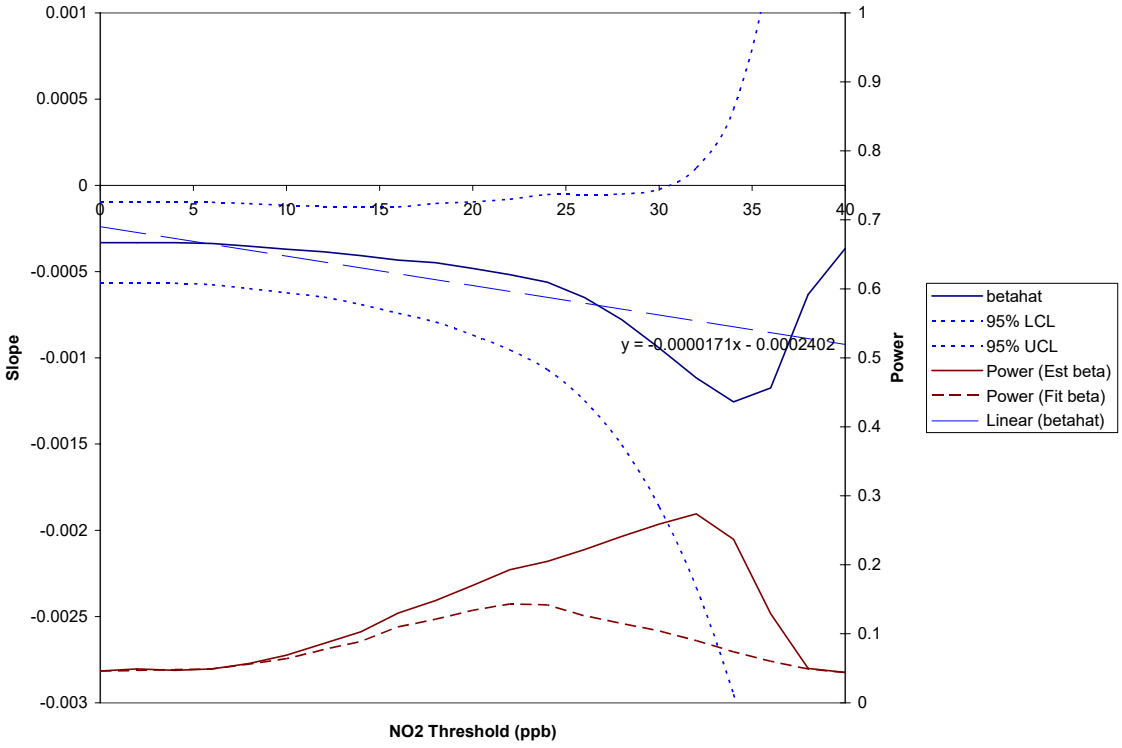


Figure 4.2-8. Estimated slope of threshold models and power to detect a threshold effect as a function of the magnitude of the postulated threshold.

The upper solid line (left axis) represents the slope of the portion of the fitted exposure-response relationship above each postulated threshold value, together with its 95% confidence limits (dotted lines). The dashed line provides a fitted linear relationship between threshold and high-exposure slope. The bottom solid line (right axis) represents the simulated power to detect a threshold effect as a function of the true threshold value, based on the estimated slopes given above. The dashed line at the bottom gives the power based on the fitted linear relationship between slope and threshold.

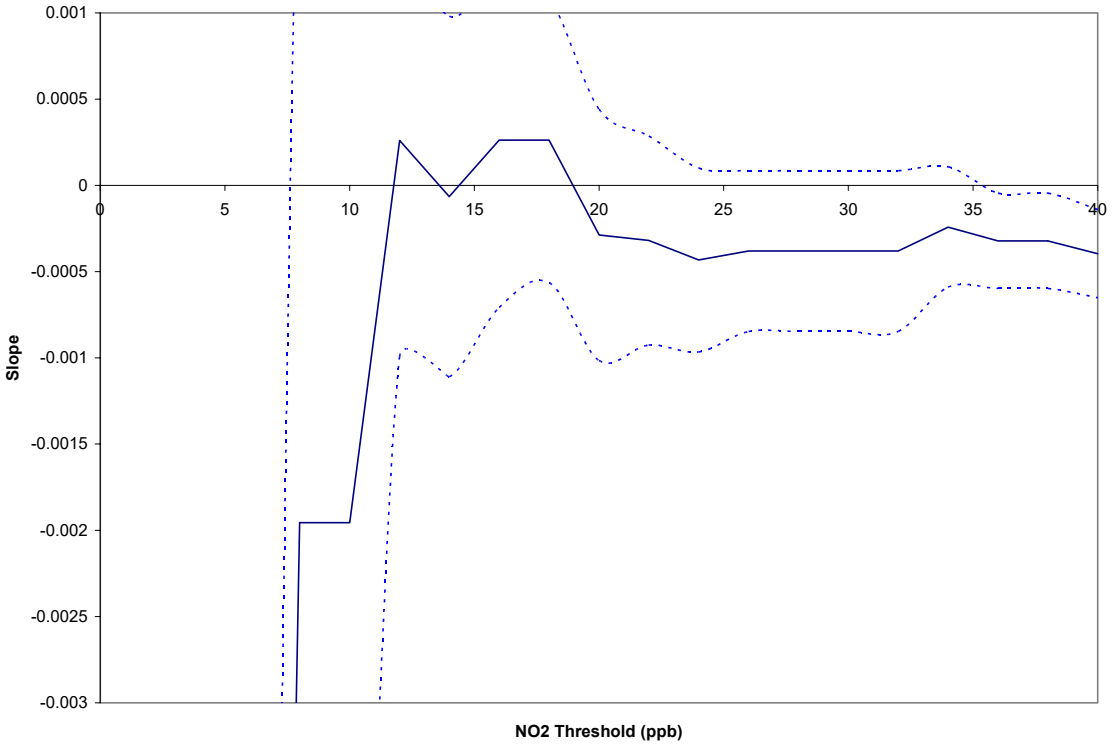


Figure 4.2-9. Estimated slopes (and 95% confidence limits) for the relationship between 4-year changes in MMEF and NO_2 concentrations, using only the subset of communities with mean exposures below the indicated threshold.

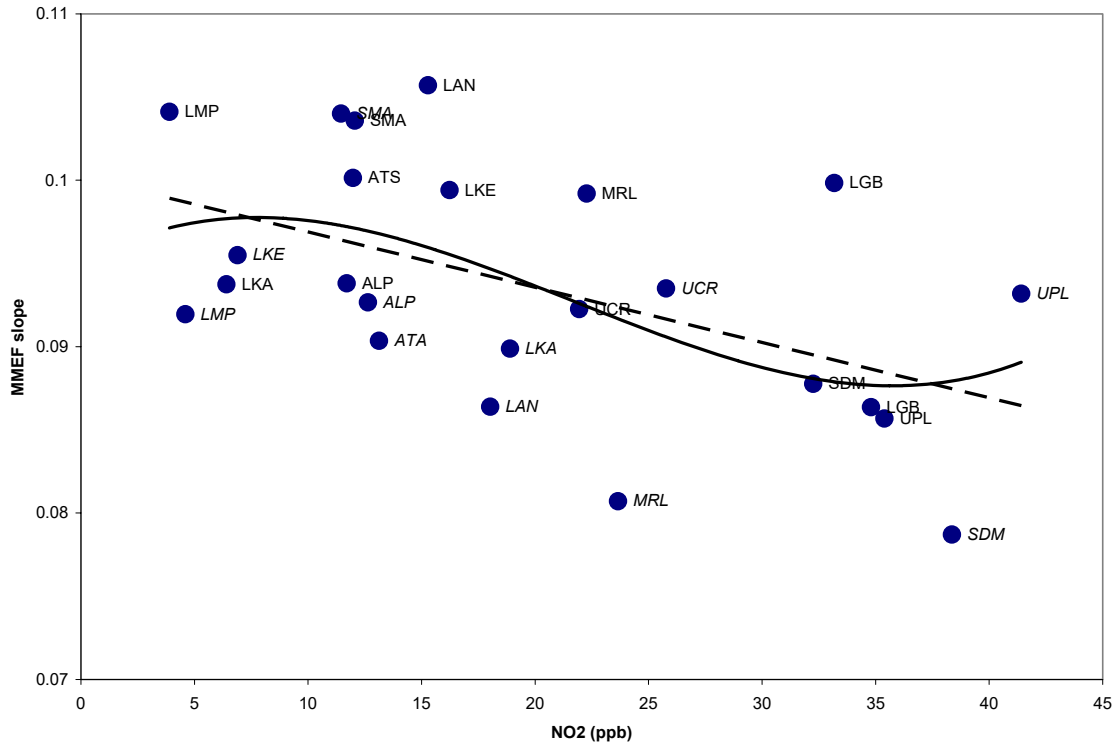
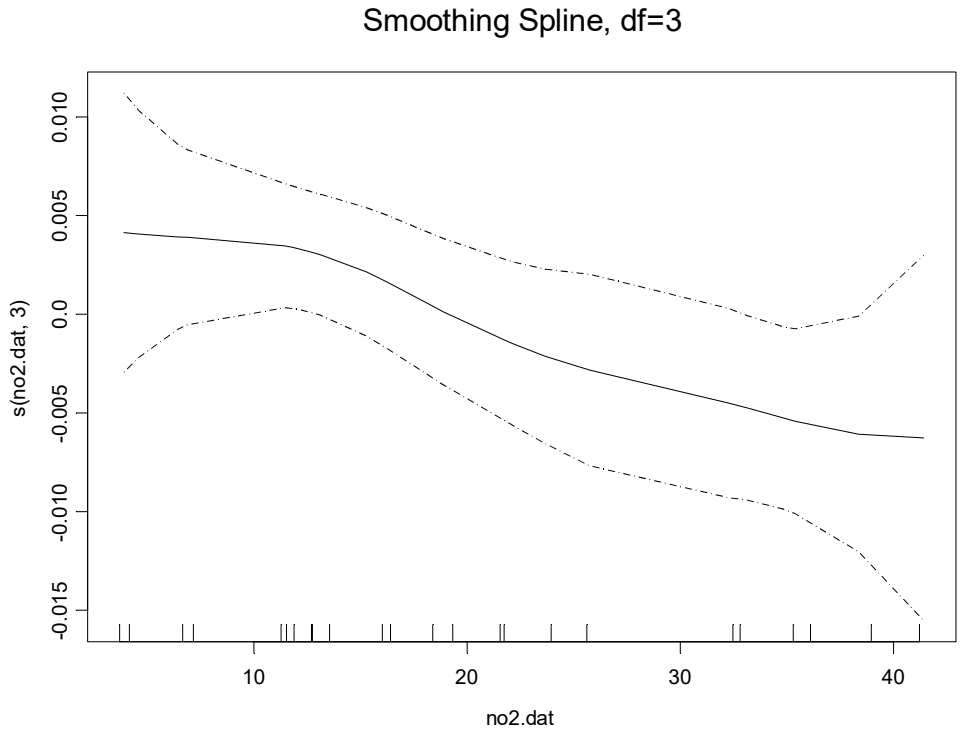


Figure 4.2-10. Fitted linear and cubic polynomial exposure-relationships for the data shown in Figure 4.2-6.



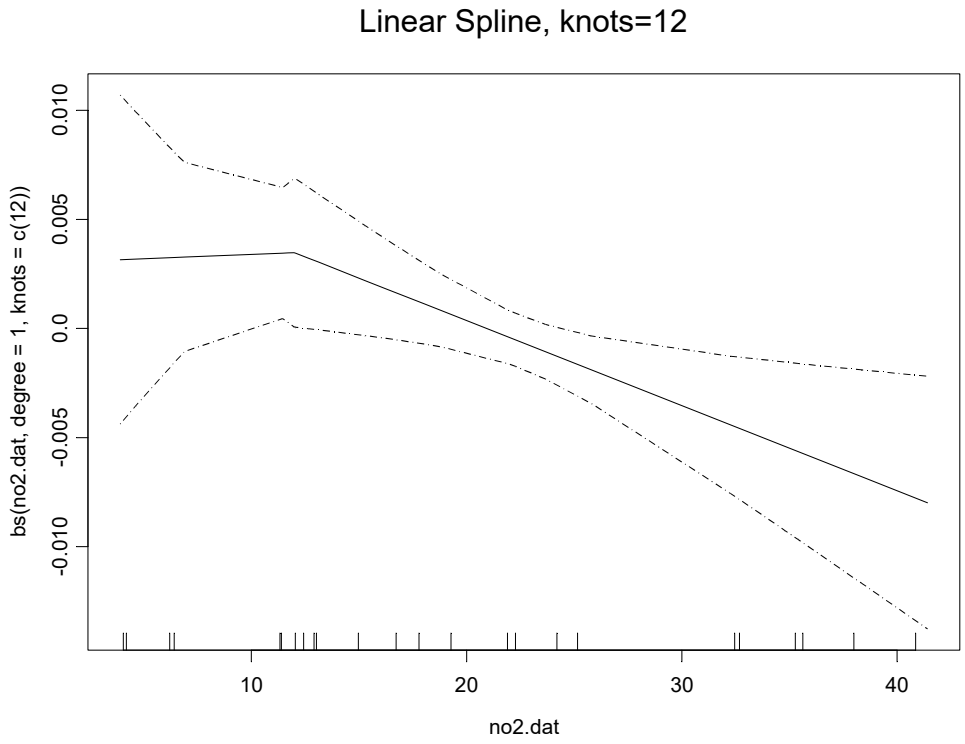


Figure 4.2-11. Exposure response relationships for the data shown in Figure 4.2-6 using nonparametric splines. Upper panel, cubic smoothing spline. Lower panel, linear spline with a knot at 12 ppb.

Table 4.2-8. Association of FVC with various measures of temporal variability in exposure to NO_2 and O_3.

Metric	NO_2	O_3
Average	**-2.2 (-4.1, -0.2)***	**-0.2 (-4.9, +4.4)**
Variances:		
Hourly	**-2.8 (-7.0, +1.4)**	**-2.3 (-3.9, -0.7)****
Daily	**-2.4 (-5.9, +1.1)**	**-6.6 (-10, -3.0)****
Weekly	**-1.8 (-5.5, +1.9)**	**-4.2 (-8.3, -0.2)***
Seasonal	**+0.5 (-3.0, +3.9)**	**-1.3 (-2.7, +0.1)**
Annual	**-0.2 (-1.2, +0.8)**	**0.0 (-0.9, +1.0)**

*p<.05 **p<.01

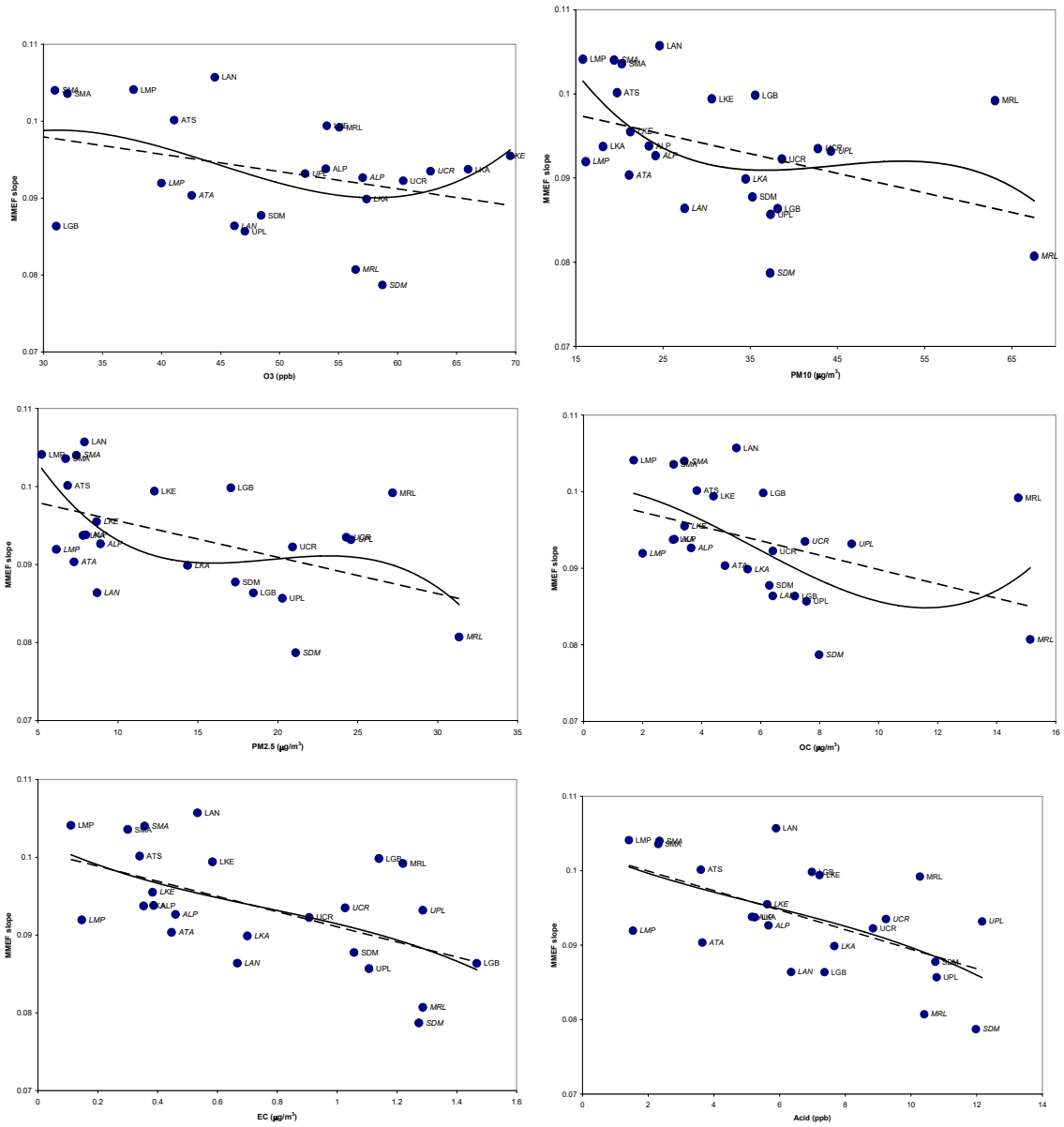


Figure 4.2-12. Exposure-response relationships for MMEF with O_3, PM_{10}, $PM_{2.5}$, OC, EC, and acid. Fitted linear and cubic polynomial curves are superimposed.

4.2.1.2. Synthesis

Our findings demonstrate an association between breathing air pollution in Southern California and deficits in lung function in adolescent children. We observed air pollution effects on lung function level at study entry, on 4-year lung function growth (age 10-14) in two independent cohorts, on 8-year growth (age 10-18), and on the maximum rate of growth during adolescence. Air pollution exposure over our 8-year study period was also linked to clinically significant deficits (FEV_1 below 80% predicted) in lung function at age 18. In a subset of children who moved away from their original study community, we observed consistent associations of lung function growth with their change in ambient air pollution exposure. The pollutants most closely associated with lung function deficits were NO_2, acid (nitric + formic + acetic), PM_{10}, and $PM_{2.5}$. Several constituents of $PM_{2.5}$, including EC, nitrate, and ammonium, also showed associations with lung function growth. The high correlation among these PM pollutants, and their high correlations with NO_2 and acid, limited our ability to distinguish the independent effects of any one of these pollutants. This is due to the fact that these pollutants are generally highest in communities in the Los Angeles basin and lower in the outlying areas. It is therefore possible that there is a 'poor air quality' effect on children's lung development that supercedes the effect of any single pollutant in the air pollution mix.

Our observed chronic health effects occurred at pollutant levels that, for the most part, were below the current state and federal ambient air standards for those pollutants. One might therefore conclude that existing standards are not currently low enough to protect children from chronic effects of air pollution. Our additional modeling did not reveal significant evidence of a threshold level at which adverse effects occurred. Rather, the data were most consistent with a linear exposure-response association, implying that any reductions in air pollution levels would translate into improvements in lung function health. This conclusion is supported by our analysis of the movers (Section 4.2.1.1.5) for whom fairly modest changes in air pollution exposure were associated with differences in lung function growth. We must stress, however, that our ability to identify a threshold was limited as was demonstrated in Section 4.2.1.1.8.

Previous studies have demonstrated that short-term exposure to high air pollution levels can result in acute health effects, ranging from reduced lung function to respiratory symptoms. The pollutant that has been most consistently linked to these acute effects has been ozone. When the CHS was initiated in the early 1990's there was relatively little known about the long-term, chronic effects of air pollution on lung function and lung function development in children. Based on the acute effect studies available at that time, we designed the CHS to optimize the statistical power for detecting an ozone effect (if it existed), and minimized the correlation of ozone with other study pollutants. True to this design, average ozone levels over the study period were relatively uncorrelated with other pollutants, while the remaining pollutants were all highly correlated with one another. We found no consistent associations between ozone and lung function level or growth. This finding is consistent with a recent study of European children that also reported no association between ozone and growth of FVC or FEV_1 over a 3.5 year follow-up period (Ihorst et al. 2004).

We cannot, however, rule out other possible explanations for the lack of an ozone finding. For example, the relative range (highest observed level divided by lowest observed level) in annual average O_3 levels across communities is only about 2.5, while the ranges for all other pollutants were at least 4. Since the relative range of the exposure (in this case, pollutant level) is a determinant of statistical power to detect an effect, our study may have suffered from lower power to detect an O_3 effect, relative to the power for other pollutants. Furthermore, it is known that O_3 levels recorded at community central site monitors are very poor surrogates for personal exposure of O_3 (Liu et al. 1997). This is partially due to the fact that O_3 level indoors are much lower than those outdoors, and in a relative sense, the indoor/outdoor ratio is lower for O_3 than the other pollutants we studied. Thus, it is likely that the use of central site levels to characterize individual exposure introduced a greater degree of measurement error for O_3 than for the other pollutants. Since measurement error often results in exposure estimates that are biased toward the null (i.e. toward no effect), our lack of an O_3 association may also be due in part to measurement error.

In our initial cross-sectional sample, pollutant effect estimates were generally larger and more significant in girls than in boys. However, subsequent air pollution effects on lung function growth did not differ significantly between boys and girls. Since girls' lungs mature at an earlier age than boys, it is possible that our initial cross-sectional findings reflected air pollution effects that had already occurred in girls and had not yet manifested in boys. Our analysis of the maximum growth rates suggests that air pollution levels affect growth during the pubertal growth spurt. Additional subgroup analyses revealed non-significant differences in air pollution effects between asthmatic and non-asthmatic children. Furthermore, the associations within the non-asthmatic subgroup remained statistically significant, suggesting that otherwise healthy children experience adverse health effects from air pollution exposure. The air pollution effects were somewhat larger in children who reported spending more time outdoors, lending further evidence that ambient levels of air pollution affect children's lung function.

The design of the CHS afforded us the opportunity to attempt replication of our own findings. Comparison of our original (cohort C) and replication (cohort D) samples revealed consistent associations between air pollution and 4-year lung function growth, and effect sizes that were of similar magnitude. Additionally, the set of pollutants showing association (the non-ozone 'package' of pollutants) was the same between the two samples, and neither sample showed consistent evidence of an association with ozone. While this replication adds significant confidence to the findings of our study, it is also essential that other investigators conduct similar studies in other populations. To date, two other groups have published studies on longitudinal follow-up of children to assess association between air pollution and lung function development. Frischer et al. (1999) reported results of 3 years of follow-up of children from eight cities in Austria. They found deficits in lung function development were associated with exposure to ozone, NO_2, sulfur dioxide (SO_2), and PM_{10}. In the second study, Jedrychowski et al. (1999) studied children from two cities in Poland that differed in their concentrations of particulate matter, and found reduced lung function growth over a 2-year period in the more polluted area. Collectively, the CHS and these other longitudinal studies strengthen earlier evidence (Bascom et al. 1990; Bascom 1996; Raizenne et al. 1996; Peters et al. 1999a) that long-term exposure to air pollution can produce chronic health effects in children.

4.2.2. Asthma

4.2.2.1. Summary of Results

It is widely accepted that acute exposure to ozone (O_3) and other outdoor air pollutants exacerbates asthma (Koren 1995). Although the chronic effects of air pollution have been less studied, it has until recently been concluded that combustion related air pollution does not cause asthma (Clark et al. 1999), a conclusion that has been called into question by work from the CHS and by experimental work also conducted in California (Schelegle et al. 2003). Asthma is the most common chronic disease of childhood, and asthma prevalence and incidence have been increasing among children, at least in developed countries, over the past several decades (Becklake and Ernst 1997; Sears et al. 2003). Causes for this epidemic are unknown, although changes in frequency and severity of early life infections, diet, and exposure to indoor allergens and to other indoor and outdoor air pollutants have been hypothesized to be contributors to multi-factorial causes of this disease (Sears 1997). The costs associated with the recognized exacerbation of asthma are large. There are important regulatory implications, if air pollution also contributes to new cases of asthma.

In this section, the results of analyses of the relationship of measurements of air pollutants with prevalent asthma at study entry and with incident asthma during follow-up are presented. The assessments of air pollutants at the community monitors, of traffic modeled exposure, and of questionnaires are described in detail in the methods section of this report (Section 3.4). Relevant analyses examining the effect of air pollution on bronchitic symptoms and of environmental and *in utero* tobacco smoke exposure are presented elsewhere (Sections 4.2.3 and 4.3.1 and 4.3.2).

4.2.2.1.1. Prevalent asthma and wheeze

In cross sectional analyses prevalence of asthma was evaluated at study entry. Lifetime asthma was defined by a yes answer to the question "Has a doctor ever diagnosed this child as having asthma?" Current/severe asthma assumed medically diagnosed asthma, greater than one illness in the past 12 months, or one illness in the past 12 months and: (1) ever interrupted sleep; or (2) any medication in last 12 months; or (3) overnight hospital stay in the last 12 months. Lifetime wheeze was defined by a yes answer to the question "Has your child's chest ever sounded wheezy or whistling, including times when he or she had a cold?" (non-asthmatic subjects only). Associations of asthma with risk factors not associated with air pollution included hay fever, family history of asthma, history of second hand smoke exposure, water damage or pests in the home (Peters et al. 1999b). Wheeze was associated with having asthmatic parents, hay fever, and household mildew. Air quality/respiratory health relationships were assessed using multi-level models adjusted for appropriate covariates, as described in Section 3.6. Table 4.2-9 includes the results based on the 1986–1990 exposures estimated from data preceding the complete CHS monitoring network. There were no significant associations with lifetime asthma or current/severe asthma. Prevalence of wheeze was associated with exposure to NO_2 (OR 1.47; 95% CI, 1.04–2.09) in males only and acid (nitric + hydrochloric) (OR 1.26; 95% CI, 1.01–1.57). Results were similar in an analysis based on the 1994 exposure measurements. (In these cross sectional analyses, finalized early in the study, we did not specifically examine the effects of EC and OC on prevalent asthma (exposures that became available for analysis in 2000),

because these pollutants were not available for years prior to 1994. The results would likely have been very similar to effects for other particulate pollutants, both before and after the start of the study, given that EC and OC were highly correlated with PM_{10} and $PM_{2.5}$ from 1994 on (see Section 3.4), and the effects of PM_{10} were similar before and after the study began, and the effects of PM_{10} and $PM_{2.5}$ were similar after the start of the study). The statistically significant association of wheeze prevalence with acid and NO_2 in boys might be important, but since a large number of comparisons were made, this association could be entirely compatible with chance.

We have also examined the association of various traffic metrics with asthma and bronchitis. We have used selected metrics described previously in this Report, and we have used logistic regression for these analyses, adjusting for community and appropriate covariates. Thus, these are within-community analyses. Although the CALINE4 models provide multiple exposure metrics, many of these are highly correlated (Table 4.2-10). An exception to this high correlation is for distance to a freeway. Otherwise, examining any one metric is sufficient to know the effect of any of these individually estimated exposures.

Results for one representative pollutant, CO, are shown in Table 4.2-11 for asthma and wheeze. The exposures have been categorized to be able to examine the extremes of the distribution (thus P0-25 is the lower quartile, up to 0.2 ppb; and the top 5% of the distribution, P96-100 represent estimated exposures from 2.0-4.6 ppb).

Although there is some suggestion of an increased risk of asthma associated with the highest exposures to traffic, there are wide confidence intervals to these estimates. In contrast, there were decreasing rates of asthma among those living further away from a freeway, and these were significant if we restricted the analysis to those who had lived at the same address in a community with a freeway since age 2 (OR 0.94/1000 meters; 95% C.I. 0.90, 0.99; p=0.03). Other traffic metrics, including average daily traffic counts within 100 meters of the home and a traffic density weighted metric that drops to 5% of background within 150 meters of a road also were not associated with asthma.

In analyses with earlier models of local traffic exposure, which were later improved to provide better geo-coding of roadways, we observed some marginally significant associations between asthma and exposure to freeway modeled pollutants at the home, if we restricted the analysis to children living at the same address since age 2. In these analyses, large increases in physician diagnosed asthma reported by the parent were associated with the top decile of exposure (McConnell et al. 2002c). Associations were more pronounced in Long Beach, which had higher traffic-related pollutants, than in other communities, although power was limited to examine effects in subsets of children with long term residence and in individual communities. However, in what we consider better later models with more accurate geo-coding and better accounting for meteorology, the associations with simple distance to freeways were significant, while the modeled exposure were not. Possible explanations for the more robust effect of exposure to traffic from freeways include an effect specific to diesel vehicles, which are more common on freeways, and better measurement of traffic counts on freeways (resulting in stronger associations than for non-freeway estimates of traffic exposure).

4.2.2.1.2. Incident asthma

Incident asthma was defined as a report of doctor diagnosed asthma on a follow-up questionnaire, after excluding children with any lifetime history of asthma at study entry. Each child's lifetime history of wheeze was determined retrospectively from the baseline questionnaire at study entry, as was the child's participation in team sports, time spent outside, and other relevant baseline covariates. Results are presented for follow-up of all cohorts through 1998, and a corresponding 4-year average exposure period from 1994-1997, which formed the basis for a published report from the CHS (McConnell et al. 2002b). There were 265 newly reported cases of asthma during this period. Standard proportional hazards methods were used to assess individual risks for asthma. The models used stratified baseline hazards by age groups and gender.

We classified each community as among the higher 6 or lower 6 for each pollutant for most analyses presented below. The profile of representative pollutants is presented in Table 4.2-12. Even low pollution $ozone_{10\text{-}6}$ communities had relatively high average four-year concentrations, up to 51 ppb. The high and low pollution communities were essentially the same for NO_2 and the particulate pollutants. This reflects the high correlation coefficients for the four-year averages for these pollutants and for EC and OC across the 12 communities (as discussed in more detail in Section 3.4). $Ozone_{10\text{-}6}$, although highly correlated with average daily one-hour maximum O_3 (R=0.98) and with average 24 hour average O_3 (0.72), was not strongly correlated with the other pollutants. The highest correlation of $ozone_{10\text{-}6}$ with other pollutants was with acid (nitric + hydrochloric) (R=0.48).

The relationship of ozone with asthma was modified by indicators of physical activity. In all communities combined there was a 1.8-fold increased risk (95% confidence interval (CI) 1.2-2.8) for asthma among children who played 3 or more team sports in the previous year. There was a linear trend of increasing asthma over the total of 8 possible team sports played (RR 1.1 per team sport played; 95% CI 1.0-1.3). In high $ozone_{10\text{-}6}$ communities, there was a 3.3-fold increased risk of asthma among children playing 3 or more sports, an increase which was not observed in low $ozone_{10\text{-}6}$ communities (Table 4.2-13). In high O_3 communities there was a trend of increasing asthma with number of team sports played, of a total of 8 (RR 1.3 per sport; 95% CI 1.1-1.6; results not tabulated). There was a significant interaction between total number of sports played and O_3 (p=0.004). In assessing interaction, we also considered models that used indicator variables for each sport or dummy variables for none, 1, 2, and 3 sports. The model that used total number of sports was found to be most parsimonious. Additional analyses demonstrated an association with asthma in high O_3 communities for children playing at least one high activity sport, compared with no sports (RR 1.6, C.I 1.1-2.5), but not for children playing only a low activity sport (RR 1.2; CI 0.7-2.1). In low O_3 communities, for high activity sports the relative risk was 1.0 (95% CI 0.7-1.4); for low activity sports the relative risk was 0.9 (95% CI 0.5-1.7). In models with each individual sport entered as a dummy variable, only tennis was significantly associated with asthma (RR 5.2; CI 1.3-20.4), and only in high O_3 communities, but power was limited for identifying the effect of specific sports. The results were not changed substantially by likely potential confounders, and the effects were similar in children with and without a history of wheeze at study entry, and among boys and girls.

The effect of team sports was similar in communities with high and low PM (and associated pollutants, all of which gave identical high/low groupings of communities as PM). In both groups of communities there was a modest increase in asthma among children playing team sports, which was largest among those playing three or more sports (Table 4.2-14). Thus, there was no indication of effect modification by PM.

Additional analyses of these data have suggested that there is a dose-response relationship between the risk of asthma associated with sports and ozone exposure. Figure 4.2-13 shows the risk of asthma per team sport in each community, ordered by ozone. As the level of ozone increased, there was an increasing risk of asthma across the entire range of ozone exposure. A similar pattern of increasing relative risk of asthma associated with team sports in each community was observed across the range of ozone in the 12 communities in cross sectional analyses of lifetime asthma at study entry.

Table 4.2-9. Odds ratios of respiratory illness on 1986-1990 ambient air pollutants*

Symptom Pollutant†	All Subjects OR (CI)	Males OR (CI)	Females OR (CI)
Ever asthma			
Peak O_3	0.93 (0.72, 1.21)	1.15 (0.91, 1.44)	0.72 (0.50, 1.04)
PM_{10}	0.93 (0.76, 1.13)	1.00 (0.82, 1.21)	0.85 (0.62, 1.17)
NO_2	0.95 (0.72, 1.26)	0.94 (0.72, 1.22)	0.99 (0.62, 1.57)
Acid	1.00 (0.72, 1.38)	1.03 (0.76, 1.40)	0.99 (0.58, 1.69)
Current asthma			
Peak O_3	0.95 (0.70, 1.29)	1.02 (0.75, 1.39)	0.84 (0.50, 1.40)
PM_{10}	1.09 (0.86, 1.37)	1.09 (0.87, 1.37)	1.03 (0.69, 1.55)
NO_2	1.14 (0.83, 1.56)	1.16 (0.85, 1.58)	1.03 (0.59, 1.80)
Acid	1.02 (0.70, 1.49)	1.01 (0.69, 1.47)	1.04 (0.54, 1.98)
Wheeze			
Peak O_3	1.08 (0.87, 1.35)	1.30 (0.89, 1.89)	0.95 (0.67, 1.35)
PM_{10}	1.05 (0.89, 1.25)	1.26 (0.96, 1.66)	0.91 (0.70, 1.19)
NO_2	1.09 (0.86, 1.37)	1.47 (1.04, 2.09)‡	0.85 (0.59, 1.21)
Acid	1.26 (1.01, 1.57)‡	1.55 (1.03, 2.32)‡	1.08 (0.71, 1.66)

* Single pollutant models adjusted for personal and environmental factors.
† Odds ratios are scaled to the interquartile range for each pollutant as follows: 40 ppb of O_3, 25 μg/m^3 of PM_{10}, 15 μg/m^3 of $PM_{2.5}$, 25 ppb of NO_2, and 1.7 ppb of acid ($HCl+HNO_3$, measured on a mole basis). Four models are fit for each symptom or condition, one for each pollutant.
‡ p , 0.05.

Table 4.2-10. Correlations of selected modeled traffic metrics derived from CALINE4 models

	NO_x	NO_2	NO	OC	EC	CO	PC	Distance
NO_x	1.0							
NO_2	0.99	1.0						
NO	0.98	0.94	1.0					
OC	1.00	0.98	0.97	1.0				
EC	0.99	0.99	0.88	0.99	1.0			
CO	1.00	0.98	0.97	0.99	0.99	1.0		
PC	1.00	0.99	0.97	0.99	0.99	0.99	1.0	
Distance	-0.50	-0.53	-0.43	-0.45	-0.49	-0.48	-0.47	1.0

Table 4.2-11. Traffic modeled CO and asthma.

Total CO estimate[b]	Ever Asthma N (%)	Ever Asthma OR* (95% CI)	Current Wheeze N (%)	Current Wheeze OR* (95% CI)
P0-25: 0.2 ppb	128 (14.3)	1.00 ---	162 (18.8)	1.00 ---
P26-50: 0.3 ppb	123 (19.8)	0.85 (0.64-1.14)	157 (18.4)	1.04 (0.80-1.36)
P51-75: 0.8 ppb	128 (14.3)	0.96 (0.67-1.37)	181 (21.0)	1.24 (0.90-1.73)
P76-90: 1.5 ppb	74 (13.9)	0.82 (0.47-1.42)	92 (18.0)	1.01 (0.60-1.67)
P91-95: 2.0 ppb	28 (15.9)	1.39 (0.54-3.58)	36 (20.6)	1.63 (0.47-2.89)
P96-100: 4.6 ppb	25 (14.0)	1.24 (0.43-3.55)	35 (20.5)	1.66 (0.40-2.85)

*Odds ratio compared with lower quartile of traffic modeled CO
a Adjusted for gender, race, age (centered at age 10) and community
b P is is percentile of exposure distribution

Table 4.2-12. Average 1994-1997 pollution profiles in high and low pollution communities, divided at the 12 community median for each pollutant into 6 high and 6 low communities*

	Low Pollution				High Pollution			
Pollutant	Mean	(SD)	Median	Range	Mean	(SD)	Median	Range
Maximum 1-hr ozone	50.1	11.0	47.6	37.7-67.9	75.4	6.8	73.5	69.3-87.2
$Ozone_{10-6}$	40.0	7.9	40.7	30.6-50.9	59.6	5.3	56.9	55.8-69.0
24 hour ozone	25.1	3.1	25.1	20.6-28.7	38.5	11.0	33.1	30.7-59.8
PM_{10}	21.6	3.8	20.8	16.2-27.3	43.3	12.0	39.7	33.5-66.9
$PM_{2.5}$	7.6	1.0	7.7	6.1-8.6	21.4	6.0	21.8	13.5-30.7
NO_2	10.8	4.6	12.1	4.4-17.0	29.2	8.5	29.5	17.9-39.4
Acid	1.8	0.7	1.7	0.9-2.6	3.9	0.7	3.7	3.3-4.9

*Note that these are the same 6 high and 6 low communities for PM, NO_2 and acid, but not for other pollutants.
Results are in ppb of ozone, NO_2, and inorganic acid vapor ($HCl + HNO_3$), and in $\mu g/m^3$ of PM

Table 4.2-13. Effect of number of team sports played on the risk of new asthma diagnosis in high and low ozone communities*

	Low Ozone Communities				High Ozone Communities			
# Sports	N (incidence)		**RR**	(95% CI)	N (incidence)		RR	(95% CI)
0	58	(.027)	1.0	---	46	(.018)	1.0	---
1	50	(.033)	1.3	(0.9-1.9)	40	(.021)	1.3	(0.8-2.0)
2	20	(.023)	0.8	(0.5-1.4)	16	(.020)	1.3	(0.7-2.3)
≥3	9	(.019)	0.8	(0.4-1.6)	20	(.050)	3.3	(1.9-5.8)

*N = # of cases of asthma (incidence); RR = relative risk (hazard ratio), adjusted for ethnicity, and for stratified baseline hazards by sex and age group; CI = confidence interval.

[Reprinted with permission from Elsevier (*The Lancet*, 2002, Vol 359, pp 386-91)]

Table 4.2-14. Effect of number of team sports played on the risk of new asthma diagnosis in high and low PM (and other pollutant) communities*

	Low PM Communities				High PM Communities			
# Sports	N (incidence)		**RR**	(95% CI)	N (incidence)		RR	(95% CI)
0	49	(.023)	1.0	---	55	(.021)	1.0	---
1	54	(.032)	1.5	1.0-2.2	36	(.021)	1.1	(0.7-1.7)
2	22	(.024)	1.2	0.7-1.9	14	(.018)	0.9	(0.5-1.7)
≥3	13	(.033)	1.7	0.9-3.2	16	(.033)	2.0	(1.1-3.6)

*N = # of cases of asthma (incidence); RR = relative risk (hazard ratio), adjusted for ethnicity, and for stratified baseline hazards by sex and age group; CI = confidence interval.

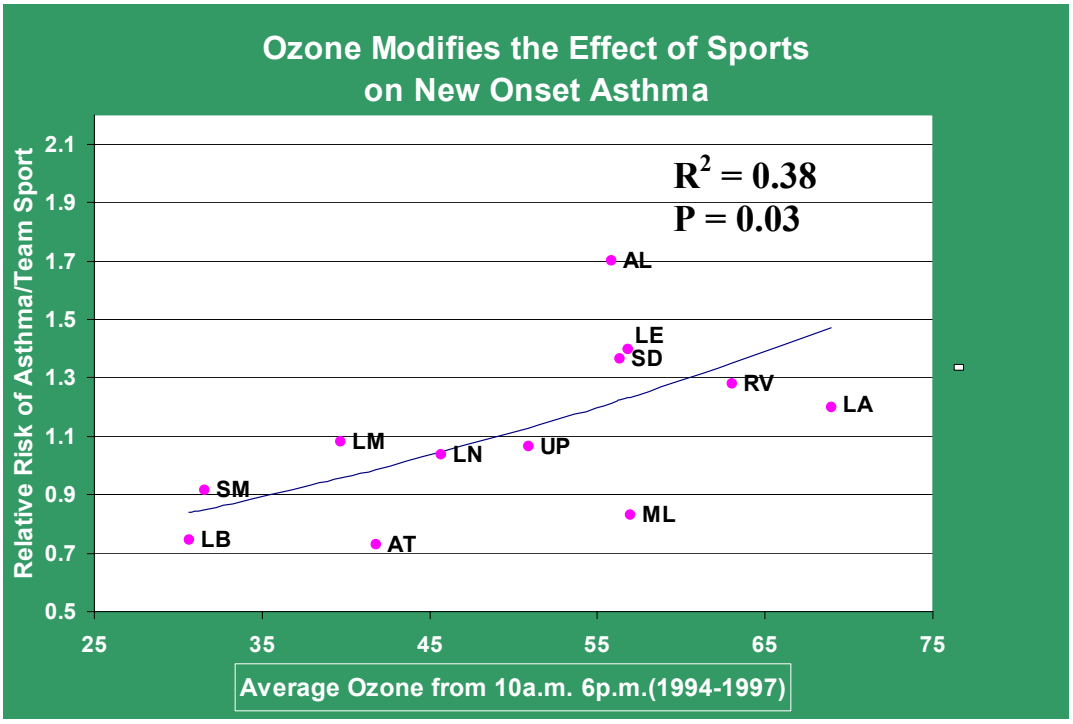


Figure 4.2-13. The risk of new onset asthma associated with number of team sports increases with increasing ozone in the community.

(LB=Long Beach; SM=Santa Maria; LM=Lompoc; AT=Atascadero; LN=Lancaster; UP=Upland; AL=Alpine; SD=San Dimas; LE=Lake Elsinore; ML=Mira Loma; RV=Riverside; LA=Lake Arrowhead).

4.2.2.2. Synthesis

The most important result from this series of analyses of asthma prevalence and incidence is the evidence that pollution causes asthma (playing multiple team sports in a high O_3 environment was associated with subsequent physician diagnosed asthma). The results are consistent with a large increased risk both for new onset asthma and for exacerbation of previously undiagnosed asthma, because playing multiple sports was associated with asthma in children with no lifetime history of wheezing at baseline, as well as in children with a previous history of wheezing. The larger effect of high activity sports than of low activity sports, and an independent effect of time spent outdoors, also only in high O_3 communities, strengthens the inference that exposure to O_3 modifies the effect of sports on the development of asthma in some children. Exercise-induced asthma by itself is unlikely to have been an explanation for these results, because asthma onset was associated with exercise only in polluted communities. The increasing risk of number of team sports played in each community as the exposure increased across the range of community ozone exposure demonstrates a dose response relationship, which also suggests that the observed association is causal (see Figure 4.2-13).

Because sports is a plausible indicator of high intensity, repeated outdoor periods of increased ventilation, children engaged in competitive sports are a subgroup for whom exercise will increase the dose of pollutant to the lung (McArdle et al. 1996). In addition, outdoor activity (independent of exercise) should be an important modifier of exposure to ambient O_3, because outdoor O_3 concentrations in these 12 communities has been shown to be as much as five times higher than indoor concentrations (Avol et al. 1998a; Tager et al. 1998). Ozone concentrations between 10 a.m. and 6 p.m. are generally higher than other times of day (and correspond to when most team sports are played outdoors in southern California's mild climate).

The results of the examination of the interaction of sports and ozone are the strongest of a series of epidemiologic studies that, together with emerging evidence from animal studies, have refuted the commonly held belief that air pollution does not cause asthma. Although the interacting effects of sports with O_3 on the development of asthma has not previously been investigated in epidemiologic studies, experimental studies have demonstrated acute effects of O_3 in exercising subjects (Horstman et al. 1990; Koren 1995). Toxicologic studies provide insight into biological plausibility of a role for ozone as a cause for asthma. A new rhesus monkey model of asthma, which is very similar to the human disease, has demonstrated that ozone, in combination with exposure to house dust mite, is a strong stimulus to the development of asthma (Miller et al. 2003; Schelegle et al. 2003). Ozone also enhances the response in human asthmatic subjects to other allergens present in ambient air (Osebold et al. 1988; Kehrl et al. 1999). In our study we did not measure allergen exposure, but the increased pulmonary dose of ambient O_3 resulting from heavy exercise, combined with the ubiquitous exposures of all children to outdoor and indoor allergens, is one possible pathway by which ozone might cause new onset asthma. Recent large cross sectional studies of children and adults and one other prospective study have also found associations of asthma prevalence and incidence with O_3 and related pollutants (Baldi et al. 1999; Guo et al. 1999; McDonnell et al. 1999; Wang et al. 1999).

An apparent paradox is that there is a large interaction between sports and ozone, yet ozone by itself in the absence of sports was not associated with overall increased risk of asthma in the cross sectional analysis. One possible explanation is that prevalence and incidence rates of asthma vary greatly between study communities, and these differences cannot be explained based on adjustment for individual characteristics thought to be risk factors for asthma (for example, mold, pets, or household pests). Therefore, even a large effect of sports in combination with ozone might not be detected in epidemiologic studies. In fact, relatively few children (7.9%) played 3 or more team sports, so the risk of new onset asthma attributable to sports was modest. The large and unexplained variability between communities may be the explanation for the lack of association of asthma with ozone in the numerous, primarily cross sectional studies with relatively small number of communities to compare (Clark et al. 1999). A principal strength of the analysis of sports and time spent outside is that information was collected from the individual and therefore was not subject to much of the ecologic bias characteristic of the relationship between air pollution and asthma.

Although our *a priori* hypothesis was that there would be an enhanced effect of pollution on risk of asthma among children playing sports, a plausible biological hypothesis could be made that asthma could be caused by exposure to pollutants beside O_3, for example to ambient NO_2, based on the enhanced response of asthmatics to bronchial allergen challenge with dust mite allergen after exposure to NO_2 (Jenkins et al. 1999). Although no effect of sports on asthma was observed in communities with high levels of pollutants other than O_3, it should be noted that statistical power was limited to rule out an independent association of non-O_3 pollutants with the development of newly diagnosed asthma, or to identify such a multi-pollutant interaction between sports, O_3 and other pollutants.

The major strengths of this study included the individual assessment of sports, which avoided the biases associated with ecologic comparisons of between-community differences. Participation in team sports was determined prior to the prospective evaluation of the new diagnosis of asthma in communities in which O_3 and other pollutants were carefully measured. Thus, there can be little doubt as to the temporal sequence to the strong association observed. There was a dose-response relationship with total number of sports played, and the results are biologically plausible. We conclude that the incidence of new asthma diagnosis is associated with heavy exercise in communities with high levels of ambient O_3 and that under these conditions air pollution and outdoor exercise probably contribute to the development of asthma in children.

Regulatory implications of this finding are that if ozone is causing asthma then, ultimately, the solution is to reduce the levels of ozone. In the short term, parents should be cognizant of air pollution levels when their children are exercising heavily outdoors. However, this advice should be observed in the context of the findings described in Section 4.3.4 on obesity and asthma. Because lack of exercise may contribute to obesity, which we have found is a competing risk for asthma, it may not be prudent for children to limit outdoor exercise to times when ozone levels are low.

The observed association of traffic-related pollutants with asthma prevalence occurred in association with freeway traffic. This suggests that diesel exhaust, which is more common in heavy duty vehicles on freeways may be a risk factor for asthma, although the better

measurement of traffic counts on freeways may also be the explanation for the stronger effects from freeway distance. It is of interest that associations were more pronounced in Long Beach than in other communities. This may be related to the heavier traffic near homes in that community. In ongoing studies, we will be measuring NOx and $PM_{2.5}$ at multiple locations within communities to further investigate the relationship between traffic and asthma.

The results of traffic-related analyses are only partially consistent with an emerging literature that has found within-community associations of traffic-related pollution with childhood wheeze (Wjst et al. 1993; Weiland et al. 1994; Pershagen et al. 1995; Duhme et al. 1996; van Vliet et al. 1997; Kramer et al. 2000; Venn et al. 2000), and with asthma in some (Edwards et al. 1994; van Vliet et al. 1997; Hirsch et al. 1999; Venn et al. 2000), but not all studies (Wjst et al. 1993; Waldron et al. 1995; English et al. 1999; Kramer et al. 2000). Different methods used to assess exposure in these studies may explain some of the lack of consistency in results for asthma. Some have relied on subject self-report of traffic near the home (Weiland et al. 1994; Duhme et al. 1996; Ciccone et al. 1998); some relied on distance to a major roadway or the number of vehicles on a nearby busy road, based on data from highway agencies (Wjst et al. 1993; Weiland et al. 1994; van Vliet et al. 1997; English et al. 1999; Venn et al. 2000); and some have modeled exposure to specific pollutants at homes, based on traffic patterns (Pershagen et al. 1995; Hirsch et al. 1999; Kramer et al. 2000). There have been two recent birth cohort studies of respiratory disease and NO_2 and particulate pollutants modeled from traffic (Brauer et al. 2002; Gehring et al. 2002). A Dutch cohort study of newborn children found increased asthma incidence in children living in more polluted communities during the first two years of life (Brauer et al. 2002). In the other study, there was an association between dry nocturnal cough and exposure (Gehring et al. 2002). . Our findings of increased rates of lifetime asthma at study entry among children living closer to a freeway are consistent with these studies suggesting an effect of early life exposure to traffic related pollutants.

4.2.3. Other Questionnaire-Based Health Outcomes

4.2.3.1. Summary of Results

Bronchitic symptoms (chronic cough, phlegm, and reported bronchitis) were the principal non-asthma questionnaire based outcomes of interest. Both cross-sectional and longitudinal analyses were conducted examining the relationship to air pollution measured at the community monitoring stations. There were relatively few statistically significant associations observed in the entire population, but strong associations were observed in analyses restricted to children with asthma. A novel longitudinal analysis examined the relationship between risk of symptoms within communities and relatively small yearly air pollutant variation within each community from a multi-year average. This analysis identified organic carbon and NO_2 as likely pollutants responsible for increased symptoms in asthmatic children.

4.2.3.1.1. Cross-sectional analyses

Several other cross–sectional studies before and after the initiation of the CHS have examined the relationship of prevalence of bronchitis and chronic cough or phlegm production in children with air pollution. Some of these studies have found positive associations, primarily with PM (Dockery et al. 1989; Dockery et al. 1996; Braun-Fahrlander et al. 1997; Jedrychowski and Flak

1998; McConnell et al. 1999; Heinrich et al. 2000). However, there has been little investigation of the effects of components of particulate matter on these symptoms or of whether other gaseous pollutants could be responsible for the observed effects.

The symptoms of the 4th, 7th, and 10th grade children recruited in 1993 were evaluated based both on 1986-90 exposure estimated from monitoring results pre-dating this study and from the 1994 exposures measured as part of the CHS network. There were no significant associations of bronchitic symptoms either with PM or with gaseous co-pollutants, in boys or girls, or in all subjects together (see Table 4.2-9 in Section 4.2.2.). The associations with wheezing have been discussed in Section 4.2.2.

In further analyses modeled after the analytic strategy employed in the Six Cities study (Dockery et al. 1989), the population was stratified by lifetime history of asthma at study entry. In addition, we examined associations among children with a history of wheeze but no asthma and among children with neither wheeze or asthma. For each group, associations of pollutant with reported bronchitis, 3 months of chronic cough, or chronic phlegm during the previous 12 months were examined. For children with asthma, all pollutants except ozone were positively associated with the risk of bronchitis, although the association was strongest for particulate pollutants (odds ratio 1.4 per interquartile range for both PM_{10} and $PM_{2.5}$) and statistically significant for PM_{10} (Table 4.2-15). There was a strong positive association between phlegm and ambient particulates and NO_2, and a slightly weaker, but also significant, association with acid pollutants (nitric + hydrochloric). There was a modest positive but not significant association between cough and $PM_{2.5}$, NO_2, and acid. A similar pattern of pollutant effects was observed for wheezing in the previous year. There was no association between air pollution and prevalence of bronchitis or associated symptoms among children with a history of wheezing (without asthma). Among children with neither wheeze nor asthma, there was a weak inverse association between bronchitis and pollution, which was marginally significant for particulate pollutants.

The strong association observed, between exposure to PM_{10} and bronchitis is presented in Figure 4.2-14 for children with asthma (and for comparison for children with neither asthma nor wheeze). For ease of interpretation, the figures are plotted using prevalence rates. Throughout the range of exposure to PM_{10} across the 12 communities, there was increasing prevalence of bronchitis (R^2 =0.44; p=0.02). Similar associations were observed between NO_2 and phlegm (R^2 =0.54; p=0.006).

4.2.3.1.2. Longitudinal analyses of bronchitis and air pollution

The next series of analyses were prompted in part by recent toxicologic evidence indicating that organic carbon (OC) in particulate matter 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 (Li et al. 2002), which is known to promote an allergic response (Hashimoto et al. 2001; Sydbom et al. 2001). A series of analyses were conducted to examine the effect on bronchitic symptoms of different size fractions of PM and of particulate OC, elemental carbon, and of other traffic-related pollutants, including NO_2, after adjusting for other co-pollutants.

From the yearly follow-up questionnaire administered to each child in Cohorts B, C, and D, analyses were conducted restricted to children with a history of doctor diagnosed asthma at study entry, who also had completed two or more follow-up questionnaires any time during the years 1996-1999 (N=475). A child was considered to have had chronic bronchitic symptoms during the previous year, based on 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 (for the longitudinal analysis described below, there were not enough children to assess each symptom separately). Children who answered no to all 3 of these questions were considered not to have bronchitic symptoms for the corresponding year. Participation in team sports prior to the first year a child contributed information on bronchitis for this analysis was also assessed from the child's completed questionnaire. 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 pm to 6 pm (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.

Four-year mean levels (1996-1999) in each community were computed for each pollutant metric. The yearly deviations from the four-year mean were computed each year for each community. We selected the 10 AM to 6 PM O_3 metric, because this is when children were likely to be outside and, therefore, more exposed.

The modeling strategy can be conceptualized as a three-stage regression (Diggle et al. 1994; Gauderman et al. 2000; McConnell et al. 2003b), described in more detail in Section 3.6. Briefly, 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 four-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.

The between–community range of four–year average pollutant concentrations was four- to ten-fold across the 12 communities, with the exception of O_3 and of $PM_{10-2.5}$, which had approximately two–fold and 3.5–fold ranges, respectively (Table 4.2-16). The within–community ranges, i.e. the range of the yearly deviation from the four–year mean of pollutants in each of the 12 communities were small. For OC, for example, the within–community range was only 0.5 $\mu g/m^3$ 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 four–year mean (2.3 $\mu g/m^3$), the range was modest compared with the large between–community variability (1.4-11.6 $\mu g/m^3$).

The correlation of (four–year average) pollutants across the 12 communities was low for O_3 with each of the other pollutants, but most other pollutants were relatively highly correlated with each other ($R > 0.65$), as discussed in greater detail in Section 4.1. The within–community pattern of correlations was somewhat different than between–communities (Table 4.2-17). 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 organic carbon and inorganic acid (nitric + hydrochloric). 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.

There were 475 children with asthma, and 184 (38.7%) had bronchitic symptoms during the first year. The odds ratio of bronchitic symptoms among asthmatic children varied from 0.80 (for O_3) to 1.81 (for $PM_{2.5}$) across the large range of pollutants between communities (Table 4.2-18). All associations with particulate matter were of similar magnitude, except $PM_{10-2.5}$ (odds ratio 1.38), and odds ratios 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 odds ratios for within–community effects were arbitrarily expressed per $\mu g/m^3$ (or ppb). Within communities, all pollutants were positively associated with symptoms. The odds ratios for particulate matter 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 ($P<0.01$) 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 odds ratio, but this reflects the relatively narrow range (in $\mu g/m^3$) within any community.

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 (odds ratio 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.

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 4.2-19). The single-pollutant effect of $PM_{2.5}$ ($\beta = 0.085/\mu g/m^3$) was only modestly attenuated by other pollutants and remained significant after adjusting for $PM_{10-2.5}$, inorganic (nitric + hydrochloric) or organic (formic + acetic) acid. The effect of OC ($\beta = 0.345/\mu g/m^3$) remained significant, except after adjusting for $PM_{2.5}$ (which reduced the estimate modestly to $0.335/\mu g/m^3$; $P = 0.08$) or NO_2 (which reduced the effect to $0.237/\mu g/m^3$; $P = .11$). The effect of NO_2 ($\beta = 0.071$/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 $\beta = 0.039$; $P = .22$). 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 odds ratios 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 4.2-15.

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 4.2-20). The

effect estimates for NO_2 ($\beta = 0.017$/ppb) and for EC ($\beta = 0.441/\mu g/m^3$) in single pollutant models were markedly attenuated in models with $PM_{2.5}$. The effect of NO_2 was modestly reduced when adjusted for PM_{10}, EC, or OC. The effect of $PM_{2.5}$ ($\beta = 0.026/\mu g/m^3$) was markedly reduced, when adjusted for NO_2. No pollutant had a consistent significant association with symptoms in models adjusted for other pollutants. There also were no significant positive associations with any pollutant among children without asthma, either in the within-community or the between-community analysis.

Table 4.2-15. Association of bronchitic symptoms with air pollution at study entry.

Bronchitis

	Asthma (N=154/473)**		Wheeze/No Asthma (N=147/630)**		No Wheeze/No Asthma (N=117/2162)**	
	O.R.	(95% C.I.)	O.R.	(95% C.I.)	O.R.	(95% C.I.)
PM_{10}	1.4	(1.1, 1.8)	0.9	(0.7, 1.3)	0.7	(0.4, 1.0)
$PM_{2.5}$	1.4	(0.9, 2.3)	0.9	(0.6, 1.4)	0.5	(0.3, 1.0)
NO_2	1.3	(0.8, 2.2)	0.9	(0.6, 1.4)	0.8	(0.4, 1.7)
Ozone	1.0	(0.6, 1.7)	1.1	(0.7, 1.6)	0.9	(0.4, 1.8)
Acid	1.1	(0.7, 1.6)	0.9	(0.7, 1.6)	0.9	(0.5, 1.0)

Phlegm

	Asthma (N=122/475)**		Wheeze/No Asthma (N=86/625)**		No Wheeze/No Asthma (N=93/2092)**	
	O.R.	(95% C.I.)	O.R.	(95% C.I.)	O.R.	(95% C.I.)
PM_{10}	2.1	(1.4, 3.3)	0.9	(0.6, 1.4)	0.8	(0.6, 1.3)
$PM_{2.5}$	2.6	(1.2, 5.4)	1.0	(0.6, 1.8)	0.8	(0.4, 1.5)
NO_2	2.7	(1.4, 5.3)	1.0	(0.6, 1.8)	1.0	(0.5, 1.9)
Ozone	1.2	(0.5, 3.1)	0.8	(0.5, 1.4)	0.8	(0.5, 1.5)
Acid	1.9	(1.0, 3.6)	0.9	(0.6, 1.4)	1.1	(0.7, 1.8)

Cough

	Asthma (N=84/491)**		Wheeze/No Asthma (N=63/644)**		No Wheeze/No Asthma (N=84/2180)**	
	O.R.	(95% C.I.)	O.R.	(95% C.I.)	O.R.	(95% C.I.)
PM_{10}	1.1	(0.8, 1.7)	1.2	(0.9, 1.8)	0.9	(0.7, 1.2)
$PM_{2.5}$	1.3	(0.7, 2.4)	1.1	(0.6, 1.9)	0.9	(0.6, 1.3)
NO_2	1.6	(0.9, 2.7)	1.3	(0.7, 2.2)	0.8	(0.5, 1.2)
Ozone	1.1	(0.6, 2.0)	0.7	(0.5, 1.1)	0.9	(0.6, 1.3)
Acid	1.4	(0.9, 2.1)	1.0	(0.6, 1.5)	0.9	(0.7, 1.3)

*Prevalence odds ratios were calculated per interquartile range of yearly mean exposure for each pollutant (32 ppb daily peak ozone, 19 ug/m^3 daily average PM_{10}, 24 ppb daily average NO_2, 2-week average $PM_{2.5}$ (15 ug/m3), $PM_{10-2.5}$ (10 ug/m^3) and acid (1.8 ppb of HCl + HNO_3, measured on a mole basis). All models were adjusted for age, gender, race, school grade, and membership in a health insurance plan.

**N is number responding positively for each outcome/total in stratum. Total varies by outcome because of variable "don't know" responses or missing values (which were excluded).

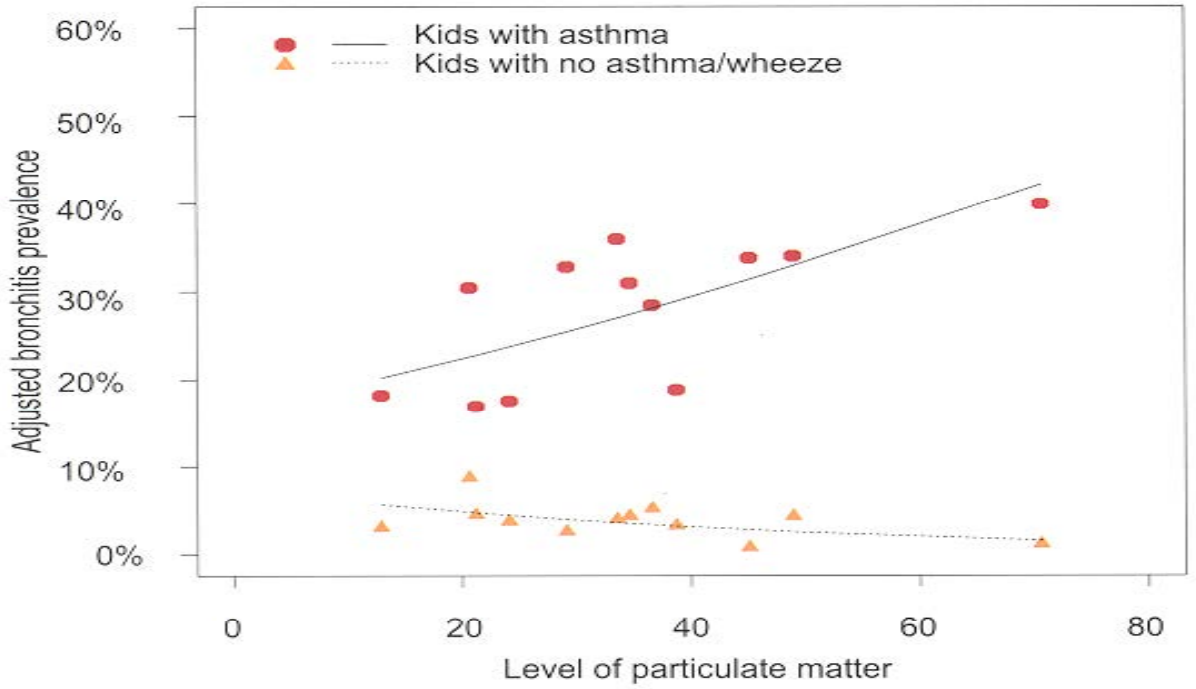


Figure 4.2-14. Association of bronchitis with PM_{10} at study entry.

Table 4.2-16. 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	(S.D.)	Min–max	Mean	(S.D.)	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
$PM_{10\text{-}2.5}$	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

*Mean and standard deviation (S.D.) of the four–year average across the 12 communities.

†Mean and standard deviation (S.D.) 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, elemental and organic carbon in $\mu g/m^3$

§Inorganic acid refers to the sum of nitric and hydrochloric acid observations

§§Organic acid refers to the sum of formic and acetic acid observations

#Effective cut-point of 2.5 microns: see Methods section for Two-Week Sampler Leg C description for additional details.

Table 4.2-17. Person 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

*P < .05; † P < .01

Note: Effective cut-point of 2.5 microns for OC and EC: see Methods section for Two-Week Sampler Leg C description for additional details. Inorganic acid refers to the sum of nitric and hydrochloric acid observations. Organic acid refers to the sum of formic and acetic acid observations.

Table 4.2-18. 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% C.I.)	OR*/Unit† (95% C.I.)	OR*/Unit† (95%C.I.)
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)§

*OR=odds ratio, 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.

†Between-community OR 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 (hydrochloric and nitric) and organic acid (formic and acetic), respectively; and 47.8, 23.0, 24.8, 1.1, and 10.2 $\mu g/m^3$ for PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, EC and OC (with effective size cut of PM_{10}), respectively). Between-community OR are also per unit of pollutant (ppb or $\mu g/m^3$) for comparison with the within-community OR.

‡$P < .05$; §$P < .01$

[#]Effective cut-point of 2.5 microns: see Methods section for Two-Week Sampler Leg C description for additional details.

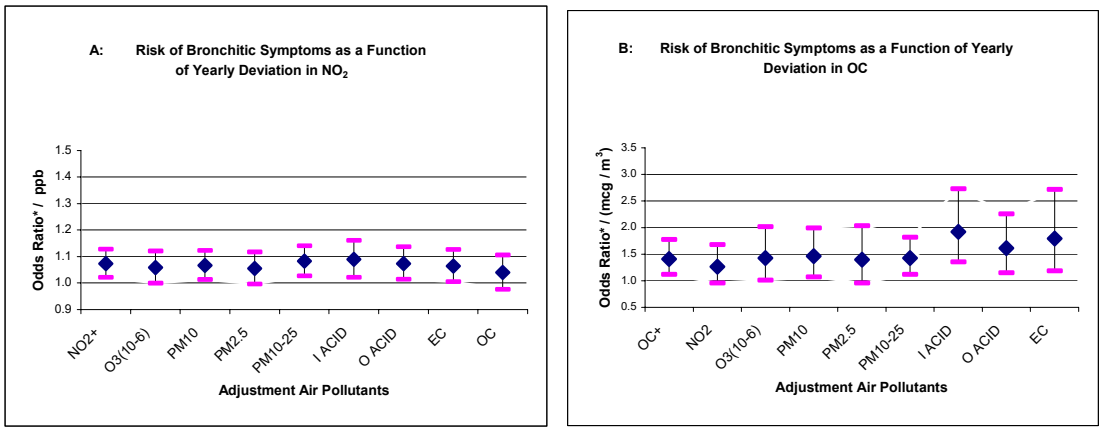
Table 4.2-19. Two pollutant models of within-community effects (difference between annual air pollutant concentration and 4-year average concentrations; N=48) among children with asthma*

Main Pollutant	Adjustment pollutants								
	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**‡

*Each row gives estimates (beta) 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 $\mu g/m^3$ for PM, elemental and organic carbon.

†P < .05; ‡P < .01

Note: Effective cut-point of 2.5 microns for OC and EC: see Methods section for Two-Week Sampler Leg C description for additional details. Inorganic acid refers to the sum of nitric and hydrochloric acid observations. Organic acid refers to the sum of formic and acetic acid observations.



*All odds ratios were adjusted for age, maternal and child's smoking history, sex, and race, and for the between-community effect of the pollutant indicated.
+NO_2+ and OC+ indicate the within-community odds ratio in a single pollutant model, adjusted only for the between-community effects of NO_2 (A) and OC (B) and for personal covariates. All other odds ratios are also for NO_2 (A), or for OC (B), but adjusted in addition for both within- and between-community effects of the adjustment pollutant indicated.

Figure 4.2-15. Odds ratios for the within-community effects of NO_2 and of organic carbon, adjusted for each of the other pollutants examined.

Table 4.2-20. Two pollutant models of <u>between-community</u> effects (4-year average concentrations; N=12) among children with asthma*

Main Pollutant	Adjustment pollutants								
	NO_2	O_3	PM_{10}	$PM_{2.5}$	$PM_{10-2.5}$	Inorganic acid	Organic acid	EC	OC
NO_2	**0.017**†	0.016†	0.014	0.009	0.017†	0.020	0.017	0.014	0.014
O_3	-0.003	**-0.006**	-0.009	-0.010	-0.007	-0.012	-0.011	-0.006	-0.008
PM_{10}	0.004	0.013	**0.011**	-0.027	0.043†	0.009	0.006	-0.001	0.010
$PM_{2.5}$	0.016	0.029‡	0.069	**0.026**†	0.043†	0.036	0.034	0.025	0.037
$PM_{10-2.5}$	0.000	0.016	-0.069	-0.027	**0.013**	0.003	-0.005	-0.011	-0.070
Inorganic acid	-0.037	0.137†	0.035	-0.069	0.089	**0.098**	-0.044	-0.073	0.044
Organic acid	-0.001	0.091†	0.039	-0.035	0.078	0.094	**0.069**	-0.027	0.050
EC	0.097	0.443†	0.450	0.018	0.557	0.658	0.567	**0.441**†	0.389
OC	0.020	0.059	0.004	-0.043	0.213†	0.043	0.021	0.004	**0.054**

*Each row gives estimates (beta) 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 $\mu g/m^3$ for PM, elemental and organic carbon.

†P < .05; ‡P < .01

Note: Effective cut-point of 2.5 microns for OC and EC: see Methods section for Two-Week Sampler Leg C description for additional details. Inorganic acid refers to the sum of nitric and hydrochloric acid observations. Organic acid refers to the sum of formic and acetic acid observations.

4.2.3.2. Synthesis

In summary, CHS results are consistent with others that have shown children with asthma are susceptible to the effects of air pollution. Bronchitic symptoms are a sensitive end point for pollutant effects among asthmatic children. In the context of this investigation, bronchitis and related chronic symptoms may represent exacerbation of asthma by air pollution, rather than conditions which can be separated from asthma. Alternatively, the results may reflect the persistent respiratory symptoms reported among asthmatic children with viral infections in communities with air pollution, especially NO_2 (Schauer et al. 1996).

The results from the cross sectional and the equivalent between-community results from the longitudinal analysis are important new contributions for two reasons: First, this is one of the few epidemiologic analyses of chronic effects that has measured multiple pollutants. By examining various co-pollutants and the various size fractions it was possible to show that the effects were consistently associated with the fine particulate fraction. We found little evidence that coarse particulate was responsible for symptoms. (Although there may be additional error in the measurement of coarse $PM_{10-2.5}$, as has been discussed in Section 3.4.1.5). However, estimates of long term averages are likely to be very precise, because there are so many measurements that contribute to the average that the standard error becomes small). Second, the primary source both for PM and NO_2 in southern California is vehicular traffic, which distinguishes the interpretation of results from those from polluted areas in the eastern United States, where there are other important sources for particulate air pollution. Southern California has little of the SO_2 and strong acid (sulfuric-acid-related) particulate sulfate characteristic of air pollution in the eastern U.S. (where similar associations between particulate pollution and bronchitis has been observed previously) (Dockery et al. 1989). Therefore, either other pollutants may produce similar effects or SO_2 and particulate sulfate are not the pollutants responsible for the observed effects in the Six and Twenty-four cities studies that represented primarily eastern U.S. cities (Dockery et al. 1989; Dockery et al. 1996).

A unique contribution of the within-community evaluation of the longitudinal data was to identify specific pollutants, NO_2 and OC, which are likely candidates to be responsible for the observed effects. It was not possible in the between-community analysis to distinguish which of the multiple pollutants measured was more likely to be responsible for the observed effects, because there was strong correlation of particulate air pollution, NO_2, and acids (see Table 4.1-5). In two-pollutant models there were no consistently significant between–community effects. In contrast, $PM_{2.5}$ was associated with symptoms both for the four–year average and for the yearly variation in concentration, and in the within-community analysis $PM_{2.5}$ was relatively robust in two–pollutant models. Of the PM constituents, yearly variability in particulate OC within communities was associated with symptoms, and the effect of yearly variation in OC persisted in two-pollutant models with other pollutants. Both 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, in the within-community analysis playing team sports modified the effect of yearly variability in NO_2, which affected only children playing team sports, a finding that strengthens the inference of a causal relationship between NO_2 and symptoms.

Although there has been relatively little human experimental or epidemiologic study of the effects of organic compounds in ambient particulate matter, our results are supported by recent studies showing organic carbon to be biologically active in pathways relevant for asthma exacerbation (Li et al. 2002). OC is largely due to emissions from gasoline and diesel vehicle exhaust in Southern California, although there are some other primary sources (Schauer et al. 1996). Diesel exhaust particulate is a likely source for the effects observed, because it enhances allergen induced TH2 type (allergic) responses in animal models and in allergic human volunteers, and common indoor and outdoor allergens have been shown to bind specifically to diesel particles (Hiura et al. 1999; Bonvallot et al. 2001; Sydbom et al. 2001). The organic fraction contains reactive oxygen species which produce a strong oxidative stress response, which we have postulated to be important to the pathogenesis of diseases associated with the pulmonary response to air pollution (Casillas et al. 1999; Gilliland et al. 1999b; Hiura et al. 1999).

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 (although it was significantly associated with symptoms in the between-community analysis), and EC is also a marker for diesel exhaust in Southern California (Manchester et al. 2001). However, formation of secondary organic aerosol from gaseous emissions of volatile organic compounds also contribute to ambient concentration of OC, especially in inland sites in the air basin (Turpin and Huntzicker 1991; Turpin and Huntzicker 1995; Strader et al. 1999). Therefore, 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 even 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 (Delfino et al. 1996; Lierl and Hornung 2003). An alternative explanation for the absence of an effect of EC in two-pollutant models is the strong correlation of OC with EC (and inorganic acid), which makes the results of these two pollutant models difficult to interpret (Table 4.2-17). Both organic acid and EC were positively associated with symptoms in single pollutant models, but were protective in 2-pollutant models with OC; see Table 4.2-19. Also, the within–community variability of OC was relatively strongly correlated with NO_2 (Table 4.2-17). This may explain the weaker associations with bronchitic symptoms in asthmatic children in the 2-pollutant model with OC and NO_2.

The effect of NO_2 on respiratory illness has been extensively evaluated in epidemiologic studies of exposure from indoor sources, and the observed associations have not been consistent (Bates 1995b; Koren 1995; Anonymous 1996; Linaker et al. 2000). 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 four–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 (McArdle et al. 1996), 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 (Dockery et al. 1989; Dockery et al. 1996; Jedrychowski and Flak 1998; Heinrich et al. 2000), although the results are consistent with our cross–sectional evaluation and with a study of children in Dresden, Germany (Hirsch et al. 1999). 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 (Anonymous 1996). In communities with air pollution, especially NO_2, more persistent respiratory symptoms have been reported among asthmatic children with viral infections (Chauhan et al. 1999).

A second important result from the within-community analysis was the consistently larger odds ratios for the effect of pollutants than those observed in between–community analysis (Table 4.2-18). If the within–community estimates of effects are correct, then other cross–sectional (between–community) studies in the literature may have under-estimated the true effect of air pollution on bronchitic symptoms in children. A distinct advantage of the within–community contrast is that there could be no confounding by poorly measured or unmeasured differences between communities, a generic limitation to ecologic comparisons across communities. These would tend to reduce the observed effect of pollution in community comparisons. 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 asthmatic children and which may not have been well measured in this study. Possible, but less likely, alternative explanations for the larger within–community effects have been discussed elsewhere in evaluating the limitations to this analysis (McConnell et al. 2003b). These 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 co-varied with air pollutants from year-to-year. The effect of personal smoking and second hand tobacco smoke exposure, which may have varied over the time of the study, was assessed by questionnaire, 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 (2000).

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 to 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 in order to account for such a possibility.

Although we have identified OC and NO_2 as likely causal pollutants for the observed associations, it should be noted that if there were 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.

There are several public health and regulatory implications of these results. First, previous cross–sectional studies of chronic symptoms have underestimated the effect of pollutants, as suggested by the much larger within–community estimates observed in this study. If so, then regulation based on those studies may not adequately protect asthmatic children. Second, we have previously observed that team sports and time spent outside modify the effect of air pollution on several respiratory outcomes in children (see Sections 4.2.1 and 4.2.2) (Gauderman et al. 2000; Gauderman et al. 2002; McConnell et al. 2002b). These increased risks associated with activity patterns have not routinely been considered in setting standards. Our results suggest that standards should be stringent enough to protect exercising children from the increased dose of pollution to the lung associated with outside physical activity. Third, 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 TSP of between 10 and 20 $\mu g/m^3$ was associated with a 20% reduction of total bronchitis prevalence (Heinrich et al. 2000). 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 its ill effects 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 organic carbon 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 particulate matter, and the sources of these constituents, might result in better approaches to intervention.

4.2.4. Ambient Air Pollution and School Absenteeism

4.2.4.1. Summary of Results

Consideration of school absenteeism, provides a more inclusive assessment of the adverse impacts of ambient air pollution on children that includes social, economic and educational effects as well as specific adverse health effects (Ostro and Rothschild 1993; Samet and Speizer 1993). Illness-related school absenteeism is an important but under-studied outcome in children, a group identified as especially sensitive to the adverse effects of ambient air pollution (Bates 1995a). Illness-related absences are common events that represent a broad spectrum of morbidity from mild transient illnesses to the most severe and prolonged illnesses that require emergency room visits or hospital admissions (Weitzman 1986). Although most absences are associated with illnesses at the low end of the morbidity spectrum, an absence indicates an illness of sufficient severity to affect the child's daily functioning, as well as child and family coping strategies (Rogers and Reese 1965; Rozelle 1968; Parcel et al. 1979; Weitzman 1986; Celano and Geller 1993).

Because the effects of air pollution on school absences are likely to be due to increases in respiratory illnesses, respiratory illness-related absenteeism serves as an important and relatively specific integrative outcome for the assessment of the effects of air pollution on children. The Children's Health Study is one of the first to have examined the effects of ambient air pollution

on school absenteeism in school-aged children residing in communities with large variations in pollutant levels.

As discussed in detail in the methods section of this report (Sections 3.1-3.6), the relationships between ozone (O_3), nitrogen dioxide (NO_2), and inhalable particles (PM_{10}) and school absenteeism were investigated in a substudy within the CHS cohort, the Air Pollution and Absence Study (APAS), and examined data on type-specific absence incidence collected by an active surveillance system for a cohort of 4th grade school children aged 9-10 years who attended schools in the 12 CHS study communities during January to June 1996. An active surveillance system ascertained the numbers and types of absences during the first 6 months of 1996. Pollutants were measured hourly at central-site monitors in each of the 12 communities. To examine acute effects of air pollution on absence rates, we fitted a two-stage time series model to the absence count data that included distributed lag effects of exposure adjusted for long-term pollutant levels.

The general modeling approach used in the analysis has been briefly described in Section 3.6. More technical details on the specific models used could also be found in (Gilliland et al. 2001b) and (Berhane and Thomas 2002). The distribution of participants' characteristics, medical conditions, ETS exposure, and outdoor activity varied among the communities (Table 4.2-21). The average daily incidence rate for all types of absences combined was 3.07 per 100 student days based on an average daily attendance of 1502 students). Average daily absence rates were highest in Lake Arrowhead and lowest in Upland. The crude average daily rates per 100 participants were 1.07 for non-illness-related absences, 1.34 for illness-related absences, and 0.61 for absences of unknown type (Table 4.2-23). The daily information success ratio averaged 0.81, and exceeded 0.72, for all subgroups. Lake Arrowhead had the highest adjusted daily rate for illness-related absences and Long Beach had the lowest rate. Illness-related absences were primarily due to respiratory illnesses, most of which had upper respiratory symptoms (Table 4.2-24). Adjusted daily rates of absences for respiratory illness, upper respiratory illness, LRI with wet cough /wheeze/asthma and LRI with wet cough varied among communities, and ethnic and education groups. Rates of absences for respiratory illness and upper respiratory illness were twice as high in Lake Arrowhead compared to rates in Long Beach. Children with asthma, wheezing, and ETS exposure had higher absence rates for all categories of respiratory illness than children without asthma, wheezing, or ETS exposure. Adjusted absence rates for GI illness did not vary as substantially as rates for respiratory illness by children's asthma status, wheezing status, or ETS exposure (Table 4.2-24).

Short-term change in O_3, but not NO_2 or PM_{10}, was associated with a substantial increase in school absences from both upper and lower respiratory illness. Ten am-6 pm average O_3 was strongly associated with illness-related absences and especially respiratory absences. The acute effects of O_3 were significantly increased at a 3-day lag, peaked at a 5-day lag, and subsequently showed a slow decrease. Overall estimates of the effect of acute change in O_3 on absences are obtained by summing the area under the distributed lag curve over the 30-day lag period. Daily 1-hour peak O_3 produced the same overall results as analyses using the 10 am-6 pm average O_3.

A 20 ppb increase in O_3 was associated with a 62.9% absence rate increase for illness, 82.9% increase for respiratory illnesses, 45.1% increase for upper respiratory illnesses, 173.9% increase

for LRI with wet cough, and 68.4% increase for LRI with wet cough/wheeze/asthma (Table 4.2-26). To determine the sensitivity of our estimates to the amount of smoothing used to remove seasonal variation, we refitted the models using 3 degrees of freedom and found that the estimates were essentially unchanged. For example, the effect of ozone on respiratory absences changed from an 82.9% increase to an 81.3% increase. Ozone-related increases in all absences and illness-related absences were larger in communities with lower levels of NO_2 or PM_{10} than in communities with higher levels of NO_2 or PM_{10} (Table 4.2-27). The acute effects of O_3 on respiratory illness-related absenteeism were also larger in communities with lower long-term average PM_{10} (454.9%) compared to communities with high average PM_{10} (42.9%).

Daily 24-hour PM_{10} was associated with all absences (Table 4.2-26). However, increased daily PM_{10} was only associated with increases in non-illness-related absences. A change of 10 $\mu g/m^3$ in PM_{10} was associated with a 22.8% increase in all types of school absences combined and with a 97.7% increase in non-illness-related absences, but a 5.7% increase in illness-related absences. Daily PM_{10} was not associated with any of the categories of respiratory illness-related absences. NO_2 was not associated with school absenteeism (Table 4.2-26).

4.2.4.2. Synthesis

The relationships between ozone (O_3), nitrogen dioxide (NO_2), and inhalable particles (PM_{10}) and school absenteeism were investigated in a cohort of 4th-grade school children who resided in 12 southern California communities. An active surveillance system ascertained the numbers and types of absences during the first 6 months of 1996. Pollutants were measured hourly at central-site monitors in each of the 12 communities. To examine acute effects of air pollution on absence rates, we fitted a two-stage time series model to the absence count data that included distributed lag effects of exposure adjusted for long-term pollutant levels.

Short-term change in O_3, but not NO_2 or PM_{10}, was associated with a substantial increase in school absences from both upper and lower respiratory illness. We found that day-to-day changes in O_3 were associated with a substantial increase in school absences from both upper and lower respiratory illnesses. Absences were significantly increased 2 to 3 days after exposure and reached a peak on day 5 after exposure. The short-term effects of O_3 on respiratory illness-related absences are consistent with a large body of evidence on the acute adverse effects of O_3 on children's respiratory health (Bascom et al. 1996; Avol et al. 1998b). Exposure to O_3 is known to be associated with increased hospital admissions for respiratory infections among children. Hospital admission ranks as a severe outcome in the range of adverse effects, and most respiratory illnesses do not lead to hospital admission for treatment. School absences due to respiratory illnesses may usefully represent the first tier of adverse effects that are far more common than severe adverse effects. Because exposures at the levels observed in this study are common, the increase in school absenteeism from respiratory illnesses associated with relatively modest day-to day changes in O_3 concentration documents an important adverse impact of O_3 on children's health and well-being.

Table 4.2-21. Percentage distributions of sociodemographic characteristics and selected medical history and exposures among participants, Air Pollution and Absence Study, January to June 1996.

	Race/Ethnicity							Parent Education*						Reporting Method**					
Community reporting	N	African Males	Some White	Hisp	American	Asian	Other Race	<12th grade	12th grade	college/ tech schl	4 yr college	Post grad	Asthma	Wheeze	Outdoor activity ETS	Outdoor activity >11.25 hr	Subject specific reporting	Whole grade
Alpine	177	49.7	73.4	20.9	0	0.6	4.5	7.9	20.3	49.2	10.7	9.0	13.6	33.9	16.4	57.6	0	100.0
Lake Elsinore	171	47.4	52.0	33.9	2.3	2.9	6.4	18.1	21.1	38.0	11.1	4.1	11.1	31.6	21.1	45.0	45.6	54.4
Lake Arrowhead	164	52.4	71.3	22.0	0.6	0	5.5	9.8	19.5	50.6	7.3	8.5	14.6	35.4	29.9	29.9	24.4	75.6
Lancaster	176	47.2	49.4	31.3	10.8	2.3	5.1	17.6	18.2	44.9	6.8	8.0	16.5	34.7	24.4	52.3	100.0	0
Lompoc	166	49.4	44.0	36.1	6.6	9.0	4.2	12.7	19.3	48.8	9.6	5.4	10.8	29.5	19.9	33.1	34.3	65.7
Long Beach	158	54.4	32.3	23.4	21.5	13.9	8.2	10.8	19.6	39.2	13.3	12.0	13.9	27.8	20.3	38.0	66.5	33.5
Mira Loma	152	48.0	40.8	52.6	2.0	1.3	2.6	27.0	24.3	31.6	7.9	1.3	14.5	34.2	24.3	42.8	100.0	0
Riverside	152	49.3	40.1	40.8	10.5	1.3	5.9	15.1	23.0	32.9	9.2	17.1	11.8	26.3	12.5	52.6	0	100.0
San Dimas	162	48.8	48.8	35.2	1.9	8.6	5.6	6.2	15.4	53.7	10.5	9.3	18.5	30.9	17.3	38.9	0	100.0
Atascadero	157	56.1	72.6	17.2	1.9	1.3	7.0	4.5	17.8	50.3	8.9	17.2	19.7	43.3	13.4	50.3	0	100.0
Santa Maria	156	49.4	22.4	62.8	0.6	7.1	3.2	21.2	22.4	30.8	7.1	5.1	12.2	19.2	12.8	34.6	100.0	0
Upland	144	47.2	66.7	17.4	4.2	7.6	4.2	2.1	7.6	46.5	22.9	20.8	11.8	27.8	8.3	34.0	100.0	0
Total	1935	49.9	51.4	32.7	5.2	4.6	5.2	12.8	19.1	43.2	10.3	9.7	14.1	31.3	18.6	42.6	46.9	53.1

*Refers to parent/guardian who completed the subject's baseline questionnaire.
** Reporting methods included schools that provided lists of whole grades and those that provided study subject-specific reports

(Reprinted with permission, Gilliland et al., 2001. The effects of ambient air pollution on school absenteeism due to respiratory illnesses. *Epidemiology*, 12(1):43-54.)

Table 4.2-22. Average daily absence incidence rates per 100 children-days and average number of children at risk per day on all days and days with active surveillance for type of absence by selected participant characteristics, Air Pollution and Absence Study, January to June 1996.

	All Days			Active Surveillance Days		
	Absence rate/100	Avg# children at risk/Day	%	Absence rate/100	Avg# children at risk/day	%
All	3.07	1502.2	100.0	3.02	996.4	100.0
Sex						
Females	3.08	751.2	50.0	3.10	500.9	50.3
Males	3.06	751.0	50.0	2.93	495.4	49.7
Ethnicity/Race						
Missing	2.40	12.5	0.8	2.04	8.0	0.8
White/non—Hisp	3.13	776.5	51.7	3.10	498.7	50.1
Hispanic	3.16	483.1	32.2	3.20	327.6	32.9
Black (Afr—Amer)	1.84	82.0	5.5	2.02	61.7	6.2
Asian/Pac. Isle	2.00	71.2	4.7	1.29	50.2	5.0
Other	3.62	78.1	5.2	3.89	51.0	5.1
Educuation of Signer						
Missing	3.14	71.2	4.7	2.97	45.1	4.5
< 12th grade	3.59	182.5	12.1	3.73	124.9	12.5
12th grade	3.25	287.2	19.1	3.19	189.9	19.1
Some coll/tech	3.16	651.4	43.4	3.05	426.9	42.8
4 yr college	2.45	159.2	10.6	2.96	110.0	11.0
Post—grad	2.39	150.8	10.0	2.35	99.9	10.0
Community						
Alpine	3.23	158.6	10.6	3.22	116.0	11.6
Lake Elsinore	3.78	109.3	7.3	3.82	93.6	9.4
Lake Arrowhead	4.34	129.1	8.6	4.36	105.3	10.6
Lancaster	3.06	128.4	8.5	3.10	90.3	9.1
Lompoc	2.84	151.4	10.1	3.17	106.1	10.7
Long Beach	2.35	149.7	10.0	2.37	124.2	12.5
Mira Loma	3.30	149.5	10.0	3.35	143.1	14.4
Riverside	2.97	151.5	10.1	2.94	143.8	14.4
San Dimas	2.80	159.7	10.6	2.50	86.0	8.6
Atascadero	2.82	134.6	9.0	3.06	103.7	10.4
Santa Maria	2.83	112.9	7.5	2.57	83.0	8.3
Upland	2.29	143.0	9.5	2.36	114.6	11.5
Diagnosed Asthma						
Missing	3.15	45.4	3.0	3.24	30.5	3.1
No	2.98	1243.3	82.8	2.94	827.1	83.0
Yes	3.65	213.5	14.2	3.61	138.7	13.9
Reported Wheeze						
Missing	2.55	89.6	6.0	2.73	61.3	6.2
No	2.88	943.2	62.8	2.81	630.2	63.2
Yes	3.55	469.4	31.2	3.55	304.9	30.6
Any ETS*						
Missing	3.17	49.7	3.3	3.02	32.8	3.3
No	2.93	1181.0	78.6	2.86	786.4	78.9
Yes	3.67	271.5	18.1	3.72	177.2	17.8
7 Day Outdoor Act.						
Missing	3.66	174.2	11.6	3.61	117.2	11.8
<=11.25 hr	3.04	863.3	57.5	3.03	580.0	58.2
> 11.25 hr	3.10	638.9	42.5	3.00	416.4	41.8
School Report Method						
Whole grade	3.19	793.4	52.8	3.03	464.0	46.6
Participants	3.12	721.2	48.0	3.08	545.8	54.8

*ETS = environmental tobacco smoke

(Reprinted with permission, Gilliland et al., 2001. The effects of ambient air pollution on school absenteeism due to respiratory illnesses. *Epidemiology*, 12(1):43-54.)

Table 4.2-23. Average crude daily absence incidence rates per 100 children-days and performance characteristics of the active surveillance system by selected participant characteristics, Air Pollution and Absence Study, January to June 1996.

	Crude Non-Illness	Crude Any Illness	Unknown type	Information success	
	Absence rate/100	Absence rate/100	Absence rate/100	Mean success	(min ratio-max)
All	1.07	1.34	0.61	0.81	(0.70-0.99)
Sex					
Females	1.10	1.40	0.59	0.81	(0.68-0.99)
Males	1.05	1.27	0.61	0.81	(0.65-0.99)
Ethnicity/Race					
Missing	1.25	0.07	0.73	0.72	(0.57-0.93)
White/non-Hisp	1.03	1.42	0.65	0.82	(0.70-0.99)
Hispanic	1.15	1.35	0.70	0.81	(0.57-0.99)
Black (Afr-Amer)	1.05	0.71	0.26	0.81	(0.59-0.93)
Asian/pac. isle	0.39	0.81	0.10	0.82	(0.67-0.94)
Other	1.66	1.65	0.58	0.81	(0.43-1.01)
Educuation of Signer					
Missing	1.01	1.20	0.76	0.81	(0.56-0.96)
< 12th grade	1.46	1.37	0.89	0.80	(0.49-0.91)
12th grade	1.08	1.56	0.55	0.80	(0.44-0.92)
Some coll/tech	1.09	1.36	0.60	0.82	(0.69-0.99)
4 yr college	1.33	1.23	0.40	0.82	(0.56-0.94)
Post-grad	0.67	1.20	0.47	0.81	(0.54-0.97)
Community					
Alpine	0.92	1.43	0.87	0.75	(0.57-1.00)
Lake Elsinore	1.34	1.80	0.67	0.84	(0.44-1.02)
Lake Arrowhead	1.47	1.83	1.06	0.76	(0.54-0.94)
Lancaster	1.14	1.24	0.73	0.82	(0.67-1.02)
Lompoc	0.88	1.74	0.55	0.83	(0.66-0.99)
Long Beach	1.16	0.81	0.40	0.85	(0.75-0.97)
Mira Loma	1.20	1.58	0.56	0.82	(0.72-0.89)
Riverside	0.87	1.37	0.69	0.76	(0.55-0.90)
San Dimas	0.78	1.19	0.52	0.82	(0.69-0.92)
Atascadero	1.01	1.32	0.72	0.80	(0.30-0.96)
Santa Maria	0.77	1.29	0.51	0.81	(0.57-0.95)
Upland	0.79	1.19	0.37	0.86	(0.74-0.99)
Diagnosed Asthma					
Missing	1.44	1.19	0.61	0.81	(0.58-0.95)
No	1.08	1.26	0.60	0.81	(0.70-0.99)
Yes	1.02	1.88	0.71	0.81	(0.61-0.97)
Reported Wheeze					
Missing	0.90	0.88	0.95	0.80	(0.61-0.95)
No	1.03	1.23	0.55	0.81	(0.70-0.99)
Yes	1.24	1.68	0.63	0.81	(0.65-0.97)
Any ETS*					
Missing	1.37	0.98	0.68	0.79	(0.44-0.94)
No	1.00	1.28	0.59	0.81	(0.70-0.99)
Yes	1.29	1.79	0.65	0.81	(0.65-0.95)
7 Day Outdoor Act.					
Missing	1.32	1.57	0.71	0.82	(0.62-0.99)
<=11.25 hr	1.10	1.35	0.58	0.81	(0.44-0.99)
> 11.25 hr	1.05	1.36	0.58	0.81	(0.65-0.90)
School Report Method					
Whole grade	1.15	1.22	0.66	0.79	(0.56-0.91)
Participants	1.08	1.41	0.58	0.83	(0.70-0.99)

*ETS = environmental tobacco smoke

(Reprinted with permission, Gilliland et al., 2001. The effects of ambient air pollution on school absenteeism due to respiratory illnesses. *Epidemiology*, 12(1):43-54.)

Table 4.2-24. Type-specific adjusted* absence incidence rates per 100 children-days by selected participant characteristics.

	Adjusted Non-illness	Adjusted Any Illness	Adjusted Non-resp.	Adjusted Respiratory	Adjusted Upper Resp.	Lower Resp. w/wet cough	Adjusted Lower Resp. w/Wheeze	Adjusted GI Symptoms
	Absence rate/100	Absence rate/100	Absence rate/100	Absence rate/100	Absence rate/100	Absence rate/100	Absence rate/100	Absence rate/100
All	1.34	1.64	0.60	1.04	0.93	0.18	0.30	0.63
Sex								
Females	1.36	1.71	0.62	1.09	1.00	0.19	0.30	0.65
Males	1.31	1.56	0.59	0.97	0.86	0.18	0.30	0.61
Ethnicity/Race								
Missing	1.71	0.10	0.00	0.10	0.10	0.00	0.00	0.00
White/non-Hisp	1.27	1.73	0.67	1.06	0.98	0.21	0.33	0.75
Hispanic	1.40	1.65	0.57	1.08	0.98	0.19	0.26	0.57
Black (Afr-Amer)	1.35	0.86	0.10	0.75	0.68	0.13	0.47	0.21
Asian/Pac. Isle	0.45	1.00	0.21	0.79	0.68	0.10	0.17	0.14
Other	2.11	2.01	0.89	1.13	1.01	0.25	0.34	0.82
Educucaton of Signer								
Missing	1.27	1.49	0.87	0.63	0.58	0.13	0.17	0.76
< 12th grade	1.79	1.66	0.44	1.22	0.93	0.21	0.44	0.50
12th grade	1.35	1.90	0.75	1.15	1.01	0.19	0.33	0.70
Some coll/tech	1.35	1.67	0.59	1.07	0.97	0.18	0.31	0.65
4 yr college	1.76	1.47	0.37	1.10	0.99	0.14	0.38	0.48
Post-grad	0.82	1.46	0.45	1.01	1.01	0.28	0.29	0.63
Community								
Alpine	1.20	1.90	0.91	1.00	0.85	0.19	0.26	0.98
Lake Elsinore	1.67	2.08	0.76	1.32	1.17	0.28	0.56	0.90
Lake Arrowhead	1.90	2.28	0.88	1.41	1.29	0.30	0.35	0.88
Lancaster	1.42	1.47	0.49	0.98	0.91	0.12	0.24	0.64
Lompoc	1.08	2.09	0.71	1.38	1.24	0.24	0.30	0.73
Long Beach	1.36	0.96	0.24	0.72	0.61	0.21	0.31	0.35
Mira Loma	1.48	1.92	0.86	1.06	0.89	0.24	0.41	0.77
Riverside	1.20	1.82	0.72	1.09	1.06	0.20	0.31	0.85
San Dimas	0.94	1.44	0.31	1.13	0.94	0.16	0.36	0.38
Atascadero	1.27	1.61	0.83	0.78	0.60	0.11	0.28	0.66
Santa Maria	0.93	1.62	0.57	1.05	1.04	0.14	0.24	0.40
Upland	0.92	1.38	0.48	0.90	0.84	0.13	0.26	0.55
Diagnosed Asthma								
Missing	1.78	1.49	0.51	0.98	0.91	0.35	0.42	0.63
No	1.34	1.54	0.59	0.95	0.89	0.16	0.20	0.61
Yes	1.25	2.28	0.70	1.58	1.25	0.30	0.89	0.76
Reported Wheeze								
Missing	1.15	1.06	0.36	0.70	0.67	0.09	0.11	0.49
No	1.28	1.51	0.63	0.88	0.82	0.14	0.17	0.61
Yes	1.53	2.05	0.61	1.44	1.24	0.28	0.59	0.68
Any ETS**								
Missing	1.86	1.23	0.68	0.54	0.40	0.07	0.19	0.64
No	1.22	1.56	0.55	1.01	0.92	0.18	0.28	0.59
Yes	1.62	2.17	0.83	1.35	1.21	0.23	0.46	0.82
7 Day Outdoor Act.								
Missing	1.60	1.93	0.80	1.14	1.08	0.21	0.28	0.79
<=11.25 hr	1.38	1.65	0.63	1.03	0.92	0.18	0.28	0.63
> 11.25 hr	1.30	1.66	0.58	1.08	0.97	0.18	0.34	0.64
School Report Method								
Whole grade	1.45	1.55	0.52	1.03	0.91	0.20	0.31	0.64
Participants	1.33	1.69	0.61	1.08	0.98	0.19	0.32	0.60

*** Adj.for interview failure using the success ratio as described in the methods section. **ETS = environmental tobacco smoke**

(Reprinted with permission, Gilliland et al., 2001. The effects of ambient air pollution on school absenteeism due to respiratory illnesses. *Epidemiology*, 12(1):43-54.)

Table 4.2-25. Annual average air pollution and community rankings for O_3, NO_2, and PM_{10}, based on 1995 levels, Children's Health Study, 1995.

Community	Annual mean 10AM–6PM O_3 (ppb)	Rank	Annual mean daily NO_2 (ppb)	Rank	Annual mean daily PM_{10} (ug/m^3)	Rank	Stratum* (O_3, PM_{10}/NO_2)
Santa Maria	31	1	12	3	20	2	LL
Long Beach	33	2	37	10	39	9	LH
Atascadero	43	3	13	4	22	4	LL
Lompoc	45	4	5	1	15	1	LL
Lancaster	48	5	19	6	24	5	LL
Mira Loma	54	6	23	8	65	12	LH
Upland	55	7	45	12	45	11	HH
Lake Elsinore	57	8	20	7	35	7	HH
Alpine	58	9	13	5	24	6	HL
San Dimas	60	10	44	11	37	8	HH
Riverside	62	11	25	9	44	10	HH
Lake Arrowhead	65	12	7	2	21	3	HL

*** Strata were defined by ranking communities on 1995 average pollution levels and dichotomizing communities into high (H) and low (L) groups. LL = low O_3 low PM_{10} or NO_2, LH = low O_3 high PM_{10} or NO_2, HL = high O_3 low PM_{10} or NO_2, HH = high O_3 high PM_{10} or NO_2.**

(Reprinted with permission, Gilliland et al., 2001. The effects of ambient air pollution on school absenteeism due to respiratory illnesses. *Epidemiology*, 12(1):43-54.)

Table 4.2-26. Short-term effects of 10am-6pm average O_3, 24-hour average PM_{10}, and 24-hour average NO_2 on school absences incidence rates (percent change and 95% CI), Air Pollution and Absence Study, January to June 1996.[1,2]

Type of Absence	Pollutant		
	O_3	PM_{10}	NO_2
All Absences	16.3 (-2.6, 38.9)	22.8 (11.6, 35.2)	3.4 (-30.6, 54.0)
Non-Illness	21.2 (-12.9, 69.0)	97.7 (72.6,126.5)	34.6 (-43.0, 218.2)
Illness	62.9 (18.4, 124.1)	5.7 (-12.1, 27.0)	-4.6 (-42.4, 57.8)
Non-Respiratory	37.3 (5.7, 78.3)	10.2 (-14.6, 42.3)	-36.8 (-69.5, 30.8)
Respiratory	82.9 (3.9, 222.0)	-4.3 (-32.2, 35.0)	19.6 (-36.2,124.4)
URI^{+}	45.1 (21.3, 73.7)	5.5 (-6.8, 19.4)	-7.4 (-30.3, 23.0)
LRI/wc^{++}	173.9 (91.3, 292.3)	-7.7 (-49.2, 67.7)	-37.5 (-73.9, 49.4)
LRI/W/A^{+++}	68.4 (43.4, 97.8)	-7.1 (-34.1, 30.8)	5.1 (-60.3,178.0)

$^{+}$ **Upper respiratory illness (URI) using a 15-day lag period**
$^{++}$ **Lower respiratory illness (LRI) with wet cough using a 15-day lag period**
$^{+++}$ **LRI with wet cough/wheeze or asthma attack using a 15-day lag period**

1) Results are reported for 20 ppb O_3, 10 $\mu g/m^3$ PM_{10}, and 10 ppb NO_2
2) Models are fitted using community-specific polynomial distributed lag models (degree 3) with 30-day lag period except URI, LRI/wc^{+}, and LRI/W/A had 15-day lag periods.

(Reprinted with permission, Gilliland et al., 2001. The effects of ambient air pollution on school absenteeism due to respiratory illnesses. *Epidemiology*, 12(1):43-54.)

Table 4.2-27. Short-term effects of O_3 (percent change and 95% CI) on school absence incidence rates, stratified by long-term average 10am-6pm O_3 and 24-hour average PM_{10} (or NO_2),+ Air Pollution and Absence Study, January to June 1996. [1,2]

	Community Ranking			
Type of Absence	**Based on Ozone**		**Based on PM_{10}/NO_2**	
	Low Ozone	**High Ozone**	**Low PM_{10} (NO_2)**	**High PM_{10} (NO_2)**
All Absences	**14.0 (-16.7, 56.1)**	**16.2 (-5.8, 43.3)**	**68.2 (25.9,124.8)**	**6.4 (-7.1, 21.9)**
Non-Illness	**17.0 (-35.3, 111.9)**	**20.1 (-19.2, 78.6)**	**49.8 (-30.7, 223.7)**	**13.6 (-20.3,61.8)**
Illness	**87.6 (8.3, 225.2)**	**48.8 (3.0, 115.0)**	**223.5 (90.4, 449.7)**	**38.1 (8.5, 75.8)**
Non-Respiratory	**29.9 (-19.8, 110.6)**	**31.5 (-5.6, 83.0)**	**29.6 (-32.2, 147.9)**	**31.3 (-2.8, 77.4)**
Respiratory	**136.8 (-11.5, 533.1)**	**57.7 (-18.1, 203.9)**	**454.9(90.0,1520.0)**	**42.9 (-11.2,130.1)**

+ High and low strata included the same communities for either PM_{10} or NO_2

1) Results are reported for 20 ppb O_3, 10 $\mu g/m^3$ PM_{10}, and 10 ppb NO_2

2) Models are fitted using community specific polynomial distributed lag models (degree 3) with 30-day lag period

(Reprinted with permission, Gilliland et al., 2001. The effects of ambient air pollution on school absenteeism due to respiratory illnesses. *Epidemiology*, 12(1):43-54.)

4.2.5. Ambient Air Pollution and Birth Weight in California-Born CHS Participants

4.2.5.1. Summary of Results

Accumulating evidence indicates that maternal exposures to air pollutants including ozone, CO, PM_{10}, and SO_2 are associated with adverse pregnancy outcomes. Exposures to CO and PM_{10} during the first month and third trimester have received the most study and been associated with reduced birth weight. Ozone exposure and birth weight has not been as extensively studied.

To further investigate the effects of ambient air pollutants on birth weight in a region with widely varying air pollution, we examined birth weight and air pollution data for participants in the Children's Health Study who were born in California between 1975 and 1987. Information on birth weight, gestational age, maternal age, maternal residence location at birth and other pregnancy information was obtained from birth certificates. Sociodemographic variables and maternal smoking status during pregnancy was collected by questionnaire. Exposure estimates for O_3, NO_2 and PM_{10} were assigned using the zipcode of the maternal residence at birth and monthly average air pollution estimates for each zipcode by interpolating levels from monitoring locations in the Environmental Protection Agency's (EPA) Aerometric Information Retrieval System (AIRS). We fitted linear regression models to estimate the effects of air pollutants on birth weight in full term pregnancies adjusting for gestational age, sex, race/ethnicity, maternal age, parity, interval between pregnancies, pregnancy compilations, maternal smoking, and socioeconomic status.

We found that O_3 levels in the second and third trimester were independently associated with lower birth weight. Across the range of exposure, (interquartile range (IQR) 40ppb), birth weight was reduced 46.8 g (95% CI 24.3, 69.3) for third trimester exposures and 34.5g (95% CI 12.1, 56.9) for second trimester exposures. PM_{10} levels (IQR 20ug/m3) in the third trimester were also associated with reduced birth weight (24.5 g, 95% CI 3.3, 45.8); however, in two-pollutant models that included PM_{10} and O_3, only ozone retained a statistically significant association with lower birth weight.

4.2.5.2. Synthesis

In summary, O_3 exposure during the second and third trimesters of gestation is associated with lower birth weight (pending finalized analysis).

4.3. Other Important Findings (Abstracts)

As described previously, the main purpose of this ARB-supported study was to determine the health effects produced by ambient air pollutants in children. In order to evaluate the effects of these ambient pollutants, we needed to evaluate other factors that could also affect children's respiratory health. This section summarizes these scientific efforts, not central to the primary hypotheses, but, nonetheless, important contributions to our knowledge of factors involved in children's lung disease. These studies could be considered the bonuses of the study supported by ARB.

We divide this section into several parts: 1) Maternal smoking and environmental tobacco smoke, 2) Dietary factors, 3) Genetic factors, 4) Obesity, 5) Impact of respiratory illness on lung function, 6) Indoor exposures and asthma, 7) Family history, 8) New statistical methods, 9) Protocol validation, and finally, 10) Spirometric calibration.

In some cases, the abstracts have the back-up of published papers or completed manuscripts, and in other cases, the abstracts stand alone. The interested reader can determine the back-up by examining our list of publications provided at the end of this report and by viewing published papers and manuscripts included in the Appendix.

4.3.1. Maternal Smoking and Environmental Tobacco Smoke

Maternal smoking during pregnancy, environmental tobacco smoke exposure and childhood lung function (Gilliland et al. 2000)
Exposure to environmental tobacco smoke (ETS) during childhood and *in utero* exposure to maternal smoking are associated with adverse effects on lung growth and development. A study was undertaken of the associations between maternal smoking during pregnancy, exposure to ETS, and pulmonary function in 3357 school children residing in 12 Southern California communities. Current and past exposure to household ETS and exposure to maternal smoking *in utero* were assessed by a self-administered questionnaire completed by parents of 4th, 7th, and 10th grade students in 1993. Standard linear regression techniques were used to estimate the effects of *in utero* and ETS exposure on lung function, adjusting for age, sex, race, Hispanic ethnicity, height, weight, asthma, personal smoking, and selected household characteristics. *In utero* exposure to maternal smoking was associated with reduced peak expiratory flow rate (PEFR) (-3.0%, 95% CI -4.4 to -1.4), mean mid expiratory flow (MMEF) (-4.6%, 95% CI -7.0 to -2.3), and forced expiratory flow (FEF_{75}) (-6.2%, 95% CI -9.1 to -3.1), but not forced expiratory volume in one second (FEV_1). Adjusting for household ETS exposure did not substantially change these estimates. The reductions in flows associated with *in utero* exposure did not significantly vary with sex, race, grade, income, parental education, or personal smoking. Exposure to two or more current household smokers was associated with reduced MMEF (-4.1%, 95% CI -7.6 to -0. 4) and FEF_{75} (-4.4%, 95% CI -9.0 to 0.4). Current or past maternal smoking was associated with reductions in PEFR and MMEF; however, after adjustment for *in utero* exposure, deficits in MMEF and FEF_{75} associated with all measurements of ETS were substantially reduced and were not statistically significant. *In utero* exposure to maternal smoking is independently associated with decreased lung function in children of school age, especially for small airway flows.

Effects of *in utero* and environmental tobacco smoke exposure on lung function in boys and girls with and without asthma (Li et al. 2000b)
To investigate whether the effects of *in utero* exposure to maternal smoking and environmental tobacco smoke (ETS) exposure on lung function vary by sex or asthma status, we examined medical history and tobacco smoke exposure data for 5,263 participants in the Children's Health Study. At study enrollment, parents or guardians of each subject completed a questionnaire, and lung function was measured spirometrically with maximum forced expiratory flow-volume maneuvers. To assess the *in utero* effects of maternal smoking and ETS exposure on lung

function, we used regression splines that accounted for the nonlinear relationship between pulmonary function, height, and age. *In utero* exposure to maternal smoking was independently associated with deficits in lung function that were larger for children with asthma. Boys and girls with a history of *in utero* exposure to maternal smoking showed deficits in maximum midexpiratory flow (MMEF) and a decrease in the FEV_1/FVC ratio. As compared with children without asthma, boys with asthma had significantly larger deficits from *in utero* exposure in FVC, MMEF, and FEV_1/FVC, and girls with asthma had larger decreases in FEV_1/FVC. The effect of ETS exposure varied by children's gender and asthma status. Deficits in flows associated with current ETS exposure were present in children with and without asthma but were significant only among children without asthma. Past ETS exposure was associated with reduced FEV_1, MMEF, and FEV_1/FVC among boys with asthma. In contrast, past ETS exposure was associated with decreased flow rates in girls without asthma. In summary, both *in utero* exposure to maternal smoking and ETS exposure were associated with persistent deficits in lung function. The effects of *in utero* exposure were greatest among children with asthma.

Effects of maternal smoking during pregnancy and environmental tobacco smoke on asthma and wheezing in children (Gilliland et al. 2001c)
The effects of maternal smoking during pregnancy and childhood environmental tobacco smoke (ETS) exposure on asthma and wheezing were investigated in 5,762 school-aged children residing in 12 Southern California communities. Responses to a self- administered questionnaire completed by parents of 4th, 7th, and 10th grade students were used to ascertain children with wheezing or physician-diagnosed asthma. Lifetime household exposures to tobacco smoke were assessed using responses about past and current smoking histories of household members and any history of maternal smoking during pregnancy. Logistic regression models were fitted to cross-sectional data to estimate the effects of *in utero* exposure to maternal smoking and previous and current ETS exposure on the prevalence of wheezing and physician-diagnosed asthma. *In utero* exposure to maternal smoking without subsequent postnatal ETS exposure was associated with increased prevalence of physician-diagnosed asthma (OR, 1.8; 95% CI, 1.1 to 2.9), asthma with current symptoms (OR, 2.3; 95% CI, 1.3 to 4.0), asthma requiring medication use in the previous 12 mo (OR, 2.1; 95% CI, 1.2 to 3.6), lifetime history of wheezing (OR, 1.8; 95% CI, 1.2 to 2.6), current wheezing with colds (OR, 2.1; 95% CI, 1.3 to 3.4) and without colds (OR, 2.5; 95% CI, 1.4 to 4.4), persistent wheezing (OR, 3.1; 95% CI, 1.6 to 6.1), wheezing with exercise (OR, 2.4; 95% CI; 1.3 to 4.3), attacks of wheezing causing shortness of breath (OR, 2.4; 95% CI, 1.3 to 4.4) or awakening at night in the previous 12 mo (OR, 3.2; 95% CI, 1.7 to 5.8), and wheezing requiring medication (OR, 2.1; 95% CI, 1.2 to 3.7) or emergency room visits during the previous year (OR, 3.4; 95% CI, 1.4 to 7.8). In contrast, current and previous ETS exposure was not associated with asthma prevalence, but was consistently associated with subcategories of wheezing. Current ETS exposure was associated with lifetime wheezing (OR, 1.3; 95% CI, 1.1 to 1.5), current wheezing with colds (OR, 1.6; 95% CI, 1.3 to 2.0) and without colds (OR, 1.5; 95% CI, 1.1 to 1.9), wheezing with exercise (OR, 1.7; 95% CI, 1.3 to 2.2), attacks of wheezing causing shortness of breath (OR, 1.6; 95% CI, 1.2 to 2.1) or awakening at night (OR, 1.5; 95% CI, 1.1 to 2.0), and wheezing requiring medication (OR, 1.4; 95% CI, 1.1 to 1.8) or emergency room visits within the previous year (OR, 1.9; 95% CI, 1.2 to 3.0). The effects of current ETS exposure on subcategories of wheezing were most pronounced among children exposed to two or more smokers and remained significant after adjusting for maternal smoking during pregnancy. We conclude that maternal smoking during pregnancy increases the

occurrence of physician-diagnosed asthma and wheezing during childhood. In contrast, current ETS exposure is associated with wheezing, but not physician-diagnosed asthma. Taken together, our findings support the hypothesis that ETS operates as a cofactor with other insults such as intercurrent infections as a trigger of wheezing attacks, rather than as a factor that induces asthma, whereas *in utero* exposure acts to increase physician-diagnosed asthma

Effects of early onset asthma and *in utero* exposure to maternal smoking on childhood lung function (Gilliland et al. 2003c)
Both *in utero* exposures to maternal smoking and asthma are associated with chronic deficits in lung function. We hypothesized that *in utero* exposure affects lung function in children without asthma and synergistically affects children with early onset asthma. To investigate effects of *in utero* exposure and age at asthma diagnosis on lung function, we examined longitudinal medical history, tobacco smoke exposure, and lung function data from 5,933 participants in the Children's Health Study. We found that children exposed *in utero*, but without asthma, showed decreased FEV_1/FVC, FEF_{25-75}, and FEF_{25-75}/FVC ratio. Among children without *in utero* exposure, early asthma diagnosis was associated with larger decreases in FEV_1, FEF_{25-75}, and FEV_1/FVC ratio compared with later diagnosed asthma. Children with *in utero* exposure alone and early onset asthma showed deficits in FEV1 (-13.6%; 95% confidence interval [CI], -18.9 to -8.2) and FEF_{25-75} (-29.7%; 95% CI, -37.8 to -20.5) among boys; and FEF_{25-75} (-26.6%; 95% CI, -36.4 to -15.1) and FEV_1/FVC (-9.3%; 95% CI, -12.9 to -5.4) among girls. The absolute differences in FEF_{25-75} associated with *in utero* exposure increased with age in children with early onset asthma. We found little evidence for effects from environmental tobacco smoke exposure alone. In summary, deficits in lung function were largest among children with *in utero* exposure and early onset asthma.

Environmental tobacco smoke and absenteeism related to respiratory illness in schoolchildren (Gilliland et al. 2003b)
Household environmental tobacco smoke (ETS) exposure accounts for substantial morbidity among young children, but the ETS-associated morbidity burden among school-age children is less well defined. Illness-related school absenteeism is a measure of a broad spectrum of adverse effects of ETS exposure in school-age children. The authors investigated the relations between ETS exposure, asthma status, and illness-related school absenteeism in a cohort of 1,932 fourth-grade schoolchildren from 12 southern California communities during January-June 1996. Incidence rates and adjusted relative risks of illness-related absences were determined by using an active surveillance system. The effects of ETS exposure on absenteeism were assessed by using stratified incidence rates and Poisson regression to adjust for sociodemographic factors. ETS exposure was associated with an increased risk of respiratory-illness-related school absences (relative risk (RR) = 1.27, 95% confidence interval (CI): 1.04, 1.56). Children living in a household with two or more smokers were at increased risk of such absences (RR = 1.75, 95% CI: 1.33, 2.30). Children's asthma status affected their response to ETS. Compared with unexposed children without asthma, children with asthma were at increased risk of respiratory-illness-related school absences when exposed to one (RR = 2.35, 95% CI: 1.49, 3.71) or two or more (RR = 4.45, 95% CI: 2.80, 7.07) household smokers. Children without asthma also had an increased risk if exposed to two or more smokers (RR = 1.44, 95% CI: 1.04, 2.00). Therefore, ETS exposure is associated with increased respiratory-related school absenteeism among children, especially those with asthma.

Maternal and transgenerational smoking patterns are associated with early childhood asthma (Li et al. submitted)
To investigate the effects of maternal smoking before, during, and after pregnancy on childhood asthma, we conducted a case-control study nested within the Children's Health Study. Cases were children with asthma diagnosed prior to age 6 years. Controls were counter-matched on *in utero* exposure to maternal smoking within grade, sex, and community of residence. Detailed early life exposure information was obtained by telephone interview. *In utero* exposure to maternal smoking was associated with increased risk for asthma in the first 5 years of life (OR=1.4; 95% CI 1.0-2.1), and for early-onset asthma in the first 3 years of life (OR=1.7; 95% CI 1.2-2.4) and the associations did not differ in children with early transient compared with early persistent asthma. Children whose mothers smoked throughout the pregnancy had an elevated risk of asthma in the first 5 years of life (OR=1.4; 95% CI 1.0-2.2). Asthma risk did not increase with smoking intensity (dose effect) during pregnancy, or postnatal secondhand smoke exposure. Smoking cessation during pregnancy was uncommon (15%). Children of mother who quit smoking before and during pregnancy appeared to have a lower risk of asthma compared to those whose mother smoked through out pregnancy, but the difference did not reach statistical significance due to the small number of mothers who quit. Grandmaternal smoking during the mother's fetal period was associated with increased asthma risk in her grandchildren (OR=2.1; 95% CI 1.4-3.2). Maternal and grandmaternal smoking during pregnancy increases the risk of childhood asthma.

4.3.2. Dietary Factors (Vitamins & Minerals)

Effects of low vitamins A, E, and C intake on children's lung function *ATS conference abstract* (Gilliland et al. 2001d)
An emerging body of evidence supports an adverse effect of low antioxidant vitamin intake on adult lung function. The respiratory health effects of low antioxidant vitamin during childhood have yet to be fully defined. To investigate the effects of dietary intake of three antioxidant vitamins, vitamins A, E, and C, on children's lung function, we examined cross-sectional dietary data and pulmonary function tests from 2566 participants in the Children's Health Study. At follow-up visits during the 1998-1999 school year, each student completed a health update questionnaire, a validated food frequency questionnaire (FFQ), and spirometric lung function testing. To assess the effects of Vitamins A, E, and C on lung function, we used regression splines that account for the non-linear relationship between pulmonary function, height and age in children. Low vitamin C intake was associated with deficits in measures of airway flow that were larger in girls [FEV_1 -3.3%, (95% CI-6.0, -0.5), and FEF_{25-75} -5.5% (95% CI -10.5, -0.3)] than boys [FEV_1 -2.3%, (95% CI -4.8, 0.3), and FEF_{25-75} -2.4% (95% CI -7.4, 2.8)]. Children with low vitamin E intake had lower FEF_{25-75} [boys -8.9% (95% CI -14.2, -3.3); girls -2.5% (95% CI -8.3, 3.7)]. Low vitamin A intake was also associated with FEF_{25-75} only among boys with asthma [-15.6% (95% CI -27.6, -1.6)]. In summary, children with low antioxidant vitamin intake had lower lung function.

Dietary magnesium, potassium, sodium, and children's lung function (Gilliland et al. 2002a)
To investigate the effects of dietary magnesium, potassium, and sodium on children's lung function, the authors examined cross-sectional dietary data and pulmonary function tests from

2,566 children aged 11-19 years who attended schools in 12 southern California communities during 1998-1999. During school visits, each child completed a health update questionnaire, a validated food frequency questionnaire, and spirometric lung function testing. Low magnesium and potassium intakes were associated with lower lung function. Girls with low magnesium intake had lower forced expiratory flow at 75% of the forced vital capacity (FEF_{75}) (-8.3%, 95% confidence interval: -14.8, -1.4) than did girls with higher intake; reductions were larger in girls with asthma (forced expiratory flow between 25% and 75% of the forced vital capacity (FEF_{25-75}) (-16.2%, 95% confidence interval: -22.7, -9.1) and FEF_{75} (-24.9%, 95% confidence interval: -32.8, -16.1)) than in girls without asthma (FEF_{25-75} (-2.0%, 95% confidence interval: -7.4, 3.8) and FEF_{75} (-4.1%, 95% confidence interval: -11.3, 3.7)). Boys with low magnesium intake showed deficits in forced vital capacity (-2.8%, 95% confidence interval: -5.4, -0.2) compared with boys with higher intake. The effects of low magnesium intake did not vary substantially in boys with and without asthma. Among girls, low potassium intake was also associated with deficits in forced expiratory volume in 1 second (-2.7%, 95% confidence interval: -5.2, -0.1) and forced vital capacity (-2.4%, 95% confidence interval: -4.7, -0.1). In summary, low magnesium and potassium intakes were associated with lower lung volumes and flows.

Children's lung function and antioxidant vitamin, fruit, juice, and vegetable intake (Gilliland et al. 2003d)

The authors investigated the relation between children's pulmonary function and intake of fruits, vegetables, juices, and vitamins A, C, and E by examining cross-sectional data from 2,566 children in the Children's Health Study collected during 1997-1998. Low total vitamin C intake (</=10th percentile) was associated with deficits in forced vital capacity for both boys and girls and with deficits in flows that were larger in girls (forced expiratory volume in 1 second (FEV_1), -3.3%, 95% confidence interval (CI): -6.0, -0.5; forced expiratory flow between 25% and 75% of forced vital capacity (FEF_{25-75}),( )-5.5%, 95% CI: -10.5, -0.3) compared with boys (FEV_1, -2.3%, 95% CI: -4.8, 0.3; FEF_{25-75},( )-2.4%, 95% CI: -7.4, 2.8). Low dietary vitamin E intake was associated with lower FEF_{25-75} (boys: FEF_{25-75} , -8.9%, 95% CI: -14.2, -3.3; girls: FEF_{25-75}, -2.5%, 95% CI: -8.3, 3.7). Deficits in FEF_{25-75} were associated with low dietary vitamin A intake in girls (FEF_{25-75},( )-7.9%, 95% CI: -12.7, -2.8) and with low total vitamin A intake in boys with asthma (FEF_{25-75},( )-15.6%, 95% CI: -27.6, -1.6). Low intakes of orange and other fruit juices, which were the largest source of vitamin C, were associated with deficits in forced vital capacity and FEV_1 in boys. In summary, lung function levels were lower in children with inadequate dietary antioxidant vitamin intake.

Maternal fish consumption during pregnancy and risk of childhood asthma (Salam et al. in preparation)

Childhood asthma may be associated with omega-3 polyunsaturated fatty acids (n-3 PUFA) in oily-fish in maternal as well as children’s diet. We hypothesized that maternal fish consumption during pregnancy reduces children’s asthma risk. Cases and controls were selected from the Children’s Health Study, a population-based study of school-aged children in 12 Southern California communities. Cases had physician-diagnosed asthma by age 5 and controls were asthma-free at study entry, frequency-matched on age, gender and community of residence, and counter-matched on *in utero* exposure to maternal smoking. Telephone interviews were conducted with mothers to collect dietary and other exposure information. Cases were categorized as early transient, early persistent and late persistent asthma. Conditional logistic

regression models that accounted for the sampling were fitted to estimate odds ratios (ORs) and 95% confidence intervals (CIs). Maternal oily-fish intake during pregnancy was associated with reduced asthma risk among children whose mothers had a history of asthma. Among children of asthmatic mothers, maternal intake of oily-fish during pregnancy reduced asthma risk by 71% with a decrease in risk with increasing frequency of intake (P_{trend} = 0.006). Children of non-asthmatic mothers did not benefit from maternal oily-fish intake. In contrast, fish-finger consumption during pregnancy increased asthma risk in the child (OR=2.04; CI: 1.18-3.51). We observed no significant effect of maternal intake of canned or non-oily-fish during pregnancy on childhood asthma risk. Our results suggest maternal oily-fish intake may protect children from asthma; however, eating fish-fingers may increase asthma risk in the children.

4.3.3. Genetic Factors

Effects of glutathione S-transferase M1, maternal smoking during pregnancy, and environmental tobacco smoke on asthma and wheezing in children (Gilliland et al. 2002c)
The rise in childhood asthma prevalence suggests a role for environmental factors in the etiology of this evolving epidemic; however, genetics also influence the occurrence of asthma. Glutathione S-transferase (GST) M1 may play a role in asthma and wheezing occurrence among those exposed to tobacco smoke, as it functions in pathways involved in asthma pathogenesis such as xenobiotic metabolism and antioxidant defenses. Effects of GSTM1 genotype, maternal smoking during pregnancy, and childhood environmental tobacco smoke (ETS) exposure on asthma and wheezing were investigated in 2,950 children enrolled in 4th, 7th, and 10th grade classrooms in 12 Southern California communities. The effects of *in utero* exposure to maternal smoking on asthma and wheezing occurrence were largely restricted to children with GSTM1 null genotype. Among GSTM1 null children, *in utero* exposure was associated with increased prevalence of early onset asthma (odds ratio [OR] 1.6, 95% confidence interval [CI] 1.0-2.5), asthma with current symptoms (OR 1.7, 95% CI 1.1-2.8), persistent asthma (OR 1.6, 95% CI 1.1-2.4), lifetime history of wheezing (OR 1.8, 95% CI 1.3-2.5), wheezing with exercise (OR 2.1, 95% CI 1.3-3.3), wheezing requiring medication (OR 2.2, 95% CI 1.4-3.4), and emergency room visits in the past year (OR 3.7, 95% CI 1.9-7.3). Among children with GSTM1 (+) genotype, *in utero* exposure was not associated with asthma or wheezing. Our findings indicate that there are important long-term effects of *in utero* exposure in a genetically susceptible group of children.

Effects of glutathione-S-transferase M1, T1, and P1 on childhood lung function growth (Gilliland et al. 2002b)
The effects of glutathione-S-transferase (GST) M1, GSTT1, and GSTP1 genotypes on lung function growth were investigated in 1,940 children enrolled in the Children's Health Study as fourth graders (aged 8-11 years) in two cohorts during 1993 and 1996 and were followed annually over a 4-year period. Genotypes for GSTM1 and GSTT1 and GSTP1 codon 105 variants (ile105 and val105) were determined using DNA from buccal cell specimens. We used two-level regression models to estimate the effects of GSTM1, GSTT1, and GSTP1 genotypes on the adjusted annual average lung function growth. GSTM1 null was associated with deficits in annual growth rates for FVC (-0.21%; 95% confidence interval [CI], -0.40, -0.03) and FEV_1 (-0.27%; 95% CI, -0.50, -0.04). Children who were homozygous for the GSTP1 val105 allele had slower lung function growth (FVC -0.35%; 95% CI, -0.62, -0.07; and FEV_1 -0.34%; 95% CI, -

0.68, 0.00) than children with one or more ile105 alleles. Children with asthma who were homozygous for the GSTP1 val105 allele had substantially larger deficits in FVC, FEV_1, and maximal mid-expiratory flow than children without asthma. The deficits in FVC and FEV_1 growth associated with both GSTM1 null and the GSTP1 val105 allele were largest and were statistically significant in non-Hispanic white children. We conclude that GSTM1 and GSTP1 genotypes are associated with lung function growth in school children.

Effects of glutathione S-transferase P1, M1, and T1 on acute respiratory illness in school children (Gilliland et al. 2002e)
The relationships between glutathione S-transferase (GST) M1, GSTT1, and GSTP1 genotypes and acute respiratory illness were investigated in a cohort of fourth grade school children aged 9-11 years who resided in 12 southern California communities. We used respiratory illness-related absences as a measure of respiratory illness occurrence. We ascertained respiratory illness-related school absences using an active surveillance system from January 1996 through June 1996. Genotypes for GSTM1 (null versus present), GSTT1 (null versus present), and GSTP1 (Ile105Val) were determined using genomic DNA from buccal cell specimens. The effects of GST genotypes on respiratory illness were assessed using stratified absence incidence rates and Poisson regression models. GSTP1 genotype was associated with risk for respiratory illness severe enough to result in a school absence. Children who were homozygous for the Val105 variant allele had lower incidence rates of upper and lower respiratory illnesses than did children who were homozygous for the Val105 allele. Children inheriting at least one Val105 allele were protected from respiratory illnesses (relative risk, 0.80; 95% confidence interval, 0.65-0.99). GSTM1 and T1 genotypes were not associated with respiratory illness. We conclude that GSTP1 genotype influences the risk or severity of respiratory infections in school-aged children.

Effects of GSTM1, *in utero* maternal smoking and ETS exposure on asthma and wheezing in children *ATS conference abstract* (Gilliland et al. 2002d)
The effects of GSTM1 genotype, maternal smoking during pregnancy and childhood environmental tobacco smoke (ETS) exposure on asthma and wheezing were investigated in 2950 school-aged children residing in 12 Southern California communities. Tobacco smoke exposure and asthma status were ascertained by questionnaire completed by parents. Logistic regression models were fitted to estimate the effects of GSTM1 genotype, *in utero* and ETS exposure on the prevalence of wheezing and physician-diagnosed asthma. We found that the effects of *in utero* exposure on asthma and wheezing were largely restricted to children who were GSTM1 null. Among GSTM1 null children, *in utero* exposure was associated with increased prevalence of asthma with current symptoms (OR 1.8, 95% CI 1.1-3.0), and persistent asthma (1.6, 95% CI1.0-2.6), lifetime history of wheezing (OR 2.0, 95% CI 1.4-2.9), current wheezing with colds (OR 1.8, 95% CI 1.2-2.8) and without colds (OR 2.4, 95% CI 1.4-3.9), persistent wheezing (OR 2.3, 5% CI 1.2-4.3), wheezing with exercise (OR 2.3, 95% CI 1.4-3.9), attacks of wheezing causing shortness of breath (OR 2.5, 95% CI 1.4-4.3) or awakening at night (OR 1.8, 95% CI 1.0-3.3), and wheezing requiring medication (OR 2.2, 95% CI 1.3-3.5) or emergency room visits (OR 3.3, 95% CI 1.6-7.0). Among children with GSTM1, *in utero* exposure was not associated with prevalence of asthma or wheezing, nor was GSTM1 genotype among unexposed children. The effects of ETS were restricted to children who were GSTM1 null. Our findings support a role for GSTM1 in respiratory morbidity associated with tobacco smoke exposure.

GSTP1 and GSTM1 contribute to susceptibility for asthma and wheezing following *in utero* exposure to tobacco smoke *ATS conference abstract* (Gilliland et al. 2003e)
In utero and childhood second hand tobacco smoke exposure have been associated with increased risk of asthma, wheezing and asthma exacerbation. Glutathione-S-Transferases (GST), including GSTP1, GSTM1 and GSTT1, appear to contribute to susceptibility for asthma and wheezing following exposure to tobacco smoke and other toxicants. Cross-sectional data on lifetime tobacco smoke exposure, asthma and wheeze were collected from 3205 Children's Health Study participants. Logistic regression models were fitted to estimate the effects of GSTs and *in utero* exposure to maternal smoking on the prevalence of wheezing and physician-diagnosed asthma. Inheriting at least one GSTP1 val variant allele was associated with increased lifetime risk of asthma (OR 1.2, 95% CI 1.0-1.5) and persistent asthma (OR 1.2, 95% CI 1.0-1.5) that was larger for early onset asthma (OR 1.4, 95% CI 1.1-1.8). The effects of *in utero* exposure to maternal smoking on wheezing outcomes, but not asthma, were modified by GSTP1 val allele and were largest in children with both the GSTP1 val variant and GSTM1 null genotype compared with the joint wild type genotypes. GSTT1 did not modify the effects of tobacco smoke. We did not observe an effect of childhood second hand smoke exposure on asthma and wheezing. Asthma and wheezing are associated with *in utero* exposure to maternal smoking in children with GSTP1 val and GSTM1 null genotypes.

TNF$^{\alpha}$ – 308 genotype and ozone effects on asthma and wheezing: Results from the Children's Health Study (CHS) *ATS conference abstract* (Gilliland et al. 2003f)
We investigated effects of tumor necrosis factor-α 308 (TNFα) on asthma and wheezing and determined whether ambient air pollutants modify effects of TNFα. Risk factors, asthma and wheeze outcomes, TNFα genotype, and community air pollution levels were collected at entry from 2896 CHS participants. Logistic regression was used to estimate the effects of TNFα on the wheezing and physician-diagnosed asthma. We assessed modification of the TNFα associations with current asthma and wheezing with O_3, PM_{10}, $PM_{2.5}$, NO_2, and acids (nitric + hydrochloric) in a subset of 1123 fourth graders. The variant TNFα was associated with increased risk of asthma and wheezing. The effects of TNFα on wheezing outcomes were significantly larger in low than high O_3 communities (Table 1). There was no modification by the other air pollutants. TNFα-308 variant genotypes were associated with increased asthma and wheezing risk, and the effect on current wheezing decreased with increasing O_3 level.

Table 1: The effects of TNFα on wheezing outcomes in the lowest and highest ozone communities in the subgroup of CHS participants.

Wheezing outcomes in the past 12 months	Lowest O_3		Highest O_3	
	OR	(95% CI)	OR	(95% CI)
Wheeze with cold	2.2	(1.0,4.8)	0.8	(0.4,1.5)
Wheeze without cold *	3.6	(1.4,8.9)	0.6	(0.2,1.4)
Shortness of breath *	3.9	(1.5,10.5)	0.8	(0.3,2.0)
Awakened at night *	3.8	(1.2,11.8)	0.4	(0.1,1.3)
Wheeze with exercise *	3.6	(1.3,9.7)	0.6	(0.2,1.5)
Medication for wheeze *	3.7	(1.5,9.3)	0.7	(0.3,1.7)

* Significant interaction of TNFα and O_3 ($p < 0.05$).

4.3.4. Obesity

Obesity and the risk of newly diagnosed asthma in school-age children (Gilliland et al. 2003a)

To determine the relation between obesity and new-onset asthma among school-age children, the authors examined longitudinal data from 3,792 participants in the Children's Health Study (Southern California) who were asthma-free at enrollment. New cases of physician-diagnosed asthma, height, weight, lung function, and risk factors for asthma were assessed annually at five school visits between 1993 and 1998. Incidence rates were calculated, and proportional hazards regression models were fitted to estimate the adjusted relative risks of new-onset asthma associated with percentile of body mass index (weight (kg)/height (m)(2)) and indicators of overweight (>85th body mass index percentile) and obesity (>95th body mass index percentile). The risk of new-onset asthma was higher among children who were overweight (relative risk (RR) = 1.52, 95% confidence interval (CI): 1.14, 2.03) or obese (RR = 1.60, 95% CI: 1.08, 2.36). Boys had an increased risk associated with being overweight (RR = 2.06, 95% 1.33, 3.18) in comparison with girls (RR = 1.25, 95% CI: 0.83, 1.88). The effect of being overweight was greater in nonallergic children (RR = 1.77, 95% CI: 1.26, 2.49) than in allergic children (RR = 1.16, 95% CI: 0.63, 2.15). The authors conclude that being overweight is associated with an increased risk of new-onset asthma in boys and in nonallergic children.

4.3.5. Impact of Respiratory Illness on Lung Function

Sex-specific effects of asthma on pulmonary function in children (Berhane et al. 2000)
To evaluate the effects on lung function of asthma, time since diagnosis of asthma, and age at diagnosis of asthma, we examined school children in a cohort of 2,277 fourth- and seventh-graders at least twice during a 4-yr follow-up period. Sex-specific models for each lung function were fitted through mixed-effects models that used regression splines and captured age-dependent trends in the effect of asthma on lung function. In males, a history of asthma was associated with large and statistically significant deficits in maximum midexpiratory flow (MMEF) (-4.89%) and forced expiratory flow at 75% of expired FVC (FEF_{75}) (-6.62%), whereas in females these deficits were smaller (-1.93% and -2.45%, respectively) and were not statistically significant. However, larger deficits were seen in both males and females with longer time since diagnosis. In males with more than 6 yr since diagnosis, there were significant deficits in FEV_1 (-3.91%), MMEF (-7.39%), FEF_{75} (-8.12%), and peak expiratory flow rate (PEFR) (-4.65%) as compared with children with less than 3 yr since diagnosis. There were fewer females with more than 6 yr since diagnosis, but deficits were similar to those of males for FEV_1 (-2.52%), MMEF (-9.26%), and FEF_{75} (-14.28%). Large deficits in flow rates in both large and small airways were observed in males and females for whom asthma was reported to have been diagnosed before age 3 yr. There was little evidence that lung growth in children with asthma "catches up" at older ages. Therefore, because a constant percent deficit in lung function implies an increasingly large absolute deficit in older children with larger lungs, these results are consistent with prior evidence that lung function deficits in children with asthma persist into adulthood. We also suggest that in children, commonly observed differences between sexes in the impact of asthma on lung function may reflect differences in the duration and age of onset of asthma in males and females.

Impact of respiratory illness on expiratory flow rates in normal, asthmatic, and allergic children (Rappaport et al. 2002)
We examined the effects of current respiratory illness (RI) on pulmonary function (PF) in 1,103 subjects who underwent spirometry at schools twice within a 4-month period. Before spirometry, subjects were asked if they had a "cold or other chest illness" during the previous month, and if

so, whether they had fully recovered. Those who had not recovered were considered to have an RI.We found that children without RI at their first PF test who reported RI on retest had significantly lower forced expiratory volume in 1 sec (FEV_1) (-0.8%), peak expiratory flow rate (PEFR) (-2.2%), forced expiratory flow between 25-75% of vital capacity (FEF_{25-75}) (-3.5%), and forced expiratory flow at 75% of vital capacity (FEF_{75}) (-5.1%) than those without RI on both test and retest. Restriction of subjects to those without a history of doctor-diagnosed asthma did not appreciably change these findings. Children with hay fever had significantly larger RI-associated decreases for FEV_1, FEF_{25-75}, and FEF_{75}, but not PEFR, than those without hay fever. Among asthmatic subjects, those with active asthma had larger RI-associated decreases in FEF_{25-75} and FEF_{75}, but not PEFR, than those without asthma. There was limited evidence that small airway losses were greater in children less than 12.5 years old. We conclude that RI in children who are well enough to attend school may reduce expiratory flow rates. These effects are greater for children with active asthma or hay fever than in those without, and may be inversely related to age.

4.3.6. Indoor Exposures and Asthma

Indoor risk factors for asthma in a prospective study of adolescents (McConnell et al. 2002a)
The risk of asthma associated with pets and other indoor exposures has been examined in both cross-sectional and prospective studies of younger children. However, there has been little investigation of the effect of the indoor environment on incident asthma in adolescents. Risk factors for the development of asthma were examined in a cohort of 3535 Southern California school children with no history of asthma at 1993 entry into the study, who were followed for up to 5 years. Newly diagnosed cases of asthma were identified by yearly interview report. A total of 265 children reported a new diagnosis of asthma during the follow-up period; 163 of these had reported no history of wheeze at baseline. The risk associated with indoor exposures assessed by questionnaire at entry into the study was examined using Cox proportional hazards models. In children with no history of wheezing, an increased risk of developing asthma was associated with a humidifier (relative risk [RR] = 1.7; 95% confidence interval [CI] = 1.2-2.4), any pet (RR = 1.6; 95% CI = 1.0-2.5), or specifically a dog (RR = 1.4; 95% CI = 1.0-2.0) in the home. An estimated 32% of new asthma cases could be attributed to pets. We conclude that furry pets are a common and potentially remediable risk factor for new onset asthma in adolescents. Our results suggest that a humidifier in the home may contribute to the onset of asthma in this age group.

4.3.7. Family History

Family history and the risk of early onset persistent, early onset transient and late onset asthma (London et al. 2001)
Family history of asthma and allergies strongly influences asthma risk in children, but the association may differ for early-onset persistent, early-onset transient, and late-onset asthma. We analyzed the relation between family history and these types of asthma using cross-sectional data from a school-based study of 5,046 Southern California children. Parental and/or sibling history of asthma and allergy were generally more strongly associated with early-onset persistent asthma compared with early-onset transient or late-onset asthma. For children with two asthmatic parents relative to those with none, the prevalence ratio for early-onset persistent asthma was 12.1 [95% confidence interval (CI) = 7.91-18.7] compared with 7.51 (95% CI = 2.62-21.5) for

early-onset transient asthma and 5.38 (95% CI = 3.40-8.50) for late-onset asthma. Maternal smoking in pregnancy was predominantly related to the risk of early-onset persistent asthma in the presence of parental history of allergy and asthma, and the joint effects were more than additive (interaction contrast ratio = 3.10, 95% CI = 1.45-4.75). Our results confirm earlier data that parental history of asthma and allergy is most strongly associated with early-onset persistent asthma and suggest that among genetically predisposed children, an early-life environmental exposure, maternal smoking during pregnancy, favors the development of early-onset asthma that persists into later early childhood.

4.3.8. New Statistical Methods

Design and analysis of multilevel analytic studies with applications to a study of air pollution (Navidi et al. 1994)
We discuss a hybrid epidemiologic design that aims to combine two approaches to studying exposure-disease associations. The analytic approach is based on comparisons between individuals, e.g., case-control and cohort studies, and the ecologic approach is based on comparisons between groups. The analytic approach generally provides a stronger basis for inference, in part because of freedom from between-group confounding and better quality data, but the ecologic approach is less susceptible to attenuation bias from measurement error and may provide greater variability in exposure. The design we propose entails selection of a number of groups and enrollment of individuals within each group. Exposures, outcomes, confounders, and modifiers would be assessed on each individual; but additional exposure data might be available on the groups. The analysis would then combine the individual-level and the group-level comparisons, with appropriate adjustments for exposure measurement errors, and would test for compatibility between the two levels of analysis, e.g., to determine whether the associations at the individual level can account for the differences in disease rates between groups. Trade-offs between numbers of groups, numbers of individuals, and the extent of the individual and group measurement protocols are discussed in terms of design efficiency. These issues are illustrated in the context of an on-going study of the health effects of air pollution in southern California, in which 12 communities with different levels and types of pollution have been selected and 3500 school children are being enrolled in a ten-year cohort study. Exposure is being assessed through a combination of ambient monitoring, microenvironmental sampling, personal monitoring, and questionnaire data on time-activity and household characteristics. These data will be used to develop a model for personal exposure for use in the individual-level analyses, as well as for the group mean exposures for the group-level analyses.

Measurement error in air pollution exposure assessment (Navidi and Lurmann 1995)
The exposure of an individual to an air pollutant can be assessed indirectly, with a "microenvironmental" approach, or directly with a personal sampler. Both methods of assessment are subject to measurement error, which can cause considerable bias in estimates of health effects. If the exposure estimates are unbiased and the measurement error is nondifferential, the bias in a linear model can be corrected when the variance of the measurement error is known. Unless the measurement error is quite large, estimates of health effects based on individual exposures appear to be more accurate than those based on ambient levels.

Bidirectional case-crossover designs for exposures with time trends (Navidi 1998)

In the case-crossover design (Maclure, 1991, American Journal of Epidemiology 133, 144-153), only cases are sampled, and risk estimates are based on within-subject comparisons of exposures at failure times with exposures at times prior to failure, using matched case-control methods. While the design provides considerable advantages, unidirectional retrospective control sampling (selecting control times only prior to failure) can cause risk estimates to be confounded by time trends in exposure. However, when subsequent exposures are not influenced by failures, as in studies of environmental exposures such as air pollutants, it is possible to determine at times postfailure what a subject's level of exposure would have been had the subject not failed. We describe a bidirectional case-crossover design in which exposures at failure are compared with exposures both before and after failure. Simulation analyses show that relative risk estimates are resistant to confounding by time trend. We also extend the method to studies involving multiple failure times.

Some Contributions of Statistics to Environmental Epidemiology (Thomas 2000)
The field of epidemiology has come to rely particularly heavily on statistical methods because of its observational nature and the widespread acceptance of a complex "web of causation" as its conceptual basis. As much of modern chronic disease epidemiology is oriented to the study of disease incidence data, regression models for binary, Poisson, and survival time data have figured prominently in epidemiologic applications. Thus, logistic regression for case-control studies, and Poisson and Cox regression models for cohort data have become standard tools in the epidemiologist's armamentum. In other areas, methods of longitudinal data analysis have provided a similar unified framework for modeling changes in continuous outcomes over time, such as lung function measurements. Without these important statistical contributions, it is arguable that epidemiology would not have been able to progress so far in understanding diseases of complex etiology. These tools are broadly applicable to study of many different risk factors, including genetic and environmental factors and their interactions, although specialized techniques have been developed in these two subdisciplines. Environmental epidemiology can in turn be broadly defined as comprising everything that is not genetic (e.g., diet, lifestyle factors like smoking, the social milieu, medical exposures, infectious agents, etc.) or narrowly defined as focusing on the exogenous environment (e.g., air and water pollution, indoor radon, fallout from nuclear weapons development and testing, electromagnetic fields, pesticides, etc.). In this vignette, we touch only briefly on statistical methods in standard risk factor epidemiology and focus instead on some of the unique problems that arise in the latter case, owing to the geographically defined nature of many environmental exposures: (1) evaluations of disease clusters and the spatial distribution of disease in relation to possible environmental causes using Geographic Information Systems (GIS), (2) the design of studies involving geographical and temporal comparisons, (3) the control of measurement error, and (4) problems of multi-collinearity. There has been an explosion in the availability of geographically defined data on health and exposures and statistical methods to exploit such resources are still in their infancy.

Exposure measurement error in time-series studies of air pollution: concepts and consequences (Zeger et al. 2000)
Misclassification of exposure is a well-recognized inherent limitation of epidemiologic studies of disease and the environment. For many agents of interest, exposures take place over time and in multiple locations; accurately estimating the relevant exposures for an individual participant in epidemiologic studies is often daunting, particularly within the limits set by feasibility,

participant burden, and cost. Researchers have taken steps to deal with the consequences of measurement error by limiting the degree of error through a study's design, estimating the degree of error using a nested validation study, and by adjusting for measurement error in statistical analyses. In this paper, we address measurement error in observational studies of air pollution and health. Because measurement error may have substantial implications for interpreting epidemiologic studies on air pollution, particularly the time-series analyses, we developed a systematic conceptual formulation of the problem of measurement error in epidemiologic studies of air pollution and then considered the consequences within this formulation. When possible, we used available relevant data to make simple estimates of measurement error effects. This paper provides an overview of measurement errors in linear regression, distinguishing two extremes of a continuum-Berkson from classical type errors, and the univariate from the multivariate predictor case. We then propose one conceptual framework for the evaluation of measurement errors in the log-linear regression used for time-series studies of particulate air pollution and mortality and identify three main components of error. We present new simple analyses of data on exposures of particulate matter < 10 microm in aerodynamic diameter from the Particle Total Exposure Assessment Methodology Study. Finally, we summarize open questions regarding measurement error and suggest the kind of additional data necessary to address them.

Discussion on "Combining evidence on air pollution and daily mortality from the 20 largest US cities: a hierarchical modeling strategy." (Berhane and Thomas 2000)
This involved a discussion of the paper "Combining evidence on air pollution and daily mortality from the 20 largest US cities: a hierarchical modeling strategy (By Francesca Dominici, Jonathan M. Samet, and Scott L. Zeger)". The original paper develops a log-linear regression model for daily time series data from the largest 20 US cities and introduces hierarchical regression models for combining estimates of the pollution-mortality relationship across cities. In the first stage of the hierarchical model, the relative mortality rate associated with PM10 for each of the 20 cities is estimated by using semiparametric log-linear models. The second stage of the model describes between-city variation in the true relative rates as a function of selected city-specific covariates. Two variations of a spatial model are also fitted with the goal of exploring the spatial correlation of the pollutant-specific coefficients among cities. Finally, to explore the results of considering the two pollutants jointly, univariate and bivariate models are fitted and compared. All posterior distributions from the second stage are estimated by using Markov chain Monte Carlo techniques.

Our contribution to the discussion (Given on Pg. 292 of the paper) focused on two aspects of the paper, namely the use of generalized additive models to dealing with autocorrelation in the data and ways of dealing with the lag structure of the pollution effect. On the first issue, we pointed out that there seems to be no clear guideline by the paper on how to choose the amount of smoothing when applying the methods in a different context (e.g., the CHS absence monitoring data). We suggested possible approaches that could be pursued. On the second issue, we made a query on whether the proposed methods could accommodate a more elaborate examination of the lag structure (e.g., the polynomial distributed lag approach).

A two-stage model for multiple time series data of counts (Berhane and Thomas 2002)

We propose a two-stage model for time series data of counts from multiple locations. This method fits first-stage model (s) using the technique of iteratively weighted filtered least squares (IWFLS) to obtain location-specific intercepts and slopes, with possible lagged effects via polynomial distributed lag modeling. These slopes and/or intercepts are then taken to a second-stage mixed-effects meta-regression model in order to stabilize results from various locations. The representation of the models from the stages into a combined mixed-effects model, issues of inference and choices of the parameters in modeling the lag structure are discussed. We illustrate this proposed model via detailed analysis on the effect of air pollution on school absenteeism based on data from the Southern California Children's Health Study.

Functional based multi-level models for longitudinal data (6 pages of CD ROM) (Berhane 2002)
Functional based and flexible multi-level models are proposed for analysis of longitudinal data. These models allow for cluster specific smooth estimates of growth curves, in either a generalized estimating equations or mixed-effects modeling format. Attention is then focused on models that examine between-cluster effects of an ecologic covariate of interest on important functionals. A unified estimation procedure will be presented along with its computational and theoretical details. The models will be illustrated via lung function data from the Southern California Children's Health Study.

An approach to gene-environment and gene-gene interactions in complex metabolic pathways (Cortessis and Thomas 2004)
We propose an approach to modeling the joint effects of multiple genes involved in metabolic activation and detoxification of environmental exposures. A physiologically based pharmacokinetic model is used, in which the various person-specific metabolic rates are related to measurements of the genotypes and/or phenotypes at the various stages of the relevant pathways. Markov chain Monte Carlo methods are used to fit the model. We illustrate the approach by application to case-control data on colorectal polyps in relation to consumption of well done red meat and tobacco smoking via pathways involving heterocyclic amines (regulated by the genes CYP1A2, NAT1, and NAT2) and polycyclic aromatic hydrocarbons (regulated by the genes CYP1A1, EPHX1 (also called mEH), and GSTM3). In this paper, we focus on the biochemical basis for our conceptual models, deferring detailed mathematical description of the models and simulation results to a separate paper.

Statistical issues in studies of the long term effects of air pollution: the Southern California Children's Health Study (Berhane et al. in press)
In this article we discuss statistical techniques for modeling data from cohort studies that examine long-term effects of air pollution on children's health by comparing data from multiple communities with a diverse pollution profile. Under a general multi-level modeling paradigm, we discuss models for different outcome types along with their connections to the generalized mixed effects models methodology. The model specifications include linear and flexible models for continuous lung function data, logistic and/or time-to-event models for symptoms data that account for misspecifications via hidden Markov models, and Poisson models for school absence counts. The main aim of the modeling scheme is to be able to estimate effects at various levels (e.g., within subjects across time, within communities across subjects, and between communities). We also discuss in detail various recurring issues such as ecologic bias, exposure measurement error, multicollinearity in multipollutant models, interrelationships between major

endpoints and choice of appropriate exposure metrics. The key conceptual issues and recent methodologic advances are reviewed, with illustrative results from the Southern California Children's Health Study, a ten year study of the effects of air pollution on children's respiratory health.

A three level model for binary time-series data: the effects of air pollution on school absences in the Southern California Children's Health Study (Rondeau et al. submitted)
A three-level model is proposed to simultaneously examine the effects of daily exposure to air pollution and individual risk factors on health outcomes without aggregating over subjects or time. We used a logistic transition model with random effects to take into account heterogeneity and overdispersion of the observations. A distributed lag structure for pollution has been included, assuming that the event on day *t* for a subject depends on the levels of air pollution for several preceding days. We illustrate this proposed model via detailed analysis of the effect of air pollution on school absenteeism based on data from the Southern California Children's Health Study.

A Bayesian approach to functional-based multi-level modeling of longitudinal data: With applications to environmental epidemiology (Berhane in preparation-b)
Flexible multi-level models are proposed to allow for cluster specific smooth estimation of growth curves, in a mixed-effects modeling format that includes subject-specific random effects on the growth parameters. Attention is then focused on models that examine between-cluster comparisons of the effects of an ecologic covariate of interest (e.g., air pollution) on nonlinear functionals of growth curves (e.g. maximum rate of growth). A Gibbs sampling approach is used to get posterior mean estimates of non-linear functionals along with their uncertainty estimates. A second-stage ecologic random effects model is used to examine the association between a covariate of interest (e.g., air pollution) and the non-linear functionals. A unified estimation procedure will be presented along with its computational and theoretical details. The models are motivated by, and illustrated with, lung function and air pollution data from the Southern California Children's Health Study.

Exposure modeling for studies of the chronic effects of air pollution (Thomas et al. in preparation-b)
We describe several approaches that have been taken to the problem of exposure assessment for a long-term cohort study of the health effects of air pollution in Southern California school children. These combine continuous measurement of ambient levels at central site monitoring stations established in each of the 12 communities in the Children's Health Study, microenvironmental modeling, traffic density estimation, measurement of selected pollutants at a sample of homes and schools, and lifetime residence histories. Conceptual models for the effects of exposure measurement error are discussed, together with methods for correcting for such errors in assessing exposure-response relationships. We believe these approaches would be generally useful in many studies of chronic effects in environmental epidemiology.

Model selection, model averaging, and the use of prior covariates in the investigation of the health effects of multiple air pollutants (Thomas et al. in preparation-a)
We describe an approach to investigating the effects of multiple correlated air pollutants on one or more health outcomes accounting for uncertainty in the form of the true model. Standard regression methods yield estimates of effect size and their standard errors that are conditional on

a particular model specification. Bayesian model averaging techniques fit a large class of plausible models and yield estimates of effect size for each potential covariate that are averaged across models and standard errors that include both model-to-model variation and within-model sampling errors. We extend this general approach by the addition of ``prior covariates" that characterize classes of similar covariates and yield estimates of effect for these classes. Applications are described to data on lung function changes from the Southern California Children's Health Study in relation to several gaseous and particulate pollutants as well as estimates of pollutant sources. Extensions of the approach to multivariate outcomes, temporal comparisons, and subgroup comparisons are discussed. We discuss below how the different correlation structure at the individual and temporal levels can be used to help disentangle multipollutant effects.

4.3.9. Protocol Validation

Quality of spirometry test performance in children and adolescents: experience in a large field study (Enright et al. 2000)
The study objective was to determine the ability of children and adolescents to meet the American Thoracic Society (ATS) goals for spirometry quality that were based on results from adults. More than 4,000 public school students, ages 9 to 18 years were participants. Spirometry was performed annually for 3 years, with the recording of maneuver quality measures of forced expiratory time, end-of-test volume, back-extrapolated volume, and time to peak expiratory flow (PEFT), and the recording of differences between best and second-best FVC, FEV_1, and peak expiratory flow (PEF) values. Regression analyses showed significant influences of participant age, gender, ethnicity, size, clinical status, and previous testing experience, as well as differences among individual test technicians. In general, these influences were small and explained little of the variance in performance. On average, children with a history of asthma or wheeze performed better quality spirometry than did others. Only PEFT improved significantly from year to year. Overall, only 15% of girls' tests and 32% of boys' tests met the PEFT criterion derived from adults in the Lung Health Study. Most of the children met adult-based ATS goals for spirometry test performance. Age group-specific criteria are needed to ensure adequately fast PEFT and reproducible PEF values.

4.3.10. Spirometric Calibration

Standardization of multiple spirometers at widely separated times and places (Linn et al. 1996)
We designed a system for a multiyear longitudinal study of lung function in 12 widely separated communities, intending to minimize variation in instrument-related data. We used multiple rolling-seal spirometer/personal computer systems. Calibrations were checked before, during, and after each day's field testing, using multiple calibration syringes with electronic readouts. The syringes were rotated to obtain data for each syringe-spirometer combination. Before and after each annual field-testing season, a laboratory reference spirometer system was calibrated against a water-displacement device and an electronic frequency counter, and then compared against each field spirometer and syringe. Field equipment consistently met American Thoracic Society (ATS) specifications. Variance among spirometers exceeded variance among syringes. A spirometer occasionally changed its volume readout by approximately 1 to 2 %. More rarely, a

syringe changed its delivered volume by approximately 1%. Syringes' electronic readouts tracked changes in delivered volume. Syringe readouts were the most stable component of the system, and were more reproducible than the laboratory water-displacement calibration. We conclude that variation in spirometers may limit the reliability of epidemiologic findings, even when these spirometers meet ATS specifications. Frequent calibration checks traceable to an independent standard, and adjustment of individual test results, can reduce measurement error.

Temperature standardization of multiple spirometers (Linn et al. 1998)
In respiratory health surveys involving multiple spirometers, spirometer differences may introduce important biases. We investigated temperature measurement variability as a cause of spirometer differences. Digital thermometers recorded internal (cylinder) and external (outer casing) temperatures of six similar rolling-seal spirometers during field use and in laboratory tests at controlled room temperatures. Internal and external thermometers substantially agreed in recording spirometer temperature changes, which lagged room temperature changes. Offsets of individual thermometers from overall mean readings were roughly the same in field testing of 3908 students in > 60 schools over 5 months and in subsequent laboratory tests. Thermometers differed by as much as 1.3 degrees C, causing differences as large as 0.8% in vital capacity measurements. We conclude that (1) interior and exterior temperatures of typical rolling-seal spirometers do not differ greatly, although both may differ from surrounding air temperature; and (2) variations between individual digital thermometers may be large enough to bias spirometric data appreciably in large-scale surveys. Variations should be controlled by selection of similar-reading thermometers and/or correction to a uniform standard.

Effect of spirometer temperature on FEV1 in a longitudinal epidemiological study (Gilliland et al. 1999a)
To assess the magnitude of error in pulmonary function measurements introduced by variation in spirometer temperature under field conditions. In a large scale epidemiological study of school children, the influence was investigated of spirometer temperature on forced expiratory volume in 1 second (FEV_1) measured with dry rolling seal volumetric spirometers and conventional body temperature, pressure, and saturation (BTPS) corrections. Linear regression analyses were performed on data from 995 test-retest pairs on 851 different children, with 1-110 days between test and retest, and spirometer temperature differences between -13 degrees C and +9 degrees C. After adjusting for effects of growth (test-retest intervals) and circadian variation (changes in times of testing), differences in standard BTPS corrected FEV_1 showed significant ($p < 0.05$) dependence on differences in spirometer temperature between tests (-0.24%/degree C). When spirometer temperatures vary widely, standard BTPS correction does not fully adjust for gas contraction. To improve accuracy of volume measurements in epidemiological studies, additional correction for variation in spirometer temperature should be considered.

5. Discussion and Synthesis

5.1. Is Lung Function Permanently Affected by Air Pollution?

When this study began in 1992, it was well known both from the scientific data and personal experience of citizens living in polluted areas that air pollution caused acute responses. Eye irritation and chest symptoms were common on days with inversions and sunshine. Whether these acute episodes caused by the pollutants would result in chronic, irreversible, and permanent effects was the key question facing our investigative team.

This question heavily influenced our study design. After consulting with outside advisors, we decided that prospective evaluation of lung function growth would be the best indication of chronic and/or permanent effects. To avoid acute influences of pollution, we chose to evaluate subjects during the spring months and to perform the lung function tests in the morning to avoid peak air pollution exposures (particularly ozone, given that it was the only pollutant with demonstrated acute effects at the exposure levels encountered in our communities at study initiation).

At this stage, the confluence of data strongly suggests that lung function growth is slowed by pollution and that changing pollution levels influence the growth rate (see Section 4.2.1). In addition, achieved level of lung function is clearly lower in children living in the more polluted communities. A very strong dose-response relationship adds credence to this finding (see Figure 4.2-1). There is no evidence that these effects are reversible but there is the possibility that what we are seeing is a delay in the achievement of a full, normal lung function level. While such a possibility is considered unlikely, resolving this question requires re-examining the subjects at an age when maximum lung function has been achieved.

New funding from the National Institute of Environmental Health Sciences (NIEHS) will support the follow-up of the subjects at maximum attained lung function. Based on evidence obtained for the past ten years, we speculate that the new research will confirm that pollution permanently affects lung function and that this lowering will have future deleterious effects as these children achieve adulthood (see Section 5.7.1).

5.2. Are Respiratory Illnesses More Frequent and Severe in High Pollution Communities?

We found that air pollution at current ambient levels was associated with more frequent and severe respiratory illness. Ozone was associated with school absences and with asthma incidence among more active children, and there was some evidence that traffic density was associated with prevalent asthma. NO_2 and OC were associated with bronchitic symptoms among asthmatic children. There was little evidence that respiratory infections assessed at the time of pulmonary function testing was associated with the air pollutants examined.

There was a strong association of ozone with school absence for both upper and lower respiratory illness that was observed within 2-3 days of increases in ozone and peaked around 5 days after exposure. There was little effect observed of PM_{10} or NO_2 that also were measured on

a daily basis. There was a dose-response relationship, and the results were not changed by a variety of potential confounders examined. Because of the prospective design of the study, there can be little doubt as to the temporal sequence of exposure and school absence. The results demonstrated a consistent effect both within communities and in a between-community analysis over time, and this acute effect of ozone is also consistent with a large body of previous study on other acute outcomes associated with ozone in epidemiologic and toxicologic studies. Thus, our results strongly suggest that ozone causes school absences due to respiratory illness.

Bronchitic symptoms, including reported bronchitis, chronic cough and phlegm production likely represent chronic exacerbation in asthmatic children. In contrast to school absences, an association of this outcome with air pollution was observed only among children with asthma and only for the package of PM-associated pollutants. The novel modeling techniques implemented in this longitudinal analysis allowed a clear assessment of the temporal relationship of the observed associations and better control of confounding than is possible in cross sectional studies. The results were consistent in both the between-community analysis and in the within-community analysis over time, and they are also consistent with previous epidemiologic and toxicologic literature. Therefore, our results provide evidence that PM-associated pollutants cause these effects. The longitudinal analysis of symptoms also made it possible to examine the effect of components of PM and to examine the independent effects of some of the PM-correlated pollutants. There was evidence that NO_2 and OC may be the pollutants causing the observed effects (or may be surrogates for the responsible pollutants). The other unique contribution of this analysis was to identify considerably larger effects of these pollutants than was observed in cross sectional analysis. This finding has potentially important policy implications and deserves further study.

New cases of asthma were associated with ozone exposure among exercising children. Because the design was prospective, and because the effect was observed even among children with no history of wheeze at study entry, it is unlikely that the observed results occurred because previously undiagnosed asthma was merely exacerbated by ozone and exercise to the point that care was sought. There was a dose-response relationship, and the results are consistent with the limited number of comparable prospective epidemiologic studies, with emerging toxicologic data, and with the known increase in inhaled dose associated with exercise. There are important policy implications of this study, because asthma is the most common chronic disease of childhood. There was also evidence that proximity to nearby traffic was associated with prevalent asthma. Further investigation to replicate these results is required and should clarify why asthma prevalence in cross sectional studies is not consistently associated with air pollution, either in the CHS or in other studies.

5.3. Are Acute Illnesses Associated With Chronic Effects on Lung Function?

Because the primary hypotheses for the study were focused on chronic adverse respiratory effects of air pollution exposures, limited data were collected on acute respiratory illnesses. The data collected included the occurrence of early chest illnesses (collected at study entry), respiratory illnesses in the month before each pulmonary function testing session and during the active surveillance period of the air pollution and absence monitoring study. These data allowed

a limited examination of the mechanistic hypothesis that acute illnesses are associated with chronic effects on lung function.

We found that acute respiratory illnesses (RI) during childhood have acute and sub-chronic effects on lung function, especially measures of airway flow. In longitudinal analyses of lung growth, lung function level was decreased by the presence of a recent respiratory illness, but growth rates were unaffected. On a subset of children, who were tested and retested a few months apart, we found that children without RI at their first test who reported RI on retest had significantly lower FEV_1, PEFR, MMEF and FEF_{75} than those without RI on both test and retest. Children with hay fever had significantly larger RI-associated decreases than those without hay fever. Among asthmatic subjects, those with active asthma had larger RI-associated decreases than in those without asthma. There was limited evidence that small airway losses were greater in children less than 12.5 years old. We conclude that RI may reduce expiratory flow rates in children who are well enough to attend school. These effects are greater for children with active asthma or hay fever than in those without, and may be inversely related to age. To further examine the effects of RI on lung function, we examined the association between the number of reported RI at testing and lung function growth and found no associations. We also examined the association of respiratory related school absences and lung function growth in the second cohort of fourth graders and found no association with the number of absences and lung function growth. These findings suggest that RIs during childhood have acute effects on airway flows that may last weeks to months, but that the RIs are not associated with deficits in lung growth.

We also evaluated the presence of early chest illnesses before age 2 years on asthma and lung function later in childhood. We found that early chest illnesses other than asthma before age 2 were associated with increase risk for early life asthma and for reduced lung function. These data, in conjunction with findings for birth cohort studies conducted by other groups, suggest that acute respiratory illnesses early in childhood may have chronic effects on lung function. Prospective studies starting at birth or earlier are needed to address this question definitively.

5.4. Which Children Are Most Susceptible to Air Pollution Effects?

5.4.1. Introduction

A number of host factors have the potential to affect susceptibility to adverse respiratory health outcomes in general and to modify respiratory responses to ambient and indoor air pollutants. These factors can be categorized into toxicokinetic and toxicodynamic modifiers using the biological impact pathway conceptual framework (Figure 5.4-1). In this section, the discussion will focus on 1) susceptibility factors for adverse respiratory health outcomes and 2) factors that are toxicodynamic modifiers of ambient and indoor air pollution associations with adverse respiratory health outcomes.

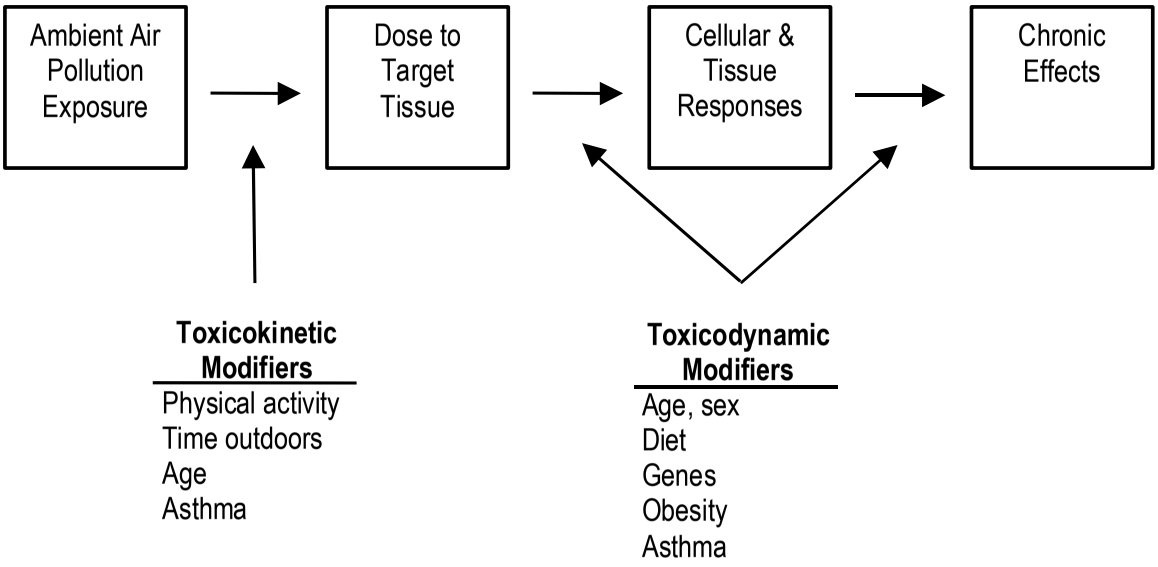


Figure 5.4-1. Biological impact pathway conceptual framework.

5.4.2. Age

Age is an important determinant of susceptibility to adverse respiratory health outcomes and is a modifier of responses to respiratory toxins. Children as a group are more susceptible than adults to the effects of many environmental exposures. The variation in age-related susceptibility extends to the childhood period as children's pulmonary system growth and development varies by age. This developmental variation leads to increased risk for asthma in children less than 5 years, increased risk from exposures during the fetal and early life periods, and increased susceptibility to the effects of air pollution during the period of rapid lung growth. With regard to lung function growth, we have observed a pattern of larger deficits in lung function growth in the fourth grade cohorts compared to the seventh and tenth grade cohorts. These differences likely reflect the fact that younger cohorts have more rapid lung growth during the period of observation. We have also observed a significant effect of maternal smoking during pregnancy on asthma and wheezing occurrence as well as on lung function development. Maternal ozone exposure during the prenatal period was associated with lower birth weight in term infants. In summary, children appear to be a susceptible group for adverse respiratory health outcomes with the fetus and young children having the greatest susceptibility.

5.4.3. Sex

Past studies of respiratory health in children have provided evidence for sex differences in the occurrence of asthma and in the life course of lung function development. Consistent with this evidence, we have observed an increased prevalence of asthma in young boys compared to girls, a trend that diminishes with increasing age. Wheezing follows a similar pattern. We have also observed that rapid lung function growth begins and ends at younger ages in girls.

We found that the associations of a number of host factors, including diet and obesity with respiratory health outcomes, vary in boys and girls. For example, the effects of diet on lung function differed in girls and boys. We found that deficits in flows with low vitamin C intake were larger in girls for FEV_1 and FEF_{25-75}. Low dietary vitamin E intake was associated with lower FEF_{25-75} in boys but not girls. The effect of vitamin A also varied by sex and asthma status. Deficits in FEF_{25-75} were associated with low dietary vitamin A intake in girls and with low total vitamin A intake in boys with asthma FEF_{25-75}. Low intakes of orange and other fruit juices, which were the largest source of vitamin C, were associated with deficits in forced vital capacity and FEV_1 in boys.

For asthma, the effects of obesity were stronger in boys than girls. In our study of overweight and obesity and new-onset asthma, the risk of new-onset asthma was higher among children who were overweight (relative risk (RR) = 1.52, 95% confidence interval (CI): 1.14, 2.03) or obese (RR = 1.60, 95% CI: 1.08, 2.36). Boys had an increased risk associated with being overweight (RR = 2.06, 95% 1.33, 3.18) in comparison with girls (RR = 1.25, 95% CI: 0.83, 1.88).

The effects of environmental exposures also varied by sex in some analyses. Ambient air pollution (NO_2) was associated with the prevalence of wheezing symptoms at study entry in boys but not girls. In analyses of lung function, we observed somewhat larger effects of air pollution on lung function growth in girls than boys, but this difference was not statistically significant. We also observed that the effect of second-hand smoke exposure on new cases of physician-diagnosed asthma was larger in boys than girls.

Taken together, results from the CHS suggest that boys in general are more susceptible to adverse respiratory symptoms and asthma outcomes than girls. Girls appear to have greater susceptibility for adverse effects on lung function development. There is limited evidence supporting sex differences in responses to ambient air pollutants; however, children of both sexes appear to have adverse respiratory effects of exposure to current levels of air pollution.

Any differences in effects between boys and girls may also arise from sex differences in exposure as well as differences in susceptibility. For example, older boys spend more time outdoors, which would likely increase their exposure to a number of ambient pollutants relative to girls. We lack sex-specific exposure data to directly examine this question.

5.4.4. Asthma

Children with asthma are a susceptible group for adverse respiratory health outcomes in general and for the effects on ambient and indoor air pollutants on asthma, wheezing and lung function development.

Ambient air pollution exposure had substantial effects on bronchitic symptoms and medication usage among children with asthma, but not among children without asthma. Yearly variability of $PM_{2.5}$ was associated with yearly prevalence of bronchitic symptoms in children with asthma (OR 1.09/ $\mu g/m^3$; 95% C.I1.01-1.17), OC (O.R. 1.41/ $\mu g/m^3$; 95% C.I. 1.12-1.78), NO_2 (O.R. 1.07/ppb; 95% C.I. 1.02-1.13) and ozone (O.R. 1.06/ppb; 95% C.I. 1.00-1.12). OC and NO_2 are

potential causes of the chronic symptoms of bronchitis in asthmatic, but not among non-asthmatic children.

With regard to lung function growth, early life asthma diagnosis was associated with chronic deficits in lung function. These deficits were largest for children with early onset asthma who were exposed *in utero* to maternal smoking. Genetic variation also appeared to interact with asthma in reducing lung growth as we observed that children with asthma who were homozygous for the GSTP1 val105 allele had substantially larger deficits in FVC, FEV_1, and MMEF growth rates than children without asthma. We observed no large modifying effects of asthma status on the associations of air pollutants with lung function growth during childhood. The effects of air pollution exposure in children with asthma over the life course are the subject of active ongoing investigations.

Illness-related school absenteeism is a measure of a broad spectrum of adverse effects of air pollutant exposure in school-age children. We found that ozone was associated with increased school absenteeism from respiratory illnesses. Although we hypothesized that children with asthma were at the greatest risk, we could not effectively examine whether children with asthma were at greater risk due to the relatively small number of asthmatic children spread across our 12 study communities.

We did observe that asthma increased susceptibility to ETS. Children exposed to ETS were at greater risk for school absenteeism; however, children with asthma were at greatest risk for school absenteeism. ETS exposure was associated with an increased risk of respiratory-illness-related school absences (relative risk (RR) = 1.27, 95% confidence interval (CI): 1.04, 1.56). Children living in a household with two or more smokers were at increased risk of such absences (RR = 1.75, 95% CI: 1.33, 2.30). Children's asthma status affected their response to ETS. Compared with unexposed children without asthma, children with asthma were at increased risk of respiratory-illness-related school absences when exposed to one (RR = 2.35, 95% CI: 1.49, 3.71) or two or more (RR = 4.45, 95% CI: 2.80, 7.07) household smokers. Children without asthma also had an increased risk if exposed to two or more smokers (RR = 1.44, 95% CI: 1.04, 2.00). Therefore, ETS exposure is associated with increased respiratory-related school absenteeism among children, especially those with asthma.

In summary, children with asthma are at increased risk for adverse respiratory health events including bronchitic symptoms, reduced lung function, and school absences. Furthermore, children with asthma appear to be highly susceptible to the adverse effects of air pollution including ozone, particulates (especially OC), NO_2, and ETS.

5.4.5. Genetic Factors

In studies conducted under separate funding, we observed that genetic variation influences the occurrence of adverse respiratory health outcomes. We found some evidence that genes involved in oxidative stress and inflammatory pathways modified the effects of ambient and indoor air pollutants on lung function and asthma occurrence.

The rise in childhood asthma prevalence suggests a role for environmental factors in the etiology of this evolving epidemic; however, genetics also influences the occurrence of asthma.

Glutathione S-transferase (GST) M1 is a candidate gene that may play a role in asthma and wheezing occurrence among those exposed to tobacco smoke, as it functions in pathways involved in asthma pathogenesis such as xenobiotic metabolism and antioxidant defenses. We found that the effects of *in utero* exposure to maternal smoking on asthma and wheezing occurrence were largely restricted to children with GSTM1 null genotype. Among children with GSTM1 (+) genotype, *in utero* exposure was not associated with asthma or wheezing. Our findings indicate that there are important long-term effects of *in utero* exposure in a genetically susceptible group of children.

We also examined the effect of glutathione-S-transferase (GST) M1, GSTT1, and GSTP1 genotypes on lung function growth. GSTM1 null was associated with deficits in annual growth rates and FEV_1. Children who were homozygous for the GSTP1 val105 allele had slower lung function growth than children with one or more ile105 alleles. Children with asthma who were homozygous for the GSTP1 val105 allele had substantially larger deficits in FVC, FEV_1, and MMEF than children without asthma. The deficits in FVC and FEV_1 growth associated with both GSTM1 null and the GSTP1 val105 allele were largest and were statistically significant in non-Hispanic white children. We conclude that GSTM1 and GSTP1 genotypes are associated with lung function growth in school children.

We observed associations of glutathione S-transferase P1, M1, and T1 with acute respiratory illness in school children. The effects of GST genotypes on respiratory illness were assessed. GSTP1 genotype was associated with risk for respiratory illness severe enough to result in a school absence. Children who were homozygous for the Val105 variant allele had lower incidence rates of upper and lower respiratory illnesses than did children who were homozygous for the Val105 allele. Children inheriting at least one Val105 allele were protected from respiratory illnesses (relative risk, 0.80; 95% confidence interval, 0.65-0.99). GSTM1 and T1 genotypes were not associated with respiratory illness. We conclude that GSTP1 genotype influences the risk or severity of respiratory infections in school-aged children.

We also found that genetic susceptibility may be important for the effects of ozone on asthma and wheezing occurrence. We found that tumor necrosis factor-α 308 (TNFα) variant was associated with increased occurrence of asthma and wheezing and that ozone modified the associations of TNFα with asthma and wheezing. The effects of TNFα on wheezing outcomes were significantly larger in low than high O_3 communities. There was no modification by the other air pollutants. TNFα-308 variant genotypes were associated with increased asthma and wheezing risk, and the effect on current wheezing decreased with increasing O_3 level consistent with a negative regulatory mechanism.

5.4.6. Dietary Factors (Vitamins & Minerals)

Inadequate dietary intake of minerals and antioxidant vitamins during childhood appears to make the lungs more susceptible to low attained level. We investigated the effects of dietary magnesium, potassium, and sodium on children's lung function among 2,566 children aged 11-19 years. Low magnesium and potassium intakes were associated with lower lung volumes and flows. The adverse effects of inadequate intake varied among children with two other susceptibility factors, sex and asthma status. Girls with low magnesium intake had lower FEF_{75} and reductions were larger in girls with asthma FEF_{25-75} (-16.2%, 95% confidence interval: -22.7,

-9.1) and FEF_{75} (-24.9%, 95% confidence interval: -32.8, -16.1)) than in girls without asthma FEF_{25-75} (-2.0%, 95% confidence interval: -7.4, 3.8) and FEF_{75} (-4.1%, 95% confidence interval: -11.3, 3.7). Boys with low magnesium intake showed deficits in FVC (-2.8%, 95% confidence interval: -5.4, -0.2) compared with boys with higher intake. The effects of low magnesium intake did not vary substantially in boys with and without asthma. Among girls, low potassium intake was also associated with deficits in FEV_1 and FVC.

We investigated the relation between children's pulmonary function and intake of fruits, vegetables, juices, and vitamins A, C, and E by examining cross-sectional data from 2,566 children in the Children's Health Study collected during 1997-1998. Low total vitamin C intake (</=10th percentile) was associated with deficits in forced vital capacity for both boys and girls and with deficits in flows that were larger in girls. Low dietary vitamin E intake was associated with deficits in FEF_{25-75}. Deficits in FEF_{25-75} were associated with low dietary vitamin A intake in girls and with low total vitamin A intake in boys with asthma. Low intakes of orange and other fruit juices, which were the largest source of vitamin C, were associated with deficits in FVC and FEV_1 in boys. In summary, lung function levels were lower in children with inadequate dietary antioxidant vitamin and magnesium intake.

5.4.7. Obesity

We found that being overweight and obesity were associated with increased risk of new physician diagnosis asthma. The risk of new-onset asthma was higher among children who were overweight (relative risk (RR) = 1.52, 95% confidence interval (CI): 1.14, 2.03) or obese (RR = 1.60, 95% CI: 1.08, 2.36). Boys had an increased risk associated with being overweight (RR = 2.06, 95% 1.33, 3.18) in comparison with girls (RR = 1.25, 95% CI: 0.83, 1.88). The effect of being overweight was greater in nonallergic children (RR = 1.77, 95% CI: 1.26, 2.49) than in allergic children (RR = 1.16, 95% CI: 0.63, 2.15). We conclude that being overweight is associated with an increased risk of new-onset asthma in boys and in nonallergic children. We did not observe that body mass index was strongly related to the effect of sports participation on asthma incidence in high ozone communities. Body mass index was also associated with lung function level and growth, but did not modify the effects of air pollution on lung function growth. In summary, being overweight and obesity are host factors associated with adverse respiratory health outcomes.

5.4.8. Summary

Findings from the CHS clearly indicate that a number of host factors are susceptibility factors for adverse respiratory health outcomes. Children with asthma have increased risk for adverse outcomes and are highly susceptible to exposure to current levels of ambient air pollution and household ETS. Age-related susceptibility to ambient and non-ambient pollutants may be a critical determinant of chronic respiratory effects. It appears that the fetal and early life periods may show uniquely high susceptibility to exposures. The ongoing studies supported by NIEHS should help to clarify all of these relationships.

5.5. Can Specific Pollutants Be Associated with Health Outcomes?

Except for ozone levels, most of the pollutants measured in this study were highly correlated, making it difficult to tease out any specific pollutant to explain the results. It must also be pointed out, that despite our best efforts to measure pollutants with *a priori* potential for adverse health effects, there are other unmeasured pollutants that could be responsible for the effects we have observed. If the latter is true, then our measured pollutants, at best, could be surrogates for the causal agents.

Despite these difficulties, adverse health outcomes associated with *ozone* are the clearest. Convincing exposure-response relationships were seen for asthma incidence and school absences, and low birth weight was strongly associated with ozone. Levels of other pollutants were not associated with these outcomes.

With respect to the adverse effects of pollution on pulmonary function growth rates, no single pollutant consistently emerged as the most important, although the analyses presented in Section 4.2.1.1.8 show that acid vapor (nitric + formic + acetic + hydrochloric) is the single best predictor of lower MMEF growth rate. We are not convinced that the evidence is strong enough to consider acid vapor to be the causal factor.

Results from a recently published paper (McConnell et al. 2003b) provide data to support the importance of *NO_2* and *organic carbon* (OC) in explaining temporal variability within a community with respect to bronchitis in children with asthma, an obviously susceptible subgroup. While the associations with NO_2 and OC are convincing, other explanations for the associations are possible (see Section 5.7.3).

In summary, the clearest associations of a specific pollutant with health outcomes are *ozone's* relationships with school absences, asthma incidence and low birth weight. NO_2 and OC are convincingly associated with bronchitis in children with asthma. Effects on lung function growth are associated with a package of correlated pollutants with some evidence implicating acid vapor as the most important. It is possible that further analyses that exploit the patterns of spatial and/or temporal variability will help disentangle multi-pollutant effects. For example, analyses of traffic density and local variability in NO_2 concentrations implicate fresh vehicle exhaust, but without corresponding measures of co-pollutants, we cannot establish a particular constituent as the causal factor.

5.6. Epidemiologic Consideration for Threshold Effects

Many of the results contained in this report demonstrate greater health effects as exposure levels increase. For example, there are highly significant statistical associations and dose-response relationships. Since most of the analyses are based on only 12 data points (representing the 12 communities), it is not possible to say that one point (community) differs from another and, of course, the communities never line up perfectly. The issue is further compounded when susceptible sub-populations show different effects (McConnell et al. 1999). In this case, there is a strong dose-response relationship between bronchitis prevalence in asthmatics and exposure to PM (see Figure 4.2-14) but no such relationship in non-asthmatic children. The same figure shows a higher risk for asthmatics even in the lowest exposure category. The thresholds of PM at which effects would occur are obviously different for asthmatics and non-asthmatics. When

children with clinically significant lung function deficits are plotted against pollution levels striking dose-response relationships are seen for NO_2, acid vapor and $PM_{2.5}$ but not ozone. There are three to five times more children with significantly low lung function in communities with high pollution levels than communities with low pollution levels. While these results do not inform us about the presence or absence of a threshold they do provide data that would justify tighter standards for "clean air" and give us indications of where the levels should be set.

Given that this study has examined several different health outcomes relating to several different pollutants, we believe it is possible to make certain observations and recommendations specific to a pollutant or package of correlated pollutants.

5.6.1. Ozone

We have demonstrated that ozone has effects on asthma incidence, school absence caused by acute respiratory illness, and low birth weight. In the case of school absence, it seems that short-term changes in O_3 level are more important than level of exposure. To obviate the effects we have seen, exposure levels and *fluctuations* would both need to be controlled.

5.6.2. Correlated Package of Pollutants

A highly correlated set of pollutants (including PM, NO_2, acids, OC, EC) show strong associations with lung function growth and final level of achieved lung function (as seniors in high school). In this case, because it is impossible to identify a specific pollutant, the problem of identifying a threshold (if one exists) is even more problematic. Despite these difficulties, the data provide guidance for determining what air qualities *are not* healthful.

5.6.3. Conclusion

Given the epidemiologic and biostatistical considerations (see Section 4.2.1.1.9) for detection of threshold effects, we conclude that our data provide little support for either the presence or absence of thresholds for health effects. Because the focus of the CHS is on chronic effects, we have limited our own investigation of thresholds to the shape of the overall exposure-response relationship. It is possible that other metrics based on the temporal variation in pollution levels would demonstrate stronger threshold behavior, but our limited investigation of this question provides little support for this hypothesis. Given the probable continuum of host susceptibility factors at the individual level, it is practically impossible to set a threshold for a population. We advocate achieving the cleanest air possible as highly susceptible individuals are likely to be affected at very low levels of exposure.

5.7. Discussion of Relevance of Findings to:

5.7.1. Children's Future Health

5.7.1.1. Current air pollution matters

Results of the CHS, in conjunction with other studies published in recent years, give further evidence for lasting adverse effects of the current mixtures of air pollution. Cohort studies in adults (Dockery et al. 1993; Pope et al. 1995; Abbey et al. 1999; Hoek et al. 2002) have limited

abilities to define the relevant exposure windows, thus, it is usually not clear to what extent air quality decades ago contribute to current findings in adults. In contrast, the young age of the CHS cohort population clearly indicates that the current and/or recent air quality is associated with observed adverse effects on the respiratory health development. Thus, CHS findings underscore the need for sustained clean air policies and a decisive implementation of clean air regulations to protect the health of current and future generations of children.

5.7.1.2. Repeated episodes of respiratory symptoms and chronic morbidity

We interpret the association of air pollution with a higher frequency of bronchitis symptoms in asthmatics as an indication of repeated acute inflammatory insults, triggered by air pollutants in susceptible children. Such effects have been observed in other studies which did not stratify by asthma status (Braun-Fahrländer et al. 1992; Dockery et al. 1996; Heinrich et al. 2000; Heinrich et al. 2002). In the long run, repeated episodes of symptoms may enhance chronic morbidity with tissue remodeling in the lung (Pinkerton et al. 2000). Incidence and prevalence studies of chronic respiratory symptoms in adults exposed to air pollution are in line with the notion of chronic effects (Abbey et al. 1995; Zemp et al. 1999).

If air pollution is causing new cases of asthma, as CHS data suggest, the long-term implications are very important. Asthma is often a long-term or life-time condition with major consequences on life style, quality of life and morbidity, requiring continuous monitoring and treatment with considerable economic consequences (Fuhlbrigge et al. 2002). As shown in a recent follow-up from age 9 to 26 years, persistence of the disease is high. At an age of 9 years, the follow-up population had 9% asthmatics and 22% children with wheezing. Two thirds of these wheezing children reported being symptomatic during the entire follow-up (persistent wheeze) (Sears et al. 2003). According to Lozano, children with asthma incur annual medical costs of $1,129 per child, which is 2.8-fold the expenses of non-asthmatic children. Hospitalizations were 3.5 times more likely among asthmatic children (Lozano et al. 1999). Cisternas et al. (2003) estimate the annual direct and indirect costs of asthma in adults to be $3,180 and $1,732. The total costs ranged from $2,646 to $12,813 per year for mild to severe asthma, respectively (Cisternas et al. 2003). Life-time costs of asthma are very high, and so primary prevention of causes of the disease would lead to enormous benefits.

5.7.1.3. Lung function – a major predictor of life expectancy

The life-time course of pulmonary function is characterized by a period of growth from birth to early adulthood. Usually, the maximum attained level is reached in the late second or early third decade, followed by a steady decline in later life. The observation of lower levels of pulmonary function among adults living in areas with higher air pollution (Schwartz 1989; Ackermann-Liebrich et al. 1997) did not provide any insight in the life-time development of pulmonary function, given exposure. CHS is the first and only large-scale study investigating the growth phase and the transition into the plateau phase in early adulthood. It emerges from our findings that ambient air pollution jeopardizes lung growth across all periods of adolescence, leading to reduced growth rates and ultimately lower attained plateau levels. This supports the interpretation that findings in adults already reflect cumulative effects of long-term exposure. Our results are in line with a few other studies investigating associations of air pollution with lung function growth (Brunekreef et al. 1997; Brunekreef and Holgate 2002). However, no study

covers such a wide age range, and the plateau phase has not been investigated in any other air pollution study. The association of cumulative exposure to air pollution with lung function across all ages is a very important finding as it provides additional evidence for the plausibility of the observed long-term effects of air pollution on longevity as reported in cohort studies (Dockery et al. 1993; Pope et al. 1995; Abbey et al. 1999; Hoek et al. 2002). The findings of the effects on lung function growth may provide the pathophysiologic link between cumulative systemic effects of air pollution and life expectancy. It is well known that lung function, measured at any point in time, strongly predicts life expectancy (Ashley et al. 1975; Beaty et al. 1982). The observed impact of air pollution on lung growth in childhood corroborates 1) the cross-sectional observations of lower lung function among adults in communities with higher pollution levels such as in NHANES II or SAPALDIA (Schwartz 1989; Ackermann-Liebrich et al. 1997) and 2) the cohort mortality findings given that subjects with lower pulmonary function are expected to die earlier. In addition, the finding in movers supports the notion of an exposure related effect on growth rates but suggests that if air quality improves, effects on lung growth are reversible (and if air quality further deteriorates, lung growth further decreases). The benefit of improved air quality on lung function has been confirmed in a German study (Frye et al. 2003). This is in line with findings in the smoking cessation literature, where cessation leads to improvements in pulmonary function, morbidity, and longevity (Pelkonen et al. 2001).

Airflow limitation is also believed to be the most accurate marker of COPD, and the CHS findings are compatible with the hypothesis of a causal contribution of air pollution on COPD in adults. The burden of COPD is substantial in both smokers and non smokers, with direct annual costs (1993) estimated to be $14.7 billion (Vollmer 2003).

5.7.1.4. Susceptibility matters

The CHS provides strong evidence that susceptibility factors modify the effects of environmental hazards, as outlined in the theoretical basis of the CHS approach (Gilliland et al. 1999b; Gilliland et al. 2002b; Gilliland et al. 2003c; Gilliland et al. 2003e). An important consequence of this concept is that the effects of current levels of air pollution will be substantially larger among susceptible subgroups than suggested from total population estimates, which reflect the mean effect across susceptible and non-susceptible people. If the pool of susceptible children is small, the effects of air pollution could be substantially larger. For example, if air pollution affects the lung growth of only a (not yet identified) smaller subgroup (e.g. some genetic trait), the true effect of air pollution on lung growth among these children will be larger than what has been published. If the susceptible subgroup consisted in only a small fraction of the population, effects among these children would be substantially larger. Thus, the currently prevailing paradigm in which effects of air pollution are considered to be very small on the individual level but being relevant only on a population level may need reconsideration (Kunzli et al. 2000a). The CHS provides a unique resource to further investigate this issue, and to take susceptibility factors into account in the assessment of the overall burden of air pollution (see Section 5.4).

5.7.2. Impacts on Society

Results of epidemiological studies such as the Children's Health Study provide key information to estimate the health impact of air pollution on society as a whole. Various measures of *impact* can be used such as estimates of the number of cases that can be attributed to air pollution; the reduction in quality of life; a measure of the life expectancy adjusted for disability; years of life

lost; and ultimately the economic consequences of these adverse effects (Ostro 1994; WHO World Health Organization Regional Office for Europe 2000; WHO World Health Organization Regional Office for Europe 2001; National Research Council 2002; Miller and Hurley 2003). The CHS has primarily published estimates of the association between ambient concentrations of air pollutants and health outcomes. These 'exposure-response' functions do not give a direct estimate of the impact of air pollution on the society but are needed to make the respective assessment. The total burden depends on this risk function, the distribution of exposure, susceptibilities, and diseases in the respective population.

In the past, estimates of the impact – or the overall burden – of air pollution had a primary focus on mortality among adults. As acknowledged by WHO advisory boards (WHO World Health Organization Regional Office for Europe 2000; WHO World Health Organization Regional Office for Europe 2001) and the National Academy of Science (National Research Council 2002), the burden of morbidity, in particular among children, has often been neglected due to the lack of data. In a recent assessment of the benefits of the new $PM_{2.5}$ regulation on the California population, CARB has already acknowledged CHS as a relevant source strengthening the evidence of effects. CHS provides highly relevant and valid new estimates that can be added to future impact assessments on the regional, state or national level. In particular the findings about onset of asthma and symptoms in asthmatics could contribute to future assessments of the overall burden of air pollution. It is well known that burden assessments and, similarly, benefit assessments of clean air policies give an incomplete picture of the total effects (WHO World Health Organization Regional Office for Europe 2000; WHO World Health Organization Regional Office for Europe 2001; National Research Council 2002) and efforts should be made to make the assessments more complete.

With the economic valuation of ozone-related school absences in the South Coast Air Basin, ARB initiated a study based entirely on the findings of CHS regarding the association between ozone concentrations and respiratory related school absences (Gilliland et al. 2001b). The application of this finding to the assessment of the economic burden of respiratory disease is a very important expansion of impact assessments as it includes a further dimension of health effects in children: the impact on parents and the whole family (Hall et al. 2002). The study estimated the benefit of the improvement in ozone concentrations from 1990-92 compared to 1997-1999. Person-days with ozone concentrations above 70ppb (10am-6pm mean) decreased from approximately 80 million person-schooldays to 20 million (South Coast Air Basin). The related economic benefit reached approximately $142-304 million in 1998, or omitted *per capita* costs of $43-93. These data have not been used in the U.S. EPA assessment of the Clean Air Act benefits but would further increase the benefits of decisive clean air policies (US Environmental Protection Agency 1997b).

In summary, the CHS results build a formidable new source of data that can be used to estimate and discuss the impact of air pollution on the population of children and their caregivers. Given that the epidemiological findings are based on investigations in the Southern California metropolitan area, the estimates of the overall impact are particularly valid for this region. We have, however, no evidence to suggest that the CHS findings are a specific consequence of the kind of air pollution encountered only in Southern California. In fact, the movers study (Avol et al. 2001) included children moving within the entire western states of the US. It will be

appropriate to use the CHS results for the estimation of the impact of air pollution and the benefits of clean air strategies across the entire U.S. Such national extrapolations have been used before, and California impact studies appropriately used results from studies conducted outside the state as well (California Air Resources Board 2002b).

5.7.3. Pollutants and Their Sources

In previous sections of this report, a number of respiratory health outcomes—including symptoms, school absences, disease (asthma), and decrements in lung function level and growth rate—have been associated with an assortment of ambient air pollutants, including O_3 and an inter-correlated package of pollutants that include NO_2, PM_{10}, $PM_{2.5}$, acids (both inorganic and organic), and elemental and organic carbon. The strength of these associations and the implications for severity of health outcomes has been previously discussed. We now turn to the relevance of these findings to the identified pollutants and their sources.

The four pollutants that formed the basis of the study design – O_3, NO_2, PM_{10}, and acids including nitric, hydrochloric, formic, and acetic acids) – represented both primary and secondary components of the ambient air pollution mix. While a portion of ambient NO_2 and PM_{10} observed in the study communities are the results of direct anthropogenic processes (most typically incomplete fuel combustion for NO_2 and re-entrained road dust, woodfires, and residential/commercial cooking for PM_{10}) (South Coast Air Quality Management District 2003), a significant contributor to the formation of O_3, NO_2, PM_{10}, and acids in the Southern California air shed is provided by daily photochemistry. The CHS study communities include some of the most photochemically active regions of Southern California. Several of the CHS communities (Mira Loma/Rubidoux, Riverside, Lake Arrowhead/Lake Gregory, San Dimas/Glendora) have reported some the highest regional and national readings for PM_{10} and O_3. Additionally, regional planners continue to struggle to achieve basin-wide reductions in ambient NO_2 (California Air Resources Board 2002a).

From this perspective, a measurable linkage between health and secondary photochemical air pollutants, especially O_3, might have been reasonably anticipated. A variety of transportation factors affect the air quality in the region, including: the presence of over 15 million motor vehicles driving over 300 million miles each day (South Coast Air Quality Management District 1997); the lack of a widely used mass transit system in the general Southern California region; Los Angeles being a major entry portal for Pacific Rim commodities delivered by ship (and subsequently distributed by truck or rail) to the United States. Due to these transportation-related considerations, the substantial daily input from motor vehicle pollutants of both gases and particles into the air also seemed a probable source of health concerns at the study outset.

As this report has detailed, both of these source categories (photochemical and primary emissions) have been implicated by CHS health data, which has linked ozone exposure to school-based respiratory absences (Gilliland et al. 2001b) and asthma incidence (McConnell et al. 2002b), and a number of primary/secondary pollutants (including nitrogen oxides, particulate carbon, PM_{10} mass, $PM_{2.5}$ mass, and acids) to diminished lung function growth rates in the combined cohort of subjects (Gauderman et al. 2000; Gauderman et al. 2002) and increased bronchititic symptoms in asthmatics (McConnell et al. 1999). The findings from the longitudinal

component of the CHS provide additional support for linkage between both primary emissions and respiratory health, as well as photochemical pollutants and respiratory health.

To the extent that health outcomes have been associated with photochemically-derived pollutants, efforts to improve health and reduce observed effects will profit from reduction strategies aimed at those primary pollutants responsible for the formation of the secondary chemicals identified in the analyses. In the Southern California area, significant sources for these emissions have most notably been transportation (especially on-road motor vehicles and heavy-duty trucks), petroleum production and marketing operations (refineries, gasoline service stations, and motor vehicle fuel usage), and industrial/commercial operations (power generation, boiler operations, chemical manufacturing, solvent evaporation, surface coatings, and so on). The continued use of oxygenates and other gasoline additives, to discourage the photochemical oxidation of reactive hydrocarbons from motor vehicle fuels, would seem to be a worthwhile and prudent approach.

Primary emissions sources in the Southern California region have been the focus of many historical investigations. The dominating presence of motor vehicles, and hence motor vehicle exhaust, in the Southern California air shed, is reflected in the substantive levels of NO_x, PM, and a number of organic gas or particulate phase compounds. Elevated levels of naphthalene and benzo(ghi) perylene (Eiguren-Fernandez et al. in press 2004), though not a focus of the CHS, confirm the impact of, and provide one significant indication of, motor vehicle emissions in the region's ambient air.

As a part of the CHS exposure assessment effort, source apportionment analyses were performed on a composite collection of $PM_{2.5}$ carbon fractions collected in the CHS community monitoring network during 1995 (Manchester-Neesvid et al. 2003). The results of these analyses are discussed in Section 4.1.1.3 of this report, and highlight (a) the high inter-correlation of many of the identified organic compounds, (b) the identification of motor vehicle emissions, wood smoke, natural gas combustion, tire wear, road dust, cigarette smoke, and even meat cooking residues in Southern California air, and (c) the seasonal nature of the regional air pollution burden. Additional research is presently underway to further characterize the source signatures useful for accurate source apportionment efforts.

5.8. Future Research Needs

5.8.1. Understanding Between-community vs. Within-community Differences by Pollution Level

We have observed both yearly variation in pollution levels within communities and spatial variation related to traffic. Although the CHS was designed primarily to examine between-community comparisons, we have observed associations of respiratory outcomes both with temporal and spatial variation in pollution. The within-community associations of OC and NO_2 with yearly variation in bronchitic symptoms among asthmatic children (Section 4.2.3) were considerably larger than the between-community associations. This is potentially important for regulators, because it suggests that estimates of the chronic effects of pollution from cross sectional studies underestimate the true effect. The better control by design of unmeasured

confounders in the within-community analysis, for example those associated with participants' homes, with other local environmental factors, and with their communities, may be one explanation for these differences, as we have discussed. Potential approaches to addressing this issue include better assessment of community ecologic confounders, including socioeconomic status and other social characteristics of neighborhoods, and school physical and social characteristics. We have considered the potential role of systematic bias and the statistical modeling strategies, and these seem to be unlikely explanations for the differences observed (McConnell et al. 2003b). Further examination of this issue would be useful to see if the results can be replicated in other studies and with other outcomes.

As this study progressed, the importance of intra-community variability in pollution became apparent. Our limited investigation of local variation in pollution has revealed important relationships. Our proposal to ARB to measure local within-community variation in particles and gases was approved by the Research Screening Committee (RSC) but not funded. Funding sources from NIH will help us learn more about the spatial distribution of gases but support needs to be found to do similar measurements of particles.

We have also observed variation in asthma prevalence associated with spatial variation in traffic within communities. Ongoing study of these associations in CHS and in a new cohort will include the measurement of NO, NO_2 and ozone at the homes of children in order to calibrate the CALINE4 models in the study communities. Finally, other avenues for exploiting within-community variation include examining the variation in individual characteristics that may modify the effect of air pollution, for example time and activity patterns, diet, genetic characteristics, and indoor allergens.

5.8.2. Exploration of the Health Effects of Specific Pollutants on Asthma Incidence and Exacerbations

Ambient air pollution is a complicated chemical mixture dependent on meteorology, the contributing sources, and atmospheric chemistry. Therefore, identifying specific single pollutants responsible for the observed effects in the CHS is difficult. This task has been further complicated by the high correlation of the package of PM-related pollutants. The limitations of between-community comparisons to identify specific pollutants in a modest number of communities with correlated pollutants is described in detail in the context of the discussion of the lung function results (Sections 4.2.1.1.8 and 4.2.1.1.9). Nevertheless, the longitudinal evaluation of bronchitic symptoms has been one of the more promising approaches to identifying specific pollutants. It has identified NO_2 and OC as pollutants that merit further investigation. Further speciation of OC to separate primary from secondary sources would be useful for epidemiologic analysis. The contribution of specific sources, for example, diesel and automobile traffic, could contribute to identifying their relative contribution to the observed associations with OC. The observed association of NO_2 with bronchitic symptoms in asthmatics, which was stronger among exercising children, suggests that further investigation is needed to determine whether NO_2 leads to viral infection, which has been suggested by animal studies and limited human study. Finally, the ongoing investigation of the effects of local traffic pollutants may help to identify the hazards of a specific source and potentially identify specific pollutants in the local mix.

The NIH-supported studies that are ongoing on the incidence and prevalence of asthma in young children should help us in the search for specific etiologic pollutants.

5.8.3. Understanding the Relative Roles of Diesel Exhaust, Auto Exhaust and Other PM Sources

Regulators and health scientists are keenly interested in understanding the relative roles of diesel exhaust, auto exhaust, and other PM sources in acute and chronic health effects. Diesel exhaust has been the focus of much research because of its high toxicity, associations with lung cancer and respiratory effects in occupational epidemiology studies, and associations with allergic airway disease in animal studies. However, large uncertainties remain in our understanding of the relative contributions of different types of sources to ambient PM and the health effects of contributions from different sources.

Source attribution of ambient PM concentrations is a challenging scientific problem. The most widely used technique is Chemical Mass Balance (CMB) modeling. CMB modeling of source contributions to ambient $PM_{2.5}$ and PM_{10} has been improved over the last twenty years, yet it can rarely distinguish more than five different types of sources due to the co-linearity of many source composition profiles. The complex physical and chemical nature of PM, the historical limitations in measurement technologies, and the scarcity of unique tracers of source contributions have limited progress. Efforts to distinguish diesel exhaust from gasoline-fueled spark-ignition engine exhaust illustrate the difficulties. Diesel PM is a complex mixture of organic compounds, elemental carbon, and other trace elements. PM from diesel emissions, as well as PM from catalyst-equipped gasoline-fueled vehicles, food cooking, biomass burning, secondary organic aerosol, and cigarette smoke are predominantly carbonaceous. The organic PM source signatures of diesel and gas vehicle exhaust are usually very similar. Notable differences in the particle size and composition have been seen for diesel exhaust and emissions from well-maintained gasoline vehicles operating at moderate speed and load. There are also significant chemical and physical differences between older and new diesel engine technologies. However, the size and chemical composition of high-emitting gasoline vehicles under heavy load is often very similar to diesel exhaust, so the variability in emissions from different vehicles within each class confounds the search for unique tracers.

Elemental carbon has been used as a tracer for diesel PM in the atmosphere. EC is not necessarily a reliable diesel tracer in ambient air because it is also present in gasoline-fueled vehicle exhaust, wood smoke, tire debris, and distillate oil-fired boiler PM. Likewise, other generic combustion species, such as polycyclic aromatic hydrocarbons, come from too many sources to have sufficient specificity. Given the carbonaceous nature of combustion PM, individual organic compounds and ratios of organic compounds still hold the most promise as molecular markers for combustion sources.

Further research is needed to reliably quantify the source contributions to atmospheric PM and to use source contributions directly in epidemiologic analyses. Continued research to identify single tracers and source fingerprints, composed of series of tracers, that are sufficiently unique in the context of atmospheric PM mixtures, is needed to advance the understanding of the relative roles of different sources in the PM problem. Additional research is needed to understand the variability in chemical composition and particle size distributions of source

emissions under different operating conditions in order to improve our understanding of source characterizations and their uncertainties.

5.8.4. Early Life Experiences

As discussed previously, age is an important determinant of susceptibility to adverse respiratory health outcomes and is a well-known modifier of responses to respiratory toxins. Children as a group are more susceptible than adults to the effects of many environmental exposures. The variation in age-related susceptibility extends to the childhood period as children's pulmonary system growth and development varies by age. This developmental variation leads to increased risk for asthma in children less than five, increased risk from exposures during the fetal and early life periods, and increase susceptibility to the effects of air pollution during the period of rapid lung growth. We have observed a significant effect of maternal smoking during pregnancy on asthma and wheezing occurrence as well as lung function development. Maternal ozone exposure during the prenatal period was associated with lower birth weight in term infants. Taken together, these findings suggest that age-related susceptibility to ambient and non-ambient pollutants may be a critical determinant of chronic respiratory effects.

It appears that the fetal and early life periods may show uniquely high susceptibility to exposures. These findings motivate the need for prospective studies of the effects of air pollutants during the *in utero* period and early life. The biologic impact pathway (see Figure 5.4-1) is useful as a framework for targeting future research efforts. Maternal exposure during the fetal period as well as toxicokinetic factors that directly influence fetal exposures have not been well characterized. Time activity patterns are likely to be different in pregnant women and vary by trimester. Breathing patterns are different in pregnant women compared to non-pregnant women. Furthermore, immune response, host defenses and metabolic profiles are likely to differ by pregnancy status and reproductive history. Some research has been conducted to examine the dose of PAHs to the fetus and the association of doses with pregnancy outcomes, but more research in this area is clearly needed. Studies of the effects of maternal ambient pollutant exposures on the child's respiratory health have not been reported and are a high priority given the demonstrated susceptibility in this developmental period. The effects of maternal diet and genetic variation may be important in understanding the effects of air pollution exposures in the fetal and early childhood periods.

5.8.5. NIEHS Funding

The National Institute of Environmental Health Sciences (NIEHS) is supporting our Program Project proposal which has four research projects and four supporting cores building on the Children's Health Study. The four projects address the question of whether the observed changes in pulmonary function persist to adulthood; involve studying asthma incidence with the goal of identifying environmental and host factors; examine the genetic variation in oxidative stress pathways that modulate response to air pollution; and develop new biostatistical methods. Core 1 provides field logistics and technical support for the data collection. Core 2 provides biostatistical and data management support. Core 3 obtains data needed for exposure assessment. Core 4 provides the genotyping and sample storage capability. Combining the four projects into one program promotes the interdisciplinary activity required to tackle complex projects while creating efficiencies that take advantage of existing resources

and cores. Our major hypotheses are: 1) Oxidative stress is the main biological pathway by which air pollution leads to adverse respiratory effects. Specific pollutants that give rise to reactive oxygen species (ROS) will have the greatest effects and these effects will be modified by genes involved in xenobiotic metabolism, inflammatory oxidant production, antioxidant production, ROS metabolism, and detoxification of oxidation products. Dietary antioxidant intake and other lifestyle factors such as physical activity will also modify these effects. 2) Pollutants contributing to these long-term effects are combustion-related and the biggest contributor is derived from motor vehicle emissions and that the contributions from diesel emissions and freshly emitted automobile emissions can be distinguished by measurements of relevant markers such as fine elementary carbon (EC) particles and CO and by spatial modeling of traffic density. 3) The respiratory effects of air pollution are multifaceted and interrelated. Thus, air pollution has effects on pulmonary function, on chronic respiratory diseases such as asthma, and on the frequency of respiratory illnesses. 4) The effects of air pollution on lung function and respiratory disease are irreversible and lead to permanent deficits continuing into adulthood.

6. Summary and Conclusions

6.1. Strengths and Limitations

This study has many strengths and some limitations. The main generic strengths of this study are that state-of-the-art exposure assessment, study design, statistical approaches, and health assessment were utilized. The world's leading experts were consulted before the study began and an External Advisory Committee, composed of leading air pollution scientists, monitored the study over its 10-year period.

More specific strengths include the prospective design of childhood follow-up (with large numbers of children) in 12 communities with widely varying air pollution levels and profiles and with high rates of subject participation. Likewise, consistent and strong efforts were made to assure data quality for both the exposure data and the health data. Anchoring study hypotheses in a biologic impact pathway was another strength.

One limitation of the study was that not all profiles for the four pollutants of interest existed. In other words, the high temporal and spatial correlation of the pollutants made it difficult to single-out individual pollutants as being associated with specific outcomes, particularly for NO_2, PM and acid vapor. Other limitations included the practical inability to characterize exposure to bioaerosols and the practical inability to perform clinical evaluations on subjects such as skin testing for allergies or bronchial reactivity testing to characterize airway hyper-responsiveness. Another limitation is relying primarily on community monitoring rather than personal assessment of exposure. The limitations of the study, in general, tend to lessen the chance of observing air pollution effects.

In sum, the strengths of the study were far greater than the limitations.

6.2. Summary

This ten-year prospective study of four cohorts of about 6,000 children living in 12 Southern California communities has yielded valuable data addressing questions of great public health significance. Given that more than 70 papers have been published from this 10-year project, we present the key results in tabular form in an effort to provide readers with a road map to pursue details to their satisfaction (see Table 6.3-1). We provide references to sections in this final report discussing the findings in more detail. We caution the reader that many of these associations have been examined in several different ways, so a crude summary of findings as either "statistically significant" or not is bound to be an oversimplification. In general, however, we can conclude that both lung function levels (at entry to the cohort or maximally attained levels) and rates of growth are consistently associated with a highly correlated package of pollutants (particulates, NO_2, acids, and various constituents thereof), but typically not with ozone or organic carbon. On the other hand, school absences and asthma incidence tend to be associated with ozone but not with the other pollutants (an exception being asthma exacerbation, which appears to be associated with $PM_{2.5}$, NO_2, and OC. Similarly, birthweight was found to be associated with ozone, but not with PM_{10}. Bronchitic symptoms were typically not associated with any measure of air pollution overall, but were associated with various pollutants among

asthmatics. We found that certain GST genotypes confer sensitivity to environmental or maternal *in utero* tobacco exposures for a broad range of endpoints, including asthma, wheeze, reduced lung function, and acute respiratory illness; whether such genetic susceptibility extends to air pollution is the subject of our current NIH-supported study.

This project has provided a wealth of data to address the six key hypotheses discussed in Sections 5.1-5.6. Inevitably, a project of this magnitude generates a set of new questions and corresponding needs for further investigation (see discussion in Section 5.8.). The team of investigators in this study has been funded by the National Institute of Environmental Health Sciences (NIEHS) to pursue these and several other important scientific issues relevant to the health effects of air pollution (see Section 5.8.5).

6.3. Conclusions

We conclude that several adverse respiratory outcomes are associated with breathing polluted air in Southern California including asthma incidence and exacerbations, effects on lung growth rates and level, and school absenteeism caused by acute respiratory illness. These adverse effects are observed despite the partially successful efforts over the past 40 years to improve air quality. It is also important to note that these deleterious effects have been detected at pollution levels that are in compliance with existing air quality regulations. A limited evaluation of the financial impact of these respiratory conditions and diseases strongly suggests that improvement in air quality would result in positive economic benefits.

Table 6.3-1. Relationships between pollutants and outcomes in the Children's Health Study.

P O L L U T A N T

O U T C O M E		Ozone	PM_{10}	$PM_{2.5}$	$PM_{10-2.5}$	NO_2	Acid[§]	OC	EC	TD
Asthma	Prevalence	4.2.2	4.2.2	4.2.2	N.A.	4.2.2	4.2.2	N.R.	N.R.	**4.2.2***
	Incidence	**4.2.2***	4.2.2	4.2.2	N.A.	4.2.2	4.2.2	4.2.2	4.2.2	4.2.2
Respiratory Symptoms		4.2.3	**4.2.3***	**4.2.3***	**4.2.3***	**4.2.3***	4.2.3	**4.2.3***	4.2.3	4.2.3
Birth Weight		**4.2.5***	4.2.5	N.A.	N.A.	4.2.5	N.A.	N.A.	N.A.	N.A.
School Absences		**4.2.4***	4.2.4	N.A.	N.A.	4.2.4	N.A.	N.A.	N.A.	N.A.
Lung Function	Growth	4.2.1	**4.2.1***	**4.2.1***	N.A.	**4.2.1***	**4.2.1***	**4.2.1***	**4.2.1***	4.2.1
	Level	4.2.1	**4.2.1***	**4.2.1***	N.A.	**4.2.1***	**4.2.1***	**4.2.1***	**4.2.1***	**4.2.1***

Number in cell refers to Final Report Section. Significant associations are indicated by bold type and an asterisk. N.A.=not applicable; N.R.=not reported; TD=traffic density (traffic counts over time); OC=organic carbon [effectively from a PM_{10} sample (see Section 3.4.1.2 for a discussion of Leg C of the two-week sampler]; EC=elemental carbon [effectively from a PM_{10} sample (see Section 3.4.1.2 for a discussion of Leg C of the two-week sampler)].
[§] acid refers to nitric, hydrochloric, formic, and acetic acid analyses (see specific section references for further discussion).

7. Recommendations

The development of good public health policy should be based on the evaluation of the overall scientific evidence (Brunekreef and Holgate 2002) rather than relying on findings from a single study such as the Children's Health Study. Thus, repeated reviews of the entire literature remain an important aspect of air pollution regulation (US Environmental Protection Agency 2003). However, CHS results substantially contribute to the assessment of the evidence. The longitudinal design, the size of the population, the range of pollution observed in the CHS communities, the focus on children's health, the availability of various indicators of susceptibility, and the California location of the CHS give high credibility to the results, which may be generalized to the entire state of California and beyond. Thus, the CHS will play a dominant role in the assessment of evidence, and the weight given to these results should be particularly high. The following aspects are of major importance:

- The association between ambient pollution and lung function growth is important as this outcome reflects an objective measure of pulmonary and systemic health, with long-term health relevance.
- The confirmation of findings across CHS cohorts is a substantial contribution. It not only demonstrates the reliability of results but is consistent with the notion that the ambient air pollution present over Southern California in the early 1990s is similar in terms of respiratory health effects to the more current mixtures. Thus, CHS results underlie the need for continuous efforts in the regulation of air pollution.
- The detection of susceptibility factors that are fully compatible with hypothesized pathways of effects makes a strong contribution to ultimately understand the mechanisms leading to the observed effects. It also opens new regulatory avenues that focus on those at highest risk.

From the policy perspective, it is not only 'causality' but also the question of 'reversibility' that matters in the judgment of the 'accountability' of regulations. Will clean air regulations be a benefit only for future generations, i.e., those not affected by air pollution in the past? Such questions require intervention studies (not readily available in this field of research) to address the salient issues. The direct and indirect contribution of CHS to assess 'accountability' of regulations is unique and of paramount importance. Two analyses may be emphasized in this context:

- The study of movers, which is methodologically comparable (but not randomized) to an intervention study, i.e., the gold standard in clinical research, strongly suggests that improvements in current air quality lead to improved development of children's lungs (Avol et al. 2001). These findings strongly support the notion that air pollution is a cause of impaired lung function, and that improved air quality leads to rather immediate beneficial effects on the development of the lungs, at least during the years of adolescent growth. The movers study, as other CHS analyses and epidemiological studies in general, cannot easily disentangle the contribution of single pollutants to the observed changes.

However, the study shows that improved air quality, characterized by the major indicators of urban air pollution, leads to prompt health benefits.

- The innovative recent CHS analysis on symptoms among asthmatics, using the annual change in concentrations within communities gives further (albeit indirect) evidence for the effectiveness of clean air 'interventions' (McConnell et al. 2003a). McConnell et al. showed that the annual frequency in bronchitis symptoms varies with the annual changes in ambient concentrations. Thus, improvements in air quality are expected to lead to rather immediate benefits among asthmatics (within the same year). In the study, changes in air quality were mostly driven by weather conditions, but one can certainly expect to observe the same pattern for changes in air quality driven by reductions in emissions.

Only a few 'intervention type' studies have been published so far, pointing in the same direction, but CHS is by far the strongest piece of evidence that improvements of the current air quality in California lead to health benefits. These findings are highly relevant and the absence of detailed knowledge about the specific contribution of single pollutants and the various underlying mechanisms do not weaken the policy conclusions that must be drawn: lowering emissions from the primary sources of air pollution and decreasing exposure to ambient air pollutants improves health of current and future generations of children and adults.

As emphasized in our recent article, it is worthwhile to distinguish between two regulatory approaches to reduce exposure to air pollution: "primary strategies" that reduce ambient concentrations of air pollutants must be the main focus of regulatory action (Kunzli et al. 2003). "Secondary strategies" that reduce children's exposure but not necessarily ambient air pollution may have a complementary and temporary role, but should not distract from the priority to reduce emissions at the sources. We maintain this distinction in the following discussion of the CHS contribution to the regulatory discussions.

A full appraisal of the regulatory framework and the integration of new scientific findings is not the core expertise of the CHS research group, thus, not the purpose of this section.

7.1. Primary Strategies: Regulations That Reduce Emissions

The setting of air quality standards, and the regulation of sources can be considered tools to reduce emissions. We discuss our findings in relation to these two approaches that ultimately relate to reductions in emissions.

7.1.1. Air Quality Standards for Criteria Pollutants

7.1.1.1. Setting air quality standards in the absence of no-effect thresholds

The CHS confirms the inherent limitations of setting air quality standards. The traditional paradigm of health-based standards assumes that effects of exposure to concentrations below some level may not occur. As discussed in Section 4.2.1.1.9, the CHS has limited power to confirm the existence of some 'safe level' of pollution and the results are fully in line with a linear no-threshold model. Formal threshold assessments of acute effects of air pollution on mortality, where power to assess the response shape is much larger, have come to the same

conclusion (Daniels et al. 2000). In the absence of evidence for safe levels of pollution, a standard will not be able to prevent all health effects but could determine the air pollution-related health burden that policy makers may consider 'acceptable'. The absence of a population threshold is in line with the notion of a broad distribution of *individual* thresholds of effects, which may be related to individual factors of susceptibility. Thus, standards ultimately determine the number of people that will be affected by short-term and long-term effects of ambient air pollution.

In other words, the hypothesis that only zero pollution can be considered 'healthy' cannot be rejected, and effects can be observed at concentrations well below the currently implemented air quality standards. Regulators are faced with the need to negotiate some 'lowest acceptable' non-zero standard values. The assessment of the health burden of pollution above various cut-off levels in conjunction with an estimation of costs and benefits for achieving these levels is, thus, a crucial tool in standard setting for no-threshold pollutants. CHS results provide important new findings that need to be taken into account in such analyses.

As recently emphasized in the Report to Congress (Office of Management and Budget 2003), benefits largely outweigh the costs of current clean air regulations. Inclusion of CHS findings will lead to a further increase in the estimated benefits of clean air policies (US Environmental Protection Agency 1997b; US Environmental Protection Agency 2000; California Air Resources Board 2002b). It is in fact encouraging that by far the largest fraction (>80%) of regulatory benefits provided in a recent Report to Congress (Office of Management and Budget 2003) stem from only four EPA clean air rules (targeting PM and NOx), leading to some $101-$119 billion benefits per year (compared to $8-$8.1 billion costs). The other benefits presented by OMB were related to more than 100 other rules, from several agencies. This highlights the dominant role of air pollution, an exposure that affects the entire population. It also shows that investments in clean air regulation are highly efficient, thus, very attractive to policy makers that care about the economy and the health of California.

7.1.1.2. Standards with long-term averaging time

Air quality standards have been based largely on acute effect studies and findings in adults played a major role. Results from the CHS emphasize the need to take long-term effects into account as the findings of CHS cannot be explained by acute short-term effects of ambient air pollution alone. Effects that are associated with long-term exposures to ambient pollutants may be used as arguments to also implement air quality standards for integrated annual averaging periods. The State of California currently regulates annual means for PM_{10} and $PM_{2.5}$. In addition, there is a Federal annual mean standard for NO_2. Longitudinal studies such as CHS provide the major grounds in the consideration of time-integrated standards.

7.1.1.2.1. NO_2

Several findings of the CHS lead to the conclusion that annual mean levels of NO_2 are associated with important health outcomes. These associations are not fully explained by long-term mean levels of PM, thus may represent health effects not associated with PM. Therefore, a long-term standard for NO_2 should be considered. Given the current fleet of vehicles, NO_2 remains a useful indicator of exposure to traffic-related pollution. A long-term standard for NO_2 would reflect a more source-specific approach to regulate pollution than in case of the PM standards.

As shown in CHS, health effects vary not only across communities but follow within-community profiles of exposure. Monitoring and regulating an indicator such as NO_2 on a smaller within-community scale can provide important information about health-relevant exposures within communities, its changes over time, and the local public health impact.

7.1.1.2.2. Ozone

The CHS findings regarding onset of asthma in high ozone communities (McConnell et al. 2002b) and the acute effects of ozone on school absences (Gilliland et al. 2001b) contribute to future evaluations of ozone standards. Currently, ozone is regulated with a 1-hour standard (California) and an 8-hour value (U.S. EPA). The CHS strongly suggests that effects of ozone occur at concentrations well below the current standards of 90 ppb (California 1-hour value) or 80 ppb (U.S. 8-hr mean) and that fluctuations, even at low levels, are important. A recent study confirms acute effects of low levels of ambient ozone on symptoms and medication use among children under treatment for asthma (Gent 2003). Both of these new findings should be important in the revision of ozone standards.

7.1.1.2.3. Particulate Matter

The associations between ambient $PM_{2.5}$ (and other PM surrogates) and various health outcomes in the CHS confirm that current levels of ambient $PM_{2.5}$ remain a health hazard, thus, confirming the appropriateness of more stringent annual mean standards for $PM_{2.5}$. Findings of the CHS strongly endorse the leadership of the California EPA in setting stricter standards, and California's strong influence on Federal regulations (California Air Resources Board 2002b).

7.1.2. Regulating Sources

As previously discussed, the CHS cannot provide a clear assignment of effects to single pollutants nor single sources. However, the dominant role of traffic in the CHS areas cannot be dismissed. The observed associations of health outcomes with ambient concentrations of NO_2 may be interpreted as effects that are strongly determined by traffic emissions. Thus, regulatory focus on traffic emissions remains a key strategy to improve the health-relevant aspects of air quality.

We emphasize that the CHS has not yet assessed the specific independent contribution of fresh exhaust emissions to children health. Exposure to these emissions is strongly determined by proximity to traffic, thus, location of homes, schools, and time spent on or along busy roads. The NO_2 concentrations as assigned in CHS do not specifically capture such proximal exposures but rather reflect some 'background' level of traffic exposure. There is experimental evidence for substantial toxicity of some of these pollutants such as ultrafines or diesel particles (Diaz-Sanchez et al. 1994; Diaz-Sanchez et al. 2000; Li et al. 2000a; Li et al. 2003). Only a few epidemiological studies have used measures of ultrafines and results are not yet conclusive, i.e. the specific and independent contribution of these constituents to the public health effect of air pollution is not well understood, but point to exposure to fresh exhaust encountered in close proximity to traffic as the most important factor. Future research activities within the CHS will also contribute to this assessment.

It is important to note that the focus on traffic-related policies should not distract from other sources that are predominant sources of primary and secondary air pollutants. In particular, large ports such as in Los Angeles, Long Beach or Oakland are substantial sources of unregulated emissions, e.g., from marine vessels. Of similar importance are large airports. In addition, such infrastructures create a high demand for light and heavy duty traffic, both locally and in more distant areas. Thus, regulations should be sensitive to such hot spots of exposure, and expansion needs to carefully take into account the effect of both local and regional air quality on health.

CHS results cannot answer engineering questions such as what specific constituents of exhaust emissions need to be tackled to prevent health effects. However, CHS results suggest that policies leading to reductions of mobile source emissions would be of great benefit to children's health. For example, regulations that lead to more timely replacement of older high emission vehicles in the fleet (including cars, trucks, and off-road vehicles) are promising approaches to improve air quality.

If the entire car and truck fleet of metropolitan areas were at or below the currently available lowest levels of emissions, population health would undoubtedly benefit. From a public health perspective, it is, thus, a major concern that high emission cars, in particular SUVs, and trucks and even partly unregulated vehicles continue to be put on the market. Given that every car and truck produced and sold today remains a source of air pollution for some 1-2 decades, future generations will have to pay the price for today's production and marketing of high emission vehicles. Given the lasting adverse health effects, and the availability of low to zero emission technologies, regulators need to set ambitious pro-active policies leading to a rigorous change in the fleet of new vehicles. Current policies in California and the U.S. give limited guidance and weak incentives to make choices that protect clean air, thus public health. The dominant role of sport utility vehicles exemplifies the problem of production, marketing and choices if the value of health is ignored in policies (U.S. Environmental Protection Agency 1999). Despite the enormous economic consequences of air pollution-related health effects, the large differences in emissions (and fuel economy) across different types of vehicles is not reflected in the costs of cars nor the vehicle taxes. In fact, the current California vehicle fee is based on the price of the vehicle rather than any health or environmental concerns; given that new (cleaner) technologies tend to be more expensive upon initial introduction to the market, the current tax system favors choices that do not reduce pollution. This paradox should be resolved in future policy making, with clean air and good health receiving higher priority.

Policies that promote the rapid development and implementation of very low or zero emission vehicles, combined with strong incentives such as emission related taxes, road tolls and fuel prices that would cover all direct and indirect costs of traffic (including the costs related to health damage), could strongly influence consumer choice (Schipper et al. 2000; Organisation for Economic Cooperation and Development 2002).

7.1.3. Air Quality to be Improved, Not Just Maintained

We also emphasize that results from the CHS highlight the need for further improvements in air quality. In other words, policies that just *maintain* the current air quality are not sufficient as current levels have a substantial health toll on children and adults. The population growth, which is expected to be very large in the next 10-20 years in California, has to be considered; thus,

drastic changes in emissions will be required to improve air quality. It has been confirmed nationally that the health and social benefits of enforcing tough new clean-air regulations during the past decade were five to seven times greater then the costs of complying with the rules, although various health effects of air pollution were not yet included in this assessment, such as school absences (see above) (Office of Management and Budget 2003). These estimates impressively demonstrate that clean air regulation is not a luxury but a path to prevent adverse health effects in the population in times of good economy, and the appropriate choice to support both economic and health prosperity.

7.1.4. Local or Regional Regulations

The CHS provides the strongest evidence for effects of the air pollution mixtures as observed in the South Coast Air Basin. The uncertainties in the extrapolation of findings beyond the region generally increase as a function of differences in characteristics of populations and air pollution. Furthermore, regulatory choices may have different efficiencies in different regions of the country. Given the dominant role of vehicle emissions, ports and airports in the Southern California region, the local topography trapping airsheds, and the predicted 50% growth of the population in the L.A. region, it is very important to consider, defend, and implement regulatory strategies with the most promising local and regional effects. The State of California has funded the CHS and other studies that clearly indicate the need for sustained clean air regulation and innovative new approaches to tackle future challenges of vehicle-related pollution. It is, thus, a public health need to have full regulatory authority to implement, on a local level, those policies that bring the most benefit to California. The California setting may call for decisions that may differ from the needs in other regions of the U.S. Thus, discussions in other states or on the federal level should not impact decisions made to protect the health of Californians. Stalled or failed Federal policies (e.g., delays due to prolonged legal challenges to new air quality standards, long phase-in periods for cleaner diesel engines, exemptions and delays in holding sports utility vehicles and other larger vehicles such as trucks, ships or school buses to the same standards as smaller cars, etc.) are a major threat to sustained health of the California people.

7.2. Secondary Strategies: Reduce Exposure or Susceptibility

Even with the most aggressive efforts to reduce emissions, the current generation of children in California will suffer adverse health effects from air pollution. Thus, policies to reduce children's current exposure to air pollution should be considered. The CHS gives some guidance to this discussion but other studies need to be taken into account.

Examples that merit further discussion include the following:

- In high pollution communities, air conditioning or filtration in schools would reduce indoor exposure to outdoor pollutants, especially ozone (Avol et al. 1998a). The impact of such strategies on total exposure may be estimated to guide decisions about the effectiveness of local investments.
- With the increasing evidence suggesting that fresh traffic exhaust is hazardous, independent of background concentrations (Brunekreef et al. 1997; van Vliet et al. 1997; McConnell et al. 2002b), prudent policy would dictate that new schools, daycare centers, parks and sports fields should not be sited adjacent to high traffic roads. The re-siting of schools or changes in traffic regimens around schools with exceptionally high levels of emissions might be

considered. As shown, primary exhaust emissions reach extremely high levels in the first 50-100 meters along busy highways (Zhu et al. 2002b), thus schools along highways require particular attention.

- Children with asthma are a susceptible group. A task force involving health care professionals and air quality regulators could develop clinical guidelines for the care of asthmatic children. These guidelines should include recommendations on how to reduce exposure to ambient air pollution. This is an important public health issue, as several CHS communities have asthma prevalence rates greater than 20% and a high incidence of new onset asthma in school children (McConnell et al. 2002b). Interdisciplinary collaboration will be essential given the complex interrelation of various individual and environmental factors affecting asthmatics.
- On high pollution days, warnings are issued to schools recommending that children to reduce outdoor exercise. Review of the action levels to trigger such warnings might be appropriate. Pollution levels can be forecast up to 5 days in advance in many urban areas, and these forecasts could be used to improve compliance with existing recommendations.
- Evidence is increasing that antioxidant intake protects children from acute oxidative damage from air pollution exposure (Gilliland et al. 2001a; Bowler and Crapo 2002; Romieu et al. 2002). Consideration should be given to Vitamin C supplementation in schools in high oxidant areas.

7.3. Tensions Between Emission Reduction and Exposure Reduction Strategies

In the long term, secondary reduction strategies are limited and, in some cases, may even increase other public health risks. Thus, it is important to keep the regulatory focus on primary strategies. We provide a few examples of potential health conflicts between primary and secondary strategies.

- The CHS gives an important example of such a policy conflict. The asthma incidence study suggests that outdoor physical activity may pose an asthma risk in high ozone communities. Policies against physical activity are, however, in strong conflict with the need for promotion of physical activity in an increasingly sedentary population. Limiting exercise on high pollution days to reduce the dose of pollutants to the lungs may increase the risk of diseases associated with the increasingly sedentary lifestyle of children (Kahn et al. 2002).
- Walking to school – a physically active healthy alternative to driving with a parent – may increase children's exposure, unless walking routes and traffic patterns around schools are considered (Chan et al. 2002; Gulliver 2002).
- Air-conditioning in schools would increase energy consumption and emissions from power plants elsewhere. Furthermore, air-conditioning may contribute to other health problems, such as sick building syndrome (Wargocki et al. 2002).
- Although promoting dietary antioxidant supplements like Vitamin C or E may be a promising intervention, there is some evidence that Vitamin C may act as a pro-oxidant (Podmore et al. 1998), and further evaluation of such an intervention is required before programs could be implemented.

- Individual decisions to move to more distant, seemingly less polluted suburban areas, may result in net increased emissions if commuting time increases (Frumkin 2002). In rapidly developing metropolitan areas, clean air regulators should closely collaborate with urban planners to prevent planning decisions that lead to increased emissions.

In summary, in the long-term, secondary strategies will fail to protect the public's health, unless they are complementary to emission reduction strategies (Bates and Caton 2002; California Air Resources Board 2002b; Organisation for Economic Cooperation and Development 2002). Despite many open scientific questions and some uncertainties in interpreting the CHS findings, this study, funded by the State of California, has provided important input for clean air regulations that will help improve and protect the health of the people in California.

8. References

Abbey , D., N. Nishino, W. McDonnel , R. Burchette , S. Knutsen, W. Beeson and J. Yang (1999). "Long-Term Inhalable Particles and Other Air Pollutants Related to Mortality in Nonsmokers." Am J Respir Crit Care Med **159**: 373-382.

Abbey, D. E., P. K. Mills, F. F. Petersen and W. L. Beeson (1991). "Long-term ambient concentrations of total suspended particulates and oxidants as related to incidence of chronic disease in California Seventh-Day Adventists." Environmental Health Perspectives **94**: 43-50.

Abbey, D. E., B. E. Ostro, F. Petersen and R. J. Burchette (1995). "Chronic respiratory symptoms associated with estimated long-term ambient concentrations of fine particulates less than 2.5 microns in aerodynamic diameter (PM2.5) and other air pollutants." J Expo Anal Environ Epidemiol **5**(2): 137-59.

Ackermann-Liebrich, U., P. Leuenberger, J. Schwartz, C. Schindler, C. Monn, G. Bolognini, J. P. Bongard, O. Brandli, G. Domenighetti, S. Elsasser, L. Grize, W. Karrer, R. Keller, H. Keller-Wossidlo, N. Kunzli, B. W. Martin, T. C. Medici, A. P. Perruchoud, M. H. Schoni, J. M. Tschopp, B. Villiger, B. Wuthrich, J. P. Zellweger and E. Zemp (1997). "Lung function and long term exposure to air pollutants in Switzerland. Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) Team." Am J Respir Crit Care Med **155**(1): 122-9.

Allen, G., C. Sioutas, P. Koutrakis, R. Reiss, F. W. Lurmann and P. T. Roberts (1997). "Evaluation of the TEOM method for measurement of ambient particulate mass in urban areas." J Air Waste Manag Assoc **47**(6): 682-9.

Almon, S. (1965). "The distributed lag between capital appropriations and expenditures." Econometrica **33**: 178-196.

Anonymous (1996). "Health effects of outdoor air pollution. Part 2. Committee of the Environmental and Occupational Health Assembly of the American Thoracic Society." American Journal of Respiratory & Critical Care Medicine **153**(2): 477-98.

Ashley, F., W. B. Kannel, P. D. Sorlie and R. Masson (1975). "Pulmonary function: relation to aging, cigarette habit, and mortality." Ann Intern Med **82**(6): 739-45.

Avol, E. L., W. J. Gauderman, S. M. Tan, S. J. London and J. M. Peters (2001). "Respiratory effects of relocating to areas of differing air pollution levels." Am J Respir Crit Care Med **164**(11): 2067-72.

Avol, E. L., W. C. Navidi and S. D. Colome (1998a). "Modeling ozone levels in and around Southern California homes." Environ Sci Tech **32**: 463-468.

Avol, E. L., W. C. Navidi, E. B. Rappaport and J. M. Peters (1998b). "Acute effects of ambient ozone on asthmatic, wheezy, and healthy children." Res Rep Health Eff Inst(82): iii, 1-18; discussion 19-30.

Baldi, I., J. F. Tessier, F. Kauffmann, H. Jacqmin-Gadda, C. Nejjari and R. Salamon (1999). "Prevalence of asthma and mean levels of air pollution: results from the French PAARC survey. Pollution Atomospherique et Affections Respiratoires Chroniques." Eur Respir J **14**(1): 132-8.

Bascom, R. (1996). "Environmental factors and respiratory hypersensitivity: the Americas." Toxicol Lett **86**(2-3): 115-30.

Bascom, R., P. Bromberg, D. Costa, R. Devlin, D. Dockery, M. Frampton, W. Lambert, J. Samet, F. Speizer and M. Utell (1996). "Health effects of outdoor air pollution." Am J Crit Care Med **153**: 3-50.

Bascom, R., R. M. Naclerio, T. K. Fitzgerald, A. Kagey-Sobotka and D. Proud (1990). "Effect of ozone inhalation on the response to nasal challenge with antigen of allergic subjects." Am Rev Respir Dis **142**(3): 594-601.

Bates, D. (1995a). "Effects of air pollution on children." Environmental Health Perspectives **103**(Suppl 6): 49-53.

Bates, D. V. (1995b). "Observations on asthma." Environ Health Perspect **103 Suppl 6**: 243-7.

Bates, D. V. and R. B. Caton (2002). A Citizen's Guide to Air Pollution. Vancouver, BC, David Suzuki Foundation.

Beaty, T., B. Cohen, C. Newill, H. Menkes, E. Diamond and C. Chen (1982). "Impaired pulmonary functions as a risk factor for mortality." Am J Epidemiol **116**(1): 102-13.

Becklake, M. R. and P. Ernst (1997). "Environmental factors." Lancet **350 Suppl 2**: SII10-3.

Benson, P. (1989). CALINE4--A dispersion model for predicting air pollutant concentrations near roadways.

Berhane, K. (2002). Functional based multi-level models for longitudinal data (6 pages of CD ROM). Proceedings of Joint Statistical Meetings, New York, August 2002.

Berhane, K. (in preparation-a). "8-year data analysis of sex-specific effects of asthma on lung function in children."

Berhane, K. (in preparation-b). "A Bayesian approach to functional-based multi-level modeling of longitudinal data: With applications to environmental epidemiology."

Berhane, K., W. J. Gauderman, D. O. Stram and D. C. Thomas (in press). "Statistical issues in studies of the long term effects of air pollution: the Southern California Children's Health Study." Statistical Science.

Berhane, K., R. McConnell, F. Gilliland, T. Islam, W. James Gauderman, E. Avol, S. J. London, E. Rappaport, H. G. Margolis and J. M. Peters (2000). "Sex-specific effects of asthma on pulmonary function in children." American Journal of Respiratory & Critical Care Medicine **162**(5): 1723-30.

Berhane, K. and D. C. Thomas (2000). "Discussion on "Combining evidence on air pollution and daily mortality from the 20 largest US cities: a hierarchical modeling strategy."" J Royal Statist Soc, Series A **163**(3): 263-302.

Berhane, K. and D. C. Thomas (2002). "A two-stage model for multiple time series data of counts." Biostatistics **3**(1): 21-32.

Birch, M. E. and R. A. Carey (1996). "Elemental carbon-based method for monitoring occupational exposures to diesel exhaust." Aerosol Science and Technology **25**: 221-241.

Bonvallot, V., A. Baeza-Squiban, A. Baulig, S. Brulant, S. Boland, F. Muzeau, R. Barouki and F. Marano (2001). "Organic compounds from diesel exhaust particles elicit a proinflammatory response in human airway epithelial cells and induce cytochrome p450 1A1 expression." Am J Respir Cell Mol Biol **25**(4): 515-21.

Bowers, K. and C. Taylor (2000). Quality Assurance Program Plan. Epidemiologic Investigation to Identify Chronic Health Effects of Ambient Air Pollutants in Southern California (Phase III- Longitudinal Study). Part IIa. Air Quality Measurements. Sacramento, CA, Air Resources Board.

Bowler, R. P. and J. D. Crapo (2002). "Oxidative stress in allergic respiratory diseases." J Allergy Clin Immunol **110**(3): 349-56.

Brauer, M., G. Hoek, P. Van Vliet, K. Meliefste, P. H. Fischer, A. Wijga, L. P. Koopman, H. J. Neijens, J. Gerritsen, M. Kerkhof, J. Heinrich, T. Bellander and B. Brunekreef (2002). "Air pollution from traffic and the development of respiratory infections and asthmatic and allergic symptoms in children." Am J Respir Crit Care Med **166**(8): 1092-8.

Braun-Fahrländer, C., U. Ackermann-Liebrich, J. Schwartz, P. Gnehm, M. Rutishauser and H. Wanner (1992). "Air pollution and respiratory symptoms in preschool children." Am Rev Respir Dis **145**: 42-7.

Braun-Fahrlander, C., J. C. Vuille, F. H. Sennhauser, U. Neu, T. Kunzle, L. Grize, M. Gassner, C. Minder, C. Schindler, H. S. Varonier and B. Wuthrich (1997). "Respiratory health and long-term exposure to air pollutants in Swiss schoolchildren. SCARPOL Team. Swiss Study on Childhood Allergy and Respiratory Symptoms with Respect to Air Pollution, Climate and Pollen." American Journal of Respiratory & Critical Care Medicine **155**(3): 1042-9.

Breslow, N. E. and D. G. Clayton (1993). "Approximate inference in generalized linear mixed models." J Am Stat Assoc **88**: 9-25.

Brunekreef, B. and S. T. Holgate (2002). "Air pollution and health." Lancet **360**(9341): 1233-42.

Brunekreef, B., N. A. Janssen, J. de Hartog, H. Harssema, M. Knape and P. van Vliet (1997). "Air pollution from truck traffic and lung function in children living near motorways." Epidemiology **8**(3): 298-303.

Burke, J. M., M. J. Zufall and H. Ozkaynak (2001). "A population exposure model for particulate matter: case study results for PM2.5 in Philadelphia, PA." Journal of Exposure Analysis and Environmental Epidemiology **11**: 470-489.

Bush, D. H. and C. A. Taylor (1999). "Quality assurance for the Southern California Children's Health Study." Paper #99-387, presented at the Annual Meeting of the Air and Waste Management Association, June 21-24, 1999, St. Louis, Missouri.

Cadle, S. H., P. A. Mulawa, E. C. Hunsanger, K. Nelson, R. A. Ragazzi, R. Barrett, G. L. Gallagher, D. R. Lawson, K. T. Knapp and R. Snow (1999). "Composition of light-duty motor vehicle exhaust particulate matter in the Denver, Colorado area." Environmental Science & Technology **33**: 2328-2339.

California Air Resources Board (1979). California annual air quality summary report.

California Air Resources Board (2002a). The 2001 California almanac of emissions and air quality. Sacramento, CA, California Environmental Protection Agency.

California Air Resources Board (2002b). Public hearing to consider amendments to the ambient air quality standards for particulate matter and sulfates. Sacramento, CA, Air Resources Board, California Environmental Protection Agency**:** 585.

Carlin, B. P. and T. A. Louis (1996). Bayes and Empirical Bayes Methods for Data Analysis. London, Chapman and Hall/CRC.

Casillas, A. M., T. Hiura, N. Li and A. E. Nel (1999). "Enhancement of allergic inflammation by diesel exhaust particles: permissive role of reactive oxygen species." Ann Allergy Asthma Immunol **83**(6 Pt 2): 624-9.

Celano, M. and R. Geller (1993). "Learning, school performance, and children with asthma: how much at risk?" J of Learning Disabil **26**(1): 23-32.

Chan, C.-C., H. Ozkaynak, J. Spengler and L. Sheldon (1991). "Driver exposure to volatile organic compounds, CO, ozone, and NO_2 under different driving conditions." Environmental Science and Technology **25**: 964-972.

Chan, L. Y., W. L. Lau, S. C. Zou, Z. X. Cao and S. C. Lai (2002). "Exposure level of carbon monoxide and respirable suspended particulate in public transportation modes while commuting in urban area of Guangzhou, China." Atmospheric Environment **36**: 5831-5840.

Chauhan, A. J., C. H. Linaker, H. Inskip, S. Smith, J. Schreiber, S. L. Johnston and S. T. Holgate (1999). "Personal exposure to nitrogen dioxide (NO2) and the risk of virus related asthma morbidity in children." American Journal of Respiratory & Critical Care Medicine **159**(3): A699.

Chinkin, L. R., D. L. Coe, T. H. Funk, H. R. Hafner, P. T. Roberts, P. A. Ryan and D. R. Lawson (2003). "Weekday versus weekend activity patterns for ozone precursor emissions in California's South Coast Air Basin." Journal of the Air & Waste Management Association **53**: 829-843.

Chinkin, L. R., H. H. Main and P. T. Roberts (2002). Weekday/weekend ozone observations in the South Coast Air Basin Volume III: Analysis of summer 2000 field measurements and supporting data.

Ciccone, G., F. Forastiere, N. Agabiti, A. Biggeri, L. Bisanti and E. Chellini (1998). "Road traffic and adverse respiratory effects in children." Occupational & Environmental Medicine **55**: 771-778.

Cisternas, M. G., P. D. Blanc, I. H. Yen, P. P. Katz, G. Earnest, M. D. Eisner, S. Shiboski and E. H. Yelin (2003). "A comprehensive study of the direct and indirect costs of adult asthma." J Allergy Clin Immunol **111**(6): 1212-8.

Clark, N. M., R. W. Brown, E. Parker, T. G. Robins, D. G. Remick, Jr., M. A. Philbert, G. J. Keeler and B. A. Israel (1999). "Childhood Asthma." Environ Health Perspect **107 Suppl 3**: 421-429.

Colome, S. D., A. L. Wilson, E. W. Becker, S. J. Cunningham and P. E. Baker (1989). Analysis of factors associated with indoor residential nitrogen dioxide: multivariate regression results. Indoor Air '87. Proceedings of the 4th International Conference on Indoor Air Quality and Climate, Federal Republic of Germany: Institute for Water, Soil and Air Hygiene, August, Berlin, Germany.

Colome, S. D., A. L. Wilson and Y. Tian (1994). California Residental Indoor Air Quality Study, Volume 2: Carbon monoxide and air exchange rate: a univariate and multivariate analysis.

Cortessis, V. and D. C. Thomas (2004). Toxicokinetic genetics: An approach to gene-environment and gene-gene interactions in complex metabolic pathways. Mechanistic Considerations in the Molecular Epidemiology of Cancer. P. Bird, P. Boffeta, P. Buffler and J. Rice. Lyon, IARC Scientific Publications. **57:** 127-150.

Daniels, M. J., F. Dominici, J. M. Samet and S. L. Zeger (2000). "Estimating particulate matter-mortality dose-response curves and threshold levels: an analysis of daily time-series for the 20 largest US cities." Am J Epidemiol **152**(5): 397-406.

DeBoor, C. (1974). A Practical Guide to Splines. New York, Springer-Verlag.

Delfino, R. J., B. D. Coate, R. S. Zeiger, J. M. Seltzer, D. H. Street and P. Koutrakis (1996). "Daily asthma severity in relation to personal ozone exposure and outdoor fungal spores." Am J Respir Crit Care Med **154**(3 Pt 1): 633-41.

Delfino, R. J., R. S. Zeiger, J. M. Seltzer and D. H. Street (1998). "Symptoms in pediatric asthmatics and air pollution: differences in effects by symptom severity, anti-

inflammatory medication use and particulate averaging time." Environ Health Perspect **106**(11): 751-61.
Detels, R., D. P. Tashkin, J. W. Sayre, S. N. Rokaw, A. H. Coulson, F. J. Massey, Jr. and D. H. Wegman (1987). "The UCLA population studies of chronic obstructive respiratory disease. 9. Lung function changes associated with chronic exposure to photochemical oxidants; a cohort study among never-smokers." Chest **92**(4): 594-603.
Diaz-Sanchez, D., A. R. Dotson, H. Takenaka and A. Saxon (1994). "Diesel exhaust particles induce local IgE production in vivo and alter the pattern of IgE messenger RNA isoforms." J Clin Invest **94**(4): 1417-25.
Diaz-Sanchez, D., M. Penichet-Garcia and A. Saxon (2000). "Diesel exhaust particles directly induce activated mast cells to degranulate and increase histamine levels and symptom severity." J Allergy Clin Immunol **106**(6): 1140-6.
Diggle, P. J., K. Y. Liang and S. L. Zeger (1994). Analysis of Longitudinal Data. New York, Oxford University Press.
Dockery, D., J. Cunningham, A. Damokosh, L. Neas, J. Spengler, P. Koutrakis, J. Ware, M. Raizenne and S. FE (1996). "Health Effects of acid aerosols on North American Children: respiratory symptoms." Env Health Perspect **104**: 500-505.
Dockery, D. W., A. C. d. Pope, X. Xu, J. D. Spengler, J. H. Ware, M. E. Fay, B. G. Ferris, Jr. and F. E. Speizer (1993). "An association between air pollution and mortality in six U.S. cities." N Engl J Med **329**(24): 1753-9.
Dockery, D. W., F. E. Speizer, D. O. Stram, J. H. Ware, J. D. Spengler and B. G. Ferris, Jr. (1989). "Effects of inhalable particles on respiratory health of children." American Review of Respiratory Disease **139**(3): 587-94.
Drye, E. E., H. Ozkaynak, B. Burbank, I. H. Billick, J. D. Spengler, P. B. Ryan, P. E. Baker and S. D. Colome (1989). "Development of models for predicting the distribution if indoor nitrogen dioxide concentrations." Journal of the Air Pollution Control Association **39**: 169-177.
Duan, N. (1982). "Models for human exposure to air pollution." Environment International **8**: 305-309.
Duhme, H., S. Weiland, U. Keil, B. Kraemer, M. Schmid, M. Stender and L. Chambless (1996). "The association between self-reported symptoms of asthma and allergic rhinitis and self-reported traffic density on street residence in adolescents." Epidemiology **7**: 578-582.
Edwards, J., S. Walters and R. K. Griffiths (1994). "Hospital admissions for asthma in preschool children: relationship to major roads in Birmingham, United Kingdom." Archives of Environmental Health **49**(4): 223-7.
Eiguren-Fernandez, A., A. H. Miguel, J. R. Froines, S. Thurairatnam and E. L. Avol (in press 2004). "Seasonal and spatial variation of polycyclic aromatic hydrocarbons in vapor-phase and $PM_{2.5}$ in Southern California urban and rural communities." Aerosol Sci & Technol.
English, P., R. Neutra, R. Scalf, M. Sullivan, L. Waller and L. Zhu (1999). "Examining associations between childhood asthma and traffic flow using a geographic information system." Environ Health Perspect **107**: 761-767.
Enright, P. L., W. S. Linn, E. L. Avol, H. G. Margolis, H. Gong, Jr. and J. M. Peters (2000). "Quality of spirometry test performance in children and adolescents : experience in a large field study." Chest **118**(3): 665-71.

Fitz, D. R. and C. Bufalino (2002). Measurement of PM_{10} emission factors from Paved Roads using on-board particle sensors. U.S. Environmental Protection Agency's 11th Annual Emission Inventory Conference, Emission Inventories--Partnering for the Future.

Fitz, D. R., A. M. Winer and S. Colome (2003). Characterizing the range of children's pollutant exposure during school bus commutes.

Folinsbee, L. J., W. F. McDonnell and D. H. Horstman (1988). "Pulmonary function and symptom responses after 6.6-hour exposure to 0.12 ppm ozone with moderate exercise." Japca **38**(1): 28-35.

Frischer, T., M. Studnicka, C. Gartner, E. Tauber, F. Horak, A. Veiter, J. Spengler, J. Kuhr and R. Urbanek (1999). "Lung function growth and ambient ozone: a three-year population study in school children." Am J Respir Crit Care Med **160**(2): 390-6.

Fruin, S. (2003). Characterizing black carbon inside vehicles: implications for refined exposure assessments for diesel exhausparticulate matter. Los Angeles, CA, University of California at Los Angeles.

Frumkin, H. (2002). "Urban sprawl and public health." Public Health Rep **117**(3): 201-17.

Frye, C., B. Hoelscher, J. Cyrys, M. Wjst, H. E. Wichmann and J. Heinrich (2003). "Association of lung function with declining ambient air pollution." Environ Health Perspect **111**(3): 383-8.

Fuhlbrigge, A. L., R. J. Adams, T. W. Guilbert, E. Grant, P. Lozano, S. L. Janson, F. Martinez, K. B. Weiss and S. T. Weiss (2002). "The burden of asthma in the United States: level and distribution are dependent on interpretation of the national asthma education and prevention program guidelines." Am J Respir Crit Care Med **166**(8): 1044-9.

Garza, V., P. Graney, D. Sperling, D. Niemeier, D. Eisinger, T. Kear and D. Chang (1997). Transportation project-level carbon monoxide protocol revised.

Gauderman, W. J., E. Avol, F. Gilliland, H. Vora, D. Thomas, K. Berhane, R. McConnell, N. Kuenzli, F. Lurmann, E. Rappaport, H. Margolis and D. Bates (in review). "The effect of air pollution on lung function development in children aged 10 to 18 years." N Engl J Med.

Gauderman, W. J., G. F. Gilliland, H. Vora, E. Avol, D. Stram, R. McConnell, D. Thomas, F. Lurmann, H. G. Margolis, E. B. Rappaport, K. Berhane and J. M. Peters (2002). "Association between air pollution and lung function growth in southern California children: results from a second cohort." Am J Respir Crit Care Med **166**(1): 76-84.

Gauderman, W. J., R. McConnell, F. Gilliland, S. London, D. Thomas, E. Avol, H. Vora, K. Berhane, E. B. Rappaport, F. Lurmann, H. G. Margolis and J. Peters (2000). "Association between air pollution and lung function growth in southern California children." American Journal of Respiratory & Critical Care Medicine **162**(4 Pt 1): 1383-90.

Gehring, U., J. Cyrys, G. Sedlmeir, B. Brunekreef, T. Bellander, P. Fischer, C. P. Bauer, D. Reinhardt, H. E. Wichmann and J. Heinrich (2002). "Traffic-related air pollution and respiratory health during the first 2 yrs of life." Eur Respir J **19**(4): 690-8.

Gent, J. T., EW; Holford, TR; Belanger,K;Bracken, M;Beckett,WS;Leaderer,BP; (2003). "Association of low-level ozone and fine particles with respiratory symptoms in children with asthma." J Am Med Assoc **290**(14): 1859-67.

George, E. I. and D. P. Foster (2000). "Calibration and empirical Bayes variable selection." Biometrika **87**: 731-747.

Gillies, J. A. and A. W. Gertler (2000). "Comparison and evaluation of chemically speciated mobile source PM2.5 particulate matter profiles." Journal of Air and Waste Management Association **50**: 1459-1480.

Gilliland, F., Y. Li and J. Peters (2001a). "Effects of Vitamin A, C, and E intake on children's lung function." Am J Respir Crit Care Med **163**: A37.

Gilliland, F. D., K. Berhane, T. Islam, R. McConnell, W. J. Gauderman, S. S. Gilliland, E. Avol and J. M. Peters (2003a). "Obesity and the risk of newly diagnosed asthma in school-age children." Am J Epidemiol **158**(5): 406-15.

Gilliland, F. D., K. Berhane, T. Islam, M. Wenten, E. Rappaport, E. Avol, W. J. Gauderman, R. McConnell and J. M. Peters (2003b). "Environmental tobacco smoke and absenteeism related to respiratory illness in schoolchildren." Am J Epidemiol **157**(10): 861-9.

Gilliland, F. D., K. Berhane, Y. F. Li, E. B. Rappaport and J. M. Peters (2003c). "Effects of early onset asthma and in utero exposure to maternal smoking on childhood lung function." Am J Respir Crit Care Med **167**(6): 917-24.

Gilliland, F. D., K. Berhane, R. McConnell, W. J. Gauderman, H. Vora, E. B. Rappaport, E. Avol and J. M. Peters (2000). "Maternal smoking during pregnancy, environmental tobacco smoke exposure and childhood lung function." Thorax **55**(4): 271-6.

Gilliland, F. D., K. Berhane, E. B. Rappaport, D. C. Thomas, E. Avol, W. J. Gauderman, S. J. London, H. G. Margolis, R. McConnell, K. T. Islam and J. M. Peters (2001b). "The effects of ambient air pollution on school absenteeism due to respiratory illnesses." Epidemiology **12**(1): 43-54.

Gilliland, F. D., K. T. Berhane, Y. F. Li, W. J. Gauderman, R. McConnell and J. Peters (2003d). "Children's Lung Function and Antioxidant Vitamin, Fruit, Juice, and Vegetable Intake." Am J Epidemiol **158**(6): 576-84.

Gilliland, F. D., K. T. Berhane, Y. F. Li, D. H. Kim and H. G. Margolis (2002a). "Dietary magnesium, potassium, sodium, and children's lung function." Am J Epidemiol **155**(2): 125-31.

Gilliland, F. D., W. J. Gauderman, H. Vora, E. Rappaport and L. Dubeau (2002b). "Effects of glutathione-S-transferase M1, T1, and P1 on childhood lung function growth." Am J Respir Crit Care Med **166**(5): 710-6.

Gilliland, F. D., Y. F. Li, L. Dubeau, K. Berhane, E. Avol, R. McConnell, W. J. Gauderman and J. M. Peters (2002c). "Effects of glutathione S-transferase M1, maternal smoking during pregnancy, and environmental tobacco smoke on asthma and wheezing in children." Am J Respir Crit Care Med **166**(4): 457-63.

Gilliland, F. D., Y.-F. Li, L. Dubeau and J. M. Peters (2002d). "Effects of GSTM1, in utero maternal smoking and ETS exposure on asthma and wheezing in children." Am J Resp Crit Care Med **165**(8): A660.

Gilliland, F. D., Y. F. Li and J. M. Peters (2001c). "Effects of maternal smoking during pregnancy and environmental tobacco smoke on asthma and wheezing in children." American Journal of Respiratory & Critical Care Medicine **163**(2): 429-36.

Gilliland, F. D., Y.-F. Li and J. M. Peters (2001d). "Effects of low vitamins A, E, and C intake on children's lung function." Am J Respir Crit Care Med **163**(5): A37.

Gilliland, F. D., Y.-F. Li, W. Tsai and L. Dubeau (2003e). "GSTP1 and GSTM1 contribute to susceptibility for asthma and wheezing following in utero exposure to tobacco smoke." Am J Resp Crit Care Med **167**(7): A942.

Gilliland, F. D., Y.-F. Li, W. Tsai, L. Dubeau, E. Avol and J. M. Peters (2003f). "TNF[a] - 308 genotype and ozone effects on asthma and wheezing: Results from the Children's Health Study (CHS)." Am J Resp Crit Care Med **167**(7): A580.

Gilliland, F. D., W. Linn, E. Rappaport, E. Avol, H. Gong and J. Peters (1999a). "Effect of spirometer temperature on FEV1 in a longitudinal epidemiological study." Occupational & Environmental Medicine **56**(10): 718-20.

Gilliland, F. D., R. McConnell, J. Peters and H. Gong, Jr. (1999b). "A theoretical basis for investigating ambient air pollution and children's respiratory health." Environ Health Perspect **107 Suppl 3**: 403-7.

Gilliland, F. D., E. B. Rappaport, K. Berhane, T. Islam, L. Dubeau, W. J. Gauderman and R. McConnell (2002e). "Effects of glutathione S-transferase P1, M1, and T1 on acute respiratory illness in school children." Am J Respir Crit Care Med **166**(3): 346-51.

Grosjean, D. and S. S. Parmar (1990). "Interferences from aldehydes and peroxyacetyl nitrate when sampling urban air organic acids on alkaline traps." Environmental Science & Technology **24**: 1021-1026.

Gulliver, J. (2002). Space-time modelling of exposure to air pollution using GIS. Epidemiology. Northampton, UK, University of Leicester**:** 238.

Guo, Y. L., Y. C. Lin, F. C. Sung, S. L. Huang, Y. C. Ko, J. S. Lai, H. J. Su, C. K. Shaw, R. S. Lin and D. W. Dockery (1999). "Climate, traffic-related air pollutants, and asthma prevalence in middle-school children in taiwan." Environ Health Perspect **107**(12): 1001-6.

Hall, J. V., V. Brajer, F. Lurmann and J. Wu (2002). Economic Valuation of Ozone-Related School Absences in the South Coast Air Basin. Sacramento, CA, California Air Resources Board and South Coast Air Quality Management District**:** 1-39.

Hashimoto, K., Y. Ishii, Y. Uchida, T. Kimura, K. Masuyama, Y. Morishima, K. Hirano, A. Nomura, T. Sakamoto, H. Takano, M. Sagai and K. Sekizawa (2001). "Exposure to diesel exhaust exacerbates allergen-induced airway responses in guinea pigs." Am J Respir Crit Care Med **164**(10 Pt 1): 1957-63.

Hastie, T. and R. Tibshirani (2000). "Bayesian Backfitting (with discussion)." Stat Science **15**(3): 196-223.

Heagerty, P. and S. L. Zeger (2000). "Marginalized multilevel models and likelihood inference." Statistical Science **15**: 1-26.

Heinrich, J., B. Hoelscher, C. Frye, I. Meyer, M. Pitz, J. Cyrys, M. Wjst, L. Neas and H. E. Wichmann (2002). "Improved air quality in reunified Germany and decreases in respiratory symptoms." Epidemiology **13**(4): 394-401.

Heinrich, J., B. Hoelscher and H. E. Wichmann (2000). "Decline of ambient air pollution and respiratory symptoms in children." Am J Respir Crit Care Med **161**(6): 1930-6.

Hering, S. V., C. A. Taylor, Jr. and K. Anderson (1994). Design and implementation of a two-week sampler for fine particle ions and gaseous acids. Fourth International Aerosol Conference, Los Angeles, CA.

Hertzberg, V. S., K. D. Rosenman, M. J. Reilly and C. H. Rice (2002). "Effect of occupational silica exposure on pulmonary function." Chest **122**(2): 721-8.

Hirsch, T., S. K. Weiland, E. von Mutius, A. F. Safeca, H. Grafe, E. Csaplovics, H. Duhme, U. Keil and W. Leupold (1999). "Inner city air pollution and respiratory health and atopy in children." Eur Respir J **14**(3): 669-77.

Hiura, T. S., M. P. Kaszubowski, N. Li and A. E. Nel (1999). "Chemicals in diesel exhaust particles generate reactive oxygen radicals and induce apoptosis in macrophages." J Immunol **163**(10): 5582-91.

Hoek, G., B. Brunekreef, S. Goldbohm, P. Fischer and P. A. van den Brandt (2002). "Association between mortality and indicators of traffic-related air pollution in the Netherlands: a cohort study." Lancet **360**(9341): 1203-9.

Horstman, D. H., L. J. Folinsbee, P. J. Ives, S. Abdul-Salaam and W. F. McDonnell (1990). "Ozone concentration and pulmonary response relationships for 6.6-hour exposures with five hours of moderate exercise to 0.08, 0.10, and 0.12 ppm." Am Rev Respir Dis **142**(5): 1158-63.

Ihorst, G., T. Frischer, F. J. Horak, M. Schumacher, M. Kopp, J. Forster, J. Mattes and J. Kuehr (2004). "Long- and medium-term ozone effects on lung growth including a broad spectrum of exposure." Eur Respir J **23**(2): 292-99.

Jedrychowski, W. and E. Flak (1998). "Effects of air quality on chronic respiratory symptoms adjusted for allergy among preadolescent children." Eur Respir J **11**(6): 1312-8.

Jedrychowski, W., E. Flak and E. Mroz (1999). "The adverse effect of low levels of ambient air pollutants on lung function growth in preadolescent children." Environ Health Perspect **107**(8): 669-74.

Jenkins, H. S., J. L. Devalia, R. L. Mister, A. M. Bevan, C. Rusznak and R. J. Davies (1999). "The effect of exposure to ozone and nitrogen dioxide on the airway response of atopic asthmatics to inhaled allergen: dose- and time- dependent effects." Am J Respir Crit Care Med **160**(1): 33-9.

Kahn, E. B., L. T. Ramsey, R. C. Brownson, G. W. Heath, E. H. Howze, K. E. Powell, E. J. Stone, M. W. Rajab and P. Corso (2002). "The effectiveness of interventions to increase physical activity. A systematic review." Am J Prev Med **22**(4 Suppl): 73-107.

Kass, R. and A. Raftery (1995). "Bayes factors." J Am Statist Assoc **90**: 773-95.

Katsouyanni , K., G. Touloumi and C. Spix (1997). "Short-term effects of ambient sulphur dioxide and particulate matter on mortality in 12 European cities: results from times series data from the APHEA project." Br Med J **314**: 1658-1663.

Kehrl, H. R., D. B. Peden, B. Ball, L. J. Folinsbee and D. Horstman (1999). "Increased specific airway reactivity of persons with mild allergic asthma after 7.6 hours of exposure to 0.16 ppm ozone." J Allergy Clin Immunol **104**(6): 1198-204.

Koontz, M., W. C. Evans and C. R. Wilkes (1998). Development of a model for assessing indoor exposure to air pollutants.

Koren, H. S. (1995). "Associations between criteria air pollutants and asthma." Environmental Health Perspectives **103**(Suppl 6): 235-42.

Kramer, U., T. Koch, U. Ranft, J. Ring and H. Behrendt (2000). "Traffic-related air pollution is associated with atopy in children living in urban areas." Epidemiology **11**(1): 64-70.

Kunzli, N., U. Ackermann-Liebrich, O. Brandli, J. M. Tschopp, C. Schindler and P. Leuenberger (2000a). "Clinically "small" effects of air pollution on FVC have a large public health impact. Swiss Study on Air Pollution and Lung Disease in Adults (SAPALDIA) - team." Eur Respir J **15**(1): 131-6.

Kunzli, N., R. Kaiser, S. Medina, M. Studnicka, O. Chanel and P. e. a. Filliger (2000b). "Public-health impact of outdoor and traffic-related air pollution: a European assessment." Lancet **356**: 795-801.

Kunzli, N., R. McConnell, D. Bates, T. M. Bastain, A. Hricko, F. Lurmann, E. Avol, F. D. Gilliland and J. M. Peters (2003). "Breathless in Los Angeles: The exhausting search for clean air." Am J Pub Hlth **93**(9): 1494-1499.

Laden, F., L. M. Neas, D. W. Dockery and J. Schwartz (2000). "Association of fine particulate matter from different sources with daily mortality in six U.S. cities." Environ Health Perspect **108**(10): 941-7.

Laird, N. M. and J. H. Ware (1982). "Random-effects models for longitudinal data." Biometrics **38**(4): 963-74.

Le Tertre, A., S. Medina, E. Samoli, B. Forsberg, P. Michelozzi, A. Boumghar, J. M. Vonk, A. Bellini, R. Atkinson, J. G. Ayres, J. Sunyer, J. Schwartz and K. Katsouyanni (2002). "Short-term effects of particulate air pollution on cardiovascular diseases in eight European cities." J Epidemiol Community Health **56**(10): 773-9.

Lee, K., J. Wallarino, T. Dumyahn, H. Ozkaynak and J. Spengler (1999). "Ozone decay rates in residences." Journal of the Air & Waste Management Association **49**: 1238-1244.

Li, N., S. Kim, M. Wang, J. Froines, C. Sioutas and A. Nel (2002). "Use of a stratified oxidative stress model to study the biological effects of ambient concentrated and diesel exhaust particulate matter." Inhal Toxicol **14**(5): 459-86.

Li, N., C. Sioutas, A. Cho, D. Schmitz, C. Misra, J. Sempf, M. Wang, T. Oberley, J. Froines and A. Nel (2003). "Ultrafine particulate pollutants induce oxidative stress and mitochondrial damage." Environ Health Perspect **111**(4): 455-60.

Li, N., M. I. Venkatesan, A. Miguel, R. Kaplan, C. Gujuluva, J. Alam and A. Nel (2000a). "Induction of heme oxygenase-1 expression in macrophages by diesel exhaust particle chemicals and quinones via the antioxidant-responsive element." J Immunol **165**(6): 3393-401.

Li, Y. F., F. D. Gilliland, K. Berhane, R. McConnell, W. J. Gauderman, E. B. Rappaport and J. M. Peters (2000b). "Effects of in utero and environmental tobacco smoke exposure on lung function in boys and girls with and without asthma." American Journal of Respiratory & Critical Care Medicine **162**(6): 2097-104.

Li, Y.-F., B. Langholz, M. T. Salam and F. Gilliland (submitted). "Maternal and transgenerational smoking patterns are associated with early childhood asthma."

Lierl, M. B. and R. W. Hornung (2003). "Relationship of outdoor air quality to pediatric asthma exacerbations." Ann Allergy Asthma Immunol **90**(1): 28-33.

Lin, S., P. M. Munsie, S. Hwang, E. Fitzgerald and M. R. Cayo (2002). "Childhood asthma hospitalization and residential exposure to state route traffic." Environmental Research, Section A **88**: 73-81.

Linaker, C. H., D. Coggon, S. T. Holgate, J. Clough, L. Josephs, A. J. Chauhan and H. M. Inskip (2000). "Personal exposure to nitrogen dioxide and risk of airflow obstruction in asthmatic children with upper respiratory infection." Thorax **55**(11): 930-3.

Linn, W. S., J. C. Solomon, H. Gong, Jr., E. L. Avol, W. C. Navidi and J. M. Peters (1996). "Standardization of multiple spirometers at widely separated times and places." American Journal of Respiratory & Critical Care Medicine **153**(4 Pt 1): 1309-13.

Linn, W. S., J. C. Solomon, H. Gong, Jr., E. L. Avol and J. M. Peters (1998). "Temperature standardization of multiple spirometers." Journal of Occupational & Environmental Medicine **40**(2): 148-52.

Lippmann, M. (1989). "Health effects of ozone. A critical review." Japca **39**(5): 672-95.

Lippmann, M. (1991). Ozone. Environmental Toxicants: Human Exposures and Their Health Effects. M. Lippmann. New York, Van Nostrand Reinhold**:** 465-519.
Liu, L. J., R. Delfino and P. Koutrakis (1997). "Ozone exposure assessment in a southern California community." Environ Health Perspect **105**(1): 58-65.
London, S. J., W. James Gauderman, E. Avol, E. B. Rappaport and J. M. Peters (2001). "Family history and the risk of early-onset persistent, early-onset transient, and late-onset asthma." Epidemiology **12**(5): 577-83.
Lozano, P., S. D. Sullivan, D. H. Smith and K. B. Weiss (1999). "The economic burden of asthma in US children: estimates from the National Medical Expenditure Survey." J Allergy Clin Immunol **104**(5): 957-63.
Lu, R., R. P. Turco and M. Z. Jacobson (1997a). "An integrated air pollution modeling system for urban and regional scales: 1. structure and performance." Journal of Geophysical Research **102**: 6063-6079.
Lu, R., R. P. Turco and M. Z. Jacobson (1997b). "An integrated air pollution modeling system for urban and regional scales: 2. simulations for SCAQS 1987." Journal of Geophysical Research **102**: 6081-6098.
Lurmann, F. W., P. T. Roberts, H. H. Main, S. V. Hering, E. L. Avol and S. D. Colome (1994). Phase II report Appendix A: exposure assessment methodology.
Ma, R., D. Krewski and R. T. Burnett (2003). "Random effects Cox models: A Poisson modelling approach." Biometrika **90**(1): 157-169.
Manchester, J. B., J. J. Schauer and G. R. Cass (2001). Determination of the elemental carbon, organic compounds, and source contributors to atmospheric particles during the Southern California Children's Health Study. Part B: The distribution of particle-phase organic compounds in the atmospheric and source contributions to atmospheric particulate matter concentrations during the Southern California Children's Health Study, 1995. Final Report prepared for the California Air Resources Board and the California Environmental Protection Agency, Contract Number 98-320.
Manchester-Neesvid, J. B., J. J. Schauer and G. R. Cass (2003). "The distribution of particle-phase organic compounds in the atmosphere and their use for source apportionment during the Southern California Children's Health Study." Journal of Air and Waste Management Association **53**: 1065-1079.
McArdle, W. D., F. I. Katch and V. L. Katch (1996). Exercise physiology: Energy, nutrition, and human performance. Philadelphia, p. 228, Williams and Wilkins.
McConnell, R., E. Avol, V. Lin and F. Lurmann (2003a). "Chronic exposure to ambient ozone varies with traffic near residence." Am J Resp Crit Care Med **167**(7): A36.
McConnell, R., K. Berhane, F. Gilliland, T. Islam, W. J. Gauderman, S. J. London, E. Avol, E. B. Rappaport, H. G. Margolis and J. M. Peters (2002a). "Indoor risk factors for asthma in a prospective study of adolescents." Epidemiology **13**(3): 288-95.
McConnell, R., K. Berhane, F. Gilliland, S. J. London, T. Islam, W. J. Gauderman, E. Avol, H. G. Margolis and J. M. Peters (2002b). "Asthma in exercising children exposed to ozone: A cohort study." Lancet **359**(9304): 386-91.
McConnell, R., K. Berhane, F. Gilliland, S. J. London, H. Vora, E. Avol, W. J. Gauderman, H. G. Margolis, F. Lurmann, D. C. Thomas and J. M. Peters (1999). "Air pollution and bronchitic symptoms in Southern California children with asthma." Environmental Health Perspectives **107**(9): 757-60.

McConnell, R., K. Berhane, F. D. Gilliland, J. Molitor, D. Thomas, F. Lurmann, E. Avol, W. J. Gauderman and J. M. Peters (2003b). "Prospective study of air pollution and bronchitic symptoms in children with asthma." Am J Resp Crit Care Med **168**(7): 790-797.

McConnell, R., K. Berhane, F. Lurmann, J. Molitor, W. J. Gauderman, E. Avol, E. Rappaport, F. D. Gilliland and J. M. Peters (2002c). "Traffic and asthma prevalence in children." Am J Respir Crit Care Med **165**(8): A492.

McDonnell, W. F., D. E. Abbey, N. Nishino and M. D. Lebowitz (1999). "Long-term ambient ozone concentration and the incidence of asthma in nonsmoking adults: the AHSMOG Study." Environ Res **80**(2 Pt 1): 110-21.

Miller, B. G. and J. F. Hurley (2003). "Life table methods for quantitative impact assessments in chronic mortality." J Epidemiol Community Health **57**(3): 200-6.

Miller, L. A., D. M. Hyde, L. J. Gershwin, E. S. Schelegle, M. V. Fanucchi, M. J. Evans, J. E. Gerriets, L. F. Putney, M. Y. Stovall, N. K. Tyler, J. L. Usachenko and C. G. Plopper (2003). "The effect of house dust mite aeroallergen and air pollutant exposures during infancy." Chest **123**(3 Suppl): 434S.

Mingchih, C., S. Kim and C. Sioutas (1999). "Experimental studies on particle impaction and bounce: effects of substrate design and material." Atmospheric Environment **33**: 2313-2322.

Motallebi, N., C. A. Taylor, Jr., K. Turkiewicz and B. E. Croes (2003). "Particulate matter in California: Part 1-intercomparison of several $PM_{2.5}$, $PM_{10-2.5}$, and PM_{10} monitoring networks." J Air Waste Manag Assoc: 1509-1516.

National Research Council (2002). Estimating Public Health Benefits of Proposed Air Pollution Regulation. Washington, DC, National Academy Press.

Navidi, W. (1998). "Bidirectional case-crossover designs for exposures with time trends." Biometrics **54**: 596-605.

Navidi, W. and F. Lurmann (1995). "Measurement error in air pollution exposure assessment." J Expo Anal Environ Epidemiol **5**(2): 111-24.

Navidi, W., D. Thomas, D. Stram and J. Peters (1994). "Design and analysis of multilevel analytic studies with applications to a study of air pollution." Environ Health Perspect **102 Suppl 8**: 25-32.

Nazaroff, W. W., A. J. Gadgil and C. J. Weschler (1993). Critique of the use of deposition velocity in modeling indoor air quality. Modeling of Indoor Air Quality Exposure, Philadelphia, PA, American Society for Testing and Materials.

Nelson, W., W. Ott and J. Robinson (1994). The National Human Activity Pattern Survey (NHAPS): Use of nationwide activity data for human exposure assessment. 87th Annual Meeting of the Air & Waste Management Association.

NIOSH (1996). Elemental Carbon (Diesel Exhaust). NIOSH Manual of Analytical Methods. Cincinnati, OH, National Institute of Occupational Safety and Health.

Office of Management and Budget, O. (2003). Informing Regulatory Decisions: 2003 Report to Congress on the Costs and Benefits of Federal Regulations and Unfunded Mandates on State, Local, and Tribal Entities. Washington D.C., Executive Office of the President of the United States.

Oosterlee, A., M. Drijver, E. Lebret and B. Brunekreef (1996). "Chronic respiratory symptoms in children and adults living along streets with high traffic density." Occupational & Environmental Medicine **53**: 241-247.

Organisation for Economic Cooperation and Development (2002). Strategies to reduce greenhouse gas emissions from road transport: Analytical methods. Paris, France, OECD Publication Service.

Osebold, J. W., Y. C. Zee and L. J. Gershwin (1988). "Enhancement of allergic lung sensitization in mice by ozone inhalation." Proc Soc Exp Biol Med **188**(3): 259-64.

Ostro, B. (1994). Estimating the Health Effects of Air Pollutants. Policy Research Working Paper. Washington DC, The World Bank Policy Department Public Economics Division.

Ostro, B. and S. Rothschild (1993). "Air pollution and acute respiratory morbidity: an observational study of mulitple pollutants." Environmental Research **50**: 238-47.

Ostro, B. D., S. Hurley and M. J. Lipsett (1999). "Air pollution and daily mortality in the Coachella Valley, California: a study of PM10 dominated by coarse particles." Environ Res **81**(3): 231-8.

Ott, W., J. Thomas, D. Mage and L. Wallace (1988). "Validation of the simulation of human activity and pollutant exposure (SHAPE) model using paired days from the Denver, CO Carbon Monoxide Field Study." Atmospheric Environment **22**: 2101-2113.

Ozkaynak, H., J. Xue, R. Weker, D. Butler, P. Koutrakis and J. Spengler (1994). The Particle TEAM (PTEAM) Study: Analysis of the data. Volume III.

Parcel, G., G. SC, P. Nader and H. Bunce (1979). "A comparison of absentee rates of elementary school children with asthma and nonasthmatic schoolmates." Pediatrics **64**: 878.

Patashnick, J. and E. G. Rupprecht (1991). "Continuous PM-10 measurements using the tapered element oscillating microbalance." Journal of the Air & Waste Management Association **41**: 1079-1083.

Pelkonen, M., I. L. Notkola, H. Tukiainen, M. Tervahauta, J. Tuomilehto and A. Nissinen (2001). "Smoking cessation, decline in pulmonary function and total mortality: a 30 year follow up study among the Finnish cohorts of the Seven Countries Study." Thorax **56**(9): 703-7.

Pershagen, G., E. Rylander, S. Norberg, M. Eriksson and S. L. Nordvall (1995). "Air pollution involving nitrogen dioxide exposure and wheezing bronchitis in children." International Journal of Epidemiology **24**(6): 1147-53.

Peters, J. (1992). Epidemiologic investigation to identify chronic health effects of ambient air pollutants in Southern California: Phase I final report and Phase II Protocol. Los Angeles, Report prepared for the California Air Resources Board, Sacramento, CA by the University of Southern California School of Medicine, Department of Preventive Medicine.

Peters, J. (1997). Epidemiologic investigation to identify chronic health effects of ambient air pollutants in Southern California: Phase II final report. Los Angeles, CA, Report prepared for the California Air Resources Board, Sacramento, CA by the University of Southern California School of Medicine, Department of Preventive Medicine.

Peters, J. M., E. Avol, W. J. Gauderman, W. S. Linn, W. Navidi, S. J. London, H. Margolis, E. Rappaport, H. Vora, H. Gong, Jr. and D. C. Thomas (1999a). "A study of twelve Southern California communities with differing levels and types of air pollution. II. Effects on pulmonary function." Am J Respir Crit Care Med **159**(3): 768-775.

Peters, J. M., E. Avol, W. Navidi, S. J. London, W. J. Gauderman, F. Lurmann, W. S. Linn, H. Margolis, E. Rappaport, H. Gong and D. C. Thomas (1999b). "A study of twelve Southern California communities with differing levels and types of air pollution. I. Prevalence of respiratory morbidity." Am J Respir Crit Care Med **159**(3): 760-767.

Pinkerton, K. E., F. H. Green, C. Saiki, V. Vallyathan, C. G. Plopper, V. Gopal, D. Hung, E. B. Bahne, S. S. Lin, M. G. Menache and M. B. Schenker (2000). "Distribution of particulate matter and tissue remodeling in the human lung." Environ Health Perspect **108**(11): 1063-9.

Podmore, I. D., H. R. Griffiths, K. E. Herbert, N. Mistry, P. Mistry and J. Lunec (1998). "Vitamin C exhibits pro-oxidant properties." Nature **392**(6676): 559.

Pope, C. A., 3rd, R. T. Burnett, M. J. Thun, E. E. Calle, D. Krewski, K. Ito and G. D. Thurston (2002). "Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution." Jama **287**(9): 1132-41.

Pope, C. A., 3rd, R. T. Burnett, G. D. Thurston, M. J. Thun, E. E. Calle, D. Krewski and J. J. Godleski (2004). "Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease." Circulation **109**(1): 71-7.

Pope, C. A., 3rd, M. J. Thun, M. M. Namboodiri, D. W. Dockery, J. S. Evans, F. E. Speizer and C. W. Heath, Jr. (1995). "Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults." Am J Respir Crit Care Med **151**(3 Pt 1): 669-74.

Pope, C. A. r., D. W. Dockery, J. D. Spengler and M. E. Raizenne (1991). "Respiratory health and PM10 pollution: A daily time series analysis." American Review of Respiratory Disease **144**(3Pt1): 668-74.

Raftery, A. E., D. Madigan and J. A. Hoeting (1997). "Bayesian model averaging for linear rgression models." J Am Statist Assoc **92**: 179-191.

Raizenne, M., L. M. Neas, A. I. Damokosh, D. W. Dockery, J. D. Spengler, P. Koutrakis, J. H. Ware and F. E. Speizer (1996). "Health effects of acid aerosols on North American children: pulmonary function." Environ Health Perspect **104**(5): 506-14.

Rappaport, E. B., F. D. Gilliland, W. S. Linn and W. J. Gauderman (2002). "Impact of respiratory illness on expiratory flow rates in normal, asthmatic, and allergic children." Pediatr Pulmonol **34**(2): 112-21.

Rodes, C. E., L. Sheldon, D. Whitaker, A. Clayton, K. M. Fitzgerald and J. Flanagan, et al. (1998). Measuring concentration of selected air pollutants inside California vehicles.

Rogers, K. and G. Reese (1965). "Health studies - presumably normal high school students." Am J Dis Children **109**: 9.

Romieu, I., F. Meneses, S. Ruiz, J. J. Sienra, J. Huerta, M. C. White and R. A. Etzel (1996). "Effects of air pollution on the respiratory health of asthmatic children living in Mexico City." Am J Respir Crit Care Med **154**((2 Pt 1)): 300-7.

Romieu, I., J. J. Sienra-Monge, M. Ramirez-Aguilar, M. M. Tellez-Rojo, H. Moreno-Macias, N. I. Reyes-Ruiz, B. E. del Rio-Navarro, M. X. Ruiz-Navarro, G. Hatch, R. Slade and M. Hernandez-Avila (2002). "Antioxidant supplementation and lung functions among children with asthma exposed to high levels of air pollutants." Am J Respir Crit Care Med **166**(5): 703-9.

Rondeau, V., K. Berhane and D. C. Thomas (submitted). "A three level model for binary time-series data: the effects of air pollution on school absences in the Southern California Children's Health Study."

Rozelle, R. (1968). "Relationship between absenteeism and grades." Educ Psychol Meas **28**: 1151.

Salam, M. T., B. Langholz and F. D. Gilliland (in preparation). "Maternal fish consumption during pregnancy and risk of childhood asthma."

Salmon, L. G., K. A. Mertz, P. R. Mayo and G. R. Cass (2001). Determination of elemental carbon, organic carbon, and source contributions to atmospheric particles during the Southern California Children's Health Study: Part A.

Samet, J. and F. Speizer (1993). "Assessment of health effects in epidemiologic studies of air pollution." Environmental Health Perspectives **101**(Suppl 4): 149-153.

Samet, J. M., F. Dominici, F. C. Curriero, I. Coursac and S. L. Zeger (2000a). "Fine particulate air pollution and mortality in 20 U.S. cities, 1987- 1994." N Engl J Med **343**(24): 1742-9.

Samet, J. M., S. L. Zeger, F. Dominici, F. Curriero, I. Coursac, D. W. Dockery, J. Schwartz and A. Zanobetti (2000b). "The National Morbidity, Mortality, and Air Pollution Study. Part II: Morbidity and mortality from air pollution in the United States." Res Rep Health Eff Inst **94**(Pt 2): 5-70; discussion 71-9.

Schauer, J., W. Rogge, L. Hildemann, M. Mazurek and G. Cass (1996). "Source apportionment or airborne particulate matter using organic compounds as tracers." Atmospheric Environment **22**: 3837-3855.

Schauer, J. J. and G. R. Cass (2000). "Source apportionment of wintertime gas-phase and particle-phase air pollutants using organic compounds as tracers." Environmental Science & Technology **34**: 1821-1832.

Schelegle, E. S., L. A. Miller, L. J. Gershwin, M. V. Fanucchi, L. S. Van Winkle, J. E. Gerriets, W. F. Walby, V. Mitchell, B. K. Tarkington, V. J. Wong, G. L. Baker, L. M. Pantle, J. P. Joad, K. E. Pinkerton, R. Wu, M. J. Evans, D. M. Hyde and C. G. Plopper (2003). "Repeated episodes of ozone inhalation amplifies the effects of allergen sensitization and inhalation on airway immune and structural development in Rhesus monkeys." Toxicol Appl Pharmacol **191**(1): 74-85.

Schipper, L., C. Marie-Lilliu and L. Fulton (2000). Diesel in Europe: Analysis of characteristics, usage patterns, energy savings, and CO2 emission implications, Energy Efficiency Technology Office, International Energy Agency.

Schwartz, J. (1989). "Lung function and chronic exposure to air pollution: a cross-sectional analysis of NHANES II." Environ Res **50**(2): 309-21.

Schwartz, J., D. W. Dockery and L. M. Neas (1996). "Is daily mortality associated specifically with fine particles?" J Air Waste Manag Assoc **46**(10): 927-39.

Sears, M. R. (1997). "Epidemiology of childhood asthma." Lancet **350**(9083): 1015-20.

Sears, M. R., J. M. Greene, A. R. Willan, E. M. Wiecek, D. R. Taylor, E. M. Flannery, J. O. Cowan, G. P. Herbison, P. A. Silva and R. Poulton (2003). "A longitudinal, population-based, cohort study of childhood asthma followed to adulthood." N Engl J Med **349**(15): 1414-22.

Sexton, K. and P. B. Ryan (1988). Assessment of human exposure to air pollution: methods, measurements and models. Air Pollution, the Automobile and Public Health. D. Kennedy. New York, NY, National Academy Press**:** 207-238.

Sherwin, R. P. (1991). "Air pollution: the pathobiologic issues." J Toxicol Clin Toxicol **29**(3): 385-400.

Sherwin, R. P. and V. Richters (1991). Centriacinar region (CAR) disease in the lungs of young adults: A preliminary report. Tropospheric Ozone and the Environment: Papers from an International Conference. R. L. Berglund, D. R. Lawson and D. McKee. Pittsburgh, PA, Air and Waste Management Association.

Silverman, B. W. (1985). "Some Aspects of the Spline Smoothing Approach to Non-parametric Regression Curve Fitting (C/R: P21-50?)." Journal of the Royal Statistical Society, Series B, Methodological **47**: 1-21.
Sioutas, C. (2003).
Solomon, P. A., T. Fall, S. M. Larson, P. Lin, F. Vasquez and G. R. Cass (1988). Acquisition of acid and aerosol concentration data for use in dry deposition studies in the South Coast Air Basin. Vol. I.
South Coast Air Quality Management District (1997). "1997 Air Quality Managment Plan." http://www.aqmd.gov/aqmp/97aqmp/, accessed October 23.
South Coast Air Quality Management District (2003). "2003 Air Quality Management Plan." http://www.aqmd.gov/aqmp/AQMD03AQMP.htm, accessed October 15.
Spix, C., H. R. Anderson, J. Schwartz, M. A. Vigotti, A. LeTertre, J. M. Vonk, G. Touloumi, F. Balducci, T. Piekarski, L. Bacharova, A. Tobias, A. Ponka and K. Katsouyanni (1998). "Short-term effects of air pollution on hospital admissions of respiratory diseases in Europe: a quantitative summary of APHEA study results. Air Pollution and Health: a European Approach." Arch Environ Health **53**(1): 54-64.
Strader, R., F. Lurmann and S. N. Pandis (1999). "Evaluation of secondary organic aerosol formation in winter." Atmos Environ **33**: 4849-4864.
Sunyer, J. (2001). "Urban air pollution and chronic obstructive pulmonary disease: a review." Eur Respir J **17**(5): 1024-33.
Sydbom, A., A. Blomberg, S. Parnia, N. Stenfors, T. Sandstrom and S. E. Dahlen (2001). "Health effects of diesel exhaust emissions." Eur Respir J **17**(4): 733-46.
Tager, I. B., N. Kunzli, F. Lurmann, L. Ngo, M. Segal and J. Balmes (1998). "Methods development for epidemiologic investigations of the health effects of prolonged ozone exposure. Part II. An approach to retrospective estimation of lifetime ozone exposure using a questionnaire and ambient monitoring data (California sites)." Res Rep Health Eff Inst(81): 27-78; discussion 109-21.
Taylor, C. A. (2000). Personal communication about Two-week Sampler Legs D & E evaluation results.
Taylor, C. A. (2003). S.O.P. 001, Standard Operating Procedure for the Two-Week Sampler. Sacramento, CA, California Air Resources Board, Research Division.
Thomas, D. C. (2000). "Some contributions of statistics to environmental epidemiology." J Am Statist Assoc **95**: 315-319.
Thomas, D. C., D. V. Conti, J. Molitor, W. J. Gauderman, K. Berhane and F. Gilliland (in preparation-a). "Model selection, model averaging, and the use of prior covariates in the investigation of the health effects of multiple air pollutants."
Thomas, D. C., W. J. Gauderman, F. Lurmann and E. Avol (in preparation-b). "Exposure modeling for studies of the chronic effects of air pollution."
Turpin, B. J. and J. J. Huntzicker (1991). "Secondary formation of organic aerosol in the Los Angeles Basin: A descriptive analysis of organic and elemental carbon concentrations." Atmos Environ **25A**: 207-215.
Turpin, B. J. and J. J. Huntzicker (1995). "Identification of secondary organic aerosol episodes and quantification of primary and secondary organic aerosol concentrations during SCAQS." Atmos Environ **29**: 3527-3544.
U.S. Environmental Protection Agency (1999). National Air Quality and Emissions Trends Report. Washington D.C., Office of Air Quality Planning and Standards.

US Environmental Protection Agency (1986). Air Quality Criteria for Ozone and Other Photochemical Oxidants, Volume V. Research Triangle Park, NC.
US Environmental Protection Agency (1997a). Development of NERL/CHAD: the National Exposure Research Laboratory Consolidated Human Activity Database.
US Environmental Protection Agency (1997b). Final report to Congress on Benefits and Costs of the Clean Air Act, 1970-1990. Washington, D.C., U.S. Environmental Protection Agency.
US Environmental Protection Agency (1997c). "National ambient air quality standards for particulate matter." Fed Regist **62**: 138.
US Environmental Protection Agency (2000). Regulatory impact analysis--Heavy-duty engine and vehicle standards and highway diesel fuel sulfur control requirements. Washington, D.C., U.S. Environmental Protection Agency.
US Environmental Protection Agency (2003). Air Quality Criteria Document for Particulate Matter (Fourth External Review Draft). Research Triangle Park, NC, U.S. Environmental Protection Agency, Office of Research and Development, National Center For Environmental Assessment.
van Vliet, P., M. Knape, J. de Hartog, N. Janssen, H. Harssema and B. Brunekreef (1997). "Motor vehicle exhaust and chronic respiratory symptoms in children living near freeways." Environmental Research **74**(2): 122-32.
Venn, A., S. Lewis, M. Cooper, R. Hubbard, I. Hill, R. Boddy, M. Bell and J. Britton (2000). "Local road traffic activity and the prevalence, severity, and persistence of wheeze in school children: combined cross sectional and longitudinal study." Occup Environ Med **57**(3): 152-8.
Vollmer, W. (2003). "Epidemiology of COPD: overview and the US perspective." Eur Respir J **22**(Suppl. 43): 1s-3s.
Waldron, G., B. Pottle and J. Dod (1995). "Asthma and the motorways--one District's experience." J Public Health Med **17**(1): 85-9.
Wang, T. N., Y. C. Ko, Y. Y. Chao, C. C. Huang and R. S. Lin (1999). "Association between indoor and outdoor air pollution and adolescent asthma from 1995 to 1996 in Taiwan." Environ Res **81**(3): 239-47.
Wang, X., D. W. Dockery, D. Wypij, D. R. Gold, F. E. Speizer, J. H. Ware and B. G. Ferris, Jr. (1993). "Pulmonary function growth velocity in children 6 to 18 years of age." Am Rev Respir Dis **148**(6 Pt 1): 1502-8.
Wargocki, P., J. Sundell, W. Bischof, G. Brundrett, P. O. Fanger, F. Gyntelberg, S. O. Hanssen, P. Harrison, A. Pickering, O. Seppanen and P. Wouters (2002). "Ventilation and health in non-industrial indoor environments: report from a European multidisciplinary scientific consensus meeting (EUROVEN)." Indoor Air **12**(2): 113-28.
Watson, J. G., J. C. Chow and C. A. Frazier (1999). X-ray fluorescence analysis of ambient air samples. Elemental Analysis of Airborne Particles. M. Creatchman. Newark,NJ, Gordon and Breach Publishers.
Watson, J. G., J. C. Chow, Z. Lu, E. M. Fujita, D. H. Lowenthal, D. R. Lawson and L. L. Ashbaugh (1994). "Chemical mass balance source apportionment of PM_{10} during the Southern California Air Quality Study." Aerosol Science and Technology **21**: 1-36.
Weiland, S., K. Mundt, A. Ruckmann and U. Keil (1994). "Self-reported wheezing and allergic rhinitis in children and traffic density on street residence." Ann Epidemiol **4**(3): 243-247.

Weitzman, M. (1986). "School absence rates as outcome measures in studies of children with chronic illness." Journal of Chronic Diseases **39**(10): 799-808.
WHO World Health Organization Regional Office for Europe (2000). Evaluation and use of epidemiological evidence for environmental health risk assessment. Guideline Document. Copenhagen, Denmark,, World Health Organization Regional Office for Europe.
WHO World Health Organization Regional Office for Europe (2001). Quantification of the Health Effects of Exposure to Air Pollution. A Report of a WHO Working Group. Copenhagen, Denmark, WHO World Health Organization Regional Office for Europe.
Wiley, J., J. Robinson, T. Piazza, K. Garrett, K. Cirksena, U. Cheng and G. Martin (1991). Activity patterns of California residents.
Wilson, W. E., D. T. Mage and L. D. Grant (2000). "Estimating separately personal exposure to ambient and nonambient particulate matter for epidemiology and risk assessment: why and how." Journal of Air and Waste Management Association **50**: 1167-1183.
Wjst, M., P. Reitmeir, S. Dold, A. Wulff, T. Nicolai, E. F. von Loeffelholz-Colberg and E. von Mutius (1993). "Road traffic and adverse effects on respiratory health in children [see comments]." Bmj **307**(6904): 596-600.
Wu, J., F. Lurmann, A. Winer, R. Lu and R. Turco (2003). Development of an individual model for use in epidemiological studies: application to the Southern California Children's Health Study (in preparation).
Wypij, D., M. Pugh and J. H. Ware (1993). "Modeling Pulmonary Function Growth With Regression Splines." Statistica Sinica **3**: 329-350.
Yamanaka, S. (1984). "Decay rates of nitrogen oxides in a typical Japanese living room." Environmental Science Technology **18**: 566-570.
Yu, O., L. Sheppard, T. Lumley, J. Q. Koenig and G. G. Shapiro (2000). "Effects of ambient air pollution on symptoms of asthma in Seattle-area children enrolled in the CAMP study." Environ Health Perspect **108**(12): 1209-14.
Zanobetti, A., J. Schwartz, E. Samoli, A. Gryparis, G. Touloumi, R. Atkinson, A. Le Tertre, J. Bobros, M. Celko, A. Goren, B. Forsberg, P. Michelozzi, D. Rabczenko, E. Aranguez Ruiz and K. Katsouyanni (2002). "The temporal pattern of mortality responses to air pollution: a multicity assessment of mortality displacement." Epidemiology **13**(1): 87-93.
Zeger, S. and M. R. Karim (1991). "Generalized linear modelswith random effects: a Gibbs sampling approach." J Am Stat Assoc **86**: 79-86.
Zeger, S. L., D. Thomas, F. Dominici, J. M. Samet, J. Schwartz, D. Dockery and A. Cohen (2000). "Exposure measurement error in time-series studies of air pollution: concepts and consequences." Environ Health Perspect **108**(5): 419-26.
Zemp, E., S. Elsasser, C. Schindler, N. Kunzli, A. P. Perruchoud, G. Domenighetti, T. Medici, U. Ackermann-Liebrich, P. Leuenberger, C. Monn, G. Bolognini, J. P. Bongard, O. Brandli, W. Karrer, R. Keller, M. H. Schoni, J. M. Tschopp, B. Villiger and J. P. Zellweger (1999). "Long-term ambient air pollution and respiratory symptoms in adults (SAPALDIA study). The SAPALDIA Team." Am J Respir Crit Care Med **159**(4 Pt 1): 1257-66.
Zhu, Y., W. C. Hinds, S. Kim, S. Shen and C. Sioutas (2002a). "Study of ultrafine particles near a major highway with heavy-duty diesel traffic." Atmospheric Environment **36**: 4323-4335.
Zhu, Y., W. C. Hinds, S. Kim and C. Sioutas (2002b). "Concentration and size distribution of ultrafine particles near a major highway." J Air Waste Manag Assoc **52**(9): 1032-42.

9. List of Inventions Reported and Copyrighted Materials Produced

The support from the Air Resources Board made the following publications possible.

1. Navidi W, Thomas D, Stram D, Peters J. Design and analysis of multilevel analytic studies with applications to a study of air pollution. Environ Health Perspect 102 (suppl 8):25-32, 1994.

2. Navidi W, Lurmann F. Measurement error in air pollution exposure assessment. J Exp Anal Environ Epidemiol 5:111-124, 1995.

3. Linn WS, Solomon JC, Gong Jr H, Avol EL, Navidi WC, Peters JM. Standardization of multiple spirometers at widely separated times and places. Am J Respir Crit Care Med 153:1309-1313, 1996.

4. Geyh AS, Wolfson JM, Koutrakis P, Mulik JD, Avol EL. Development and evaluation of a small active ozone sampler. Environ Sci Tech 31:3230-3236, 1997.

5. Allen G, Sioutas C, Koutrakis P, Reiss R, Lurmann FW, Roberts PT. Evaluation of the TEOM® method for measurement of ambient particulate mass in urban areas. J Air Waste Manage Assoc 47:682-689, 1997.

6. Linn WS, Solomon JC, Gong Jr. H, Avol EL, Peters JM. Temperature standardization of multiple spirometers. J Occ Environ Med 40:148-152, 1998.

7. Navidi W. Bidirectional case-crossover designs for exposures with time trends. Biometrics 54:596-605, 1998.

8. Avol EL, Navidi WC, Colome SD. Modeling ozone levels in and around Southern California homes. Environ Sci Technol 32:463-468, 1998.

9. Geyh AS, Roberts PT, Lurmann FW, Schoell BM, Avol EL. Initial field evaluation of the Harvard active ozone sampler for personal ozone monitoring. J Exp Anal Environ Epidemiol 2:143-149, 1999.

10. Peters JM, Avol E, Navidi W, London SJ, Gauderman WJ, Lurmann F, Linn W, Margolis H, Rappaport E, Gong Jr. H, Thomas D. A study of twelve Southern California communities with differing levels and types of air pollution. I. Prevalence of respiratory morbidity. Am J Respir Crit Care Med 159:760-767, 1999.

11. Peters JM, Avol E, Gauderman WJ, Linn WS, Navidi W, London SJ, Margolis H, Rappaport E, Vora H, Gong Jr. H, Thomas D. A study of twelve Southern California communities with differing levels and types of air pollution. II. Effects on pulmonary function. Am J Respir Crit Care Med 159:768-775, 1999.

12. Gilliland FD, McConnell RM, Peters JM, Gong H., Jr. A theoretical basis for investigating ambient air pollution and children's respiratory health. Environ Health Perspect 107(3):403-407, 1999.

13. McConnell R, Berhane K, Gilliland FD, London SJ, Vora H, Avol EL, Gauderman WJ, Margolis H, Lurmann F, Thomas D, Peters JM. Air pollution and bronchitic symptoms in Southern California children with asthma. Environ Health Perspect 107(9):757-60, 1999.

14. Gilliland FD, Linn W, Rappaport E, Avol E, Gong Jr. H, Peters J. Effects of spirometer temperature on FEV1 in a longitudinal epidemiological study. Occ Environ Med 56:718-20, 1999.

15. Gilliland FD, Berhane K, McConnell R, Gauderman WJ, Vora H, Rappaport EB, Avol E, Peters JM. Maternal smoking during pregnancy, environmental tobacco smoke exposure and childhood lung function. Thorax 55:271-276, 2000.

16. Enright PL, Linn WS, Avol EL, Margolis H, Gong Jr H, Peters JM. Quality of spirometry test performance in children and adolescents: Experience in a large field study. Chest 118:665-71, 2000.

17. Thomas DC. Some contributions of statistics to environmental epidemiology. J Am Statist Assoc 95:315-319, 2000.

18. Zeger SL, Thomas DC, Dominici F, Samet JM, Schwartz J, Dockery DW, Cohen AJ. Exposure measurement error in time-series studies of air pollution. Environ Health Perspect 108: 419-426, 2000.

19. Avol EL, Tan SM, Gauderman WJ, Vora H, London SJ, Peters JM. Follow-up of "lost" subjects in a longitudinal air pollution health study. Am J Respir Crit Care Med 61(3):A308, 2000.

20. Gauderman WJ, McConnell R, Gilliland F, London S, Thomas D, Avol E, Vora H, Berhane K, Rappaport EB, Lurmann F, Margolis HG, Peters JM. Association between air pollution and lung function growth in Southern California children. Am J Respir Crit Care Med 162:1383-90, 2000.

21. Berhane K, Thomas DC. Discussion on "Combining evidence on air pollution and daily mortality from the 20 largest US cities: a hierarchical modeling strategy." J Royal Statist Soc, Series A; 163(3):263-302, 2000.

22. Berhane K, McConnell R, Gilliland FD, Islam T, Gauderman WJ, Avol E, London SJ, Rappaport E, Margolis HG, Peters JM. Sex-specific effects of asthma on pulmonary function in children. Am J Respir Crit Care Med 162:1723-30, 2000.

23. Li Y-F, Gilliland FD, Berhane K, McConnell R, Gauderman WJ, Rappaport EB, Peters JM. Effects of in utero and environmental tobacco smoke exposure on lung function in boys and girls with asthma. Am J Respir Crit Care Med 162:2097-2104, 2000.

24. Gilliland FD, Berhane K, Rappaport E, Thomas DC, Avol E, Gauderman WJ, London SJ, Margolis HG, McConnell R, Islam T, Peters JM. The effects of ambient air pollution on school absenteeism due to respiratory illnesses. Epidemiology 12:43-54, 2001.

25. Gilliland FD, Li Y-F, Peters JM. Effects of maternal smoking during pregnancy and environmental tobacco smoke in wheezing and asthma in children. Am J Respir Crit Care Med 163:429-436, 2001.

26. London SJ, Gauderman WJ, Avol E, Rappaport E, Peters JM. Family history and the risk of early onset persistent, early onset transient and late onset asthma. Epidemiology 12:577-83, 2001.

27. Gilliland FD, Islam T, Berhane K, McConnell R, Li Y-F, Peters JM. Obesity and asthma incidence in school-aged children: Results from the children's health study. Am J Respir Crit Care Med 163(5):A37, 2001.

28. Li Y-F, Gilliland FD, Berhane K, McConnell R, Gauderman WJ, Peters JM. Effects of *in utero* exposure on lung function in children with early onset asthma. Am J Respir Crit Care Med 163(5):A263, 2001.

29. Gilliland FD, Li Y-F, Peters JM. Effects of low vitamins A, E, and C intake on children's lung function. Am J Respir Crit Care Med 163(5):A37, 2001.

30. McConnell R, Berhane K, Gilliland F, Islam T, London SJ, Gauderman WJ, Avol E, Margolis HG, Peters JM. Sports and asthma in children exposed to ozone. Am J Respir Crit Care Med 163(5):A174, 2001.

31. Thorne PS, Avol E, Anelling L, Grossman S, Peters JM. Measurement of ambient endotoxin in Southern California. Am J Respir Crit Care Med 163(5):A844, 2001.

32. Avol EL, Gauderman WJ, Tan, SM, London, SJ, Peters, JM. Respiratory Effects of Relocating to Areas of Differing Air Pollution Levels. Am J Respir Crit Care Med 164: 2067-2072, 2001.

33. Gong H Jr (contributing author): Urban air pollution and health inequities: a workshop report. Environ Health Perspect; 109 (Supplement 3):357-374, 2001.

34. Linn WS, Gong H Jr. Respiratory health risk from particulate air pollution: current evidence and research needs. Inspiration—Singapore Thoracic Society Newsletter 7(1):2-5, 2001.

35. Gilliland FD, Berhane K, Li Y-F, Kim DH, Margolis HG. Dietary magnesium, potassium, sodium and children's lung function. Am J Epidemiol 155(2):1-7, 2002.

36. McConnell R, Berhane K, Gilliland FD, Islam T, Avol E, London SJ, Gauderman WJ, Margolis HG, Thomas DC, Peters JM. Indoor risk factors for asthma in a cohort of adolescents. Epidemiology 13(3):288-295, 2002.

37. Berhane K, Thomas DC. Two-stage model for multiple time series data of counts. Biostatistics 3(1):21-32, 2002.

38. McConnell R, Berhane K, Lurmann F, Molitor J, Gauderman WJ, Avol E, Rappaport Ed, Gilliland F, Peters JM. Traffic and asthma prevalence in children. Am J Resp Crit Care Med 165(8):A492, 2002.

39. Gilliland F, Li Y-F, Dubeau L, Peters JM. Effects of GSTM1, *in utero* to maternal smoking and ETS exposure on asthma and wheezing in children. Am J Resp Crit Care Med 165(8): A660, 2002.

40. Rappaport EB, Gilliland FD, Linn WS, Gauderman WJ. Impact of respiratory illness on expiratory flow rates in normal, asthmatic, and allergic children. Pediatr Pulmonol 34(2): 112-121, 2002.

41. Gauderman WJ, Gilliland FD, Avol E, Vora H, Thomas DT, Rappaport E, Berhane K, Lurmann F, McConnell R, Stram D, Peters JM. Association between air pollution and lung function growth in Southern California children: Results from a second cohort. Am J Resp Crit Care Med 166(1):74-84, 2002.

42. Gilliland FD, Li YF, Dubeau L, Berhane K, Avol E, McConnell R, Gauderman WJ, Peters JM. Effects of GSTM1, maternal smoking during pregnancy, and environmental tobacco smoke on asthma and wheezing in children. Am J Respir Crit Care Med 166(4):457-63, 2002.

43. Gilliland FD, Rappaport E, Berhane K, Islam T, Dubeau L, Gauderman WJ, McConnell R. Effects of Glutathione *S* -Transferase P1, M1, and T1 on acute respiratory illnesses in school children. Am J Respir Crit Care Med 166(3):346-351, 2002.

44. McConnell R, Berhane K, Gilliland F, London SJ, Islam T, Gauderman WJ, Avol E, Margolis HG, Peters JM. Asthma in exercising children exposed to ozone: a cohort study. Lancet 359(9304):386-391, 2002.

45. McConnell R, Jones C, Avol E, Cozen W, Milam J, Cahero J, Richardson J. Cockroach allergen intervention: some considerations for intervention and exposure assessment. Epidemiology 13(4):S135, 2002.

46. Gauderman WJ, McConnell R, Berhane K, Lurmann F, Avol E, Gilliland F, Thomas D, Peters J. Genes, environmental exposures and childhood asthma occurrence. Epidemiology 13(4):S131, 2002.

47. Lurmann F, Funk T, Hyslop N, Roberts P, Hamond SK, McConnell R, Avol E. Measurement & modeling of personal exposure to ambient air pollution-related to motor vehicle emissions. Epidemiology 13(4):S131-32, 2002.

48. Peters JM, McConnell R, Berhane K, Millstein J, Lurmann F, Gauderman J, Avol E, Gilliland F, Thomas D. Air pollution and the incidence, prevalence and severity of childhood asthma: results from the Southern California Children's Health Study. Epidemiology 13(4):S132, 2002.

49. McConnell R, Berhane K, Gilliland F, Molitor J, Avol E, Gauderman WJ, Peters JM. Air pollution and bronchitic symptoms in children: between-community and within-community effects. Epidemiology 13(4):S148, 2002.

50. Künzli N. The public health relevance of air pollution abatement. Eur Respir J; 20:198-209, 2002.

51. Gilliland FD, Gauderman WJ, Vora H, Rappaport E, Dubeau L. Effects of glutathione-S-transferase M1, T1, and P1 on childhood lung function growth. Am J Respir Crit Care Med; 166:710-6, 2002.

52. Berhane K. Functional based multi-level models for longitudinal data. Proceedings of Joint Statistical Meetings (6 pages of CDROM), New York, August 2002.

53. Gilliland FD, Berhane K, Li Y-F, Rappaport EB, Peters JM. Effects of early onset asthma and in utero exposure to maternal smoking on childhood lung function. Am J Respir Crit Care Med; 167:917-24, 2003.

54. Xie B, Gilliland FD, Li Y-F, Rockett HR. Effects of ethnicity, family income and education on dietary intake among adolescents. Prev Med; 36:30-40, 2003.

55. Gilliland FD, Berhane K, Islam T, Wenten M, Rappaport E, Avol E, Gauderman WJ, McConnell R, Peters JM. Environmental tobacco smoke and absenteeism related to respiratory illness in schoolchildren. Am J Epidemiol 157:861-869, 2003.

56. Gilliland FD, Y-F Li, W Tsai, L Dubeau. GSTP1 and GSTM1 contribute to susceptibility for asthma and wheezing following in utero exposure to tobacco smoke. Am J Resp Crit Care Med 167(7):A942, 2003.

57. Gilliland FD, Y-F Li, W Tsai, L Dubeau, E Avol, JM Peters. TNF α-308 genotype and ozone effects on asthma and wheezing: Results from the Children's Health Study (CHS). Am J Resp Crit Care Med 167(7):A580, 2003.

58. Gilliland FD, MT Salam, Y-F Li, B Langholz. Early life risk factors for asthma: Findings from the Children's Health Study. Am J Resp Crit Care Med 167(7):A831, 2003.

59. Li YF, B Langholz, FD Gilliland. Smoking cessation during pregnancy reduces risk for asthma from *in utero* exposure to maternal smoking. Am J Resp Crit Care Med 167(7):A854, 2003.

60. McConnell R, K Berhane, J Molitor, FD Gilliland. Effect modification by pet ownership. Am J Resp Crit Care Med 167(7):A36, 2003.

61. McConnell R, E Avol, V Lin, F Lurmann. Chronic exposure to ambient ozone varies with traffic near residence. Am J Resp Crit Care Med 167(7):A36, 2003.

62. Thorne PS, N Metwali, E Avol, R McConnell. Evaluation of surface sampling for endotoxin using electrostatic wiping cloths. Am J Resp Crit Care Med 167(7):A500, 2003.

63. Kunzli N, R McConnell, D Bates, TM Bastain, A Hricko, F Lurmann, E Avol, FD Gilliland, JM Peters. Breathless in Los Angeles: The exhausting search for clean air. Am J Pub Hlth, 93(9):1494-1499, 2003.

64. Gilliland FD, Berhane K, Islam T, Wenten M, Rappaport E, Avol E, Gauderman WJ, McConnell R, Peters J. Obesity and the risk of newly diagnosed asthma in school-aged children. Am J Epidemiol, 158(5):406-415, 2003.

65. Gilliland FD, Berhane K, Li Y, Gauderman WJ, McConnell R, Peters J. Children's Lung Function and Antioxidant Vitamin, Fruit, Juice, and Vegetable Intake. Am J Epidemiol, 158(6):576-84, 2003.

66. McConnell R, K Berhane, FD Gilliland, J Molitor, D Thomas, F Lurmann, E Avol, WJ Gauderman, JM Peters. Prospective study of air pollution and bronchitic symptoms in children with asthma. Am J Resp Crit Care Med 168(7):790-797, 2003.

67. Hall JV, Brajer V, Lurmann FW Economic valuation of ozone-related school absences in the South Coast Air Basin of California. Contemp Econ Policy 21(4):407-11, 2003.

68. Cortessis V, Thomas DC. Toxicokinetic genetics: An approach to gene-environment and gene-gene interactions in complex metabolic pathways. In Bird P, Boffetta P, Buffler P, Rice J, (eds.), *Mechanistic Considerations in the Molecular Epidemiology of Cancer*, IARC Scientific Publications:Lyon, 2004.

69. Salam MT, FD Gilliland, Y.F Li, B Langholtz . Early life environmental risk factors for asthma: Findings from the Children's Health Study. Environmental Health Perspectives, 112 (6), 2004.

MANUSCRIPTS IN PRESS

70. Berhane K, Gauderman WJ, Stram DO, Thomas DC (in press). Statistical issues in studies of the long-term effects of air pollution: the Southern California Children's Health Study (with discussion). Statistical Science.

SUBMITTED MANUSCRIPTS

71. Millstein J, Gilliland FD, Berhane KT, Gauderman WJ, McConnell R, Avol E, Rappaport E, Peters JM (submitted). Associations of monthly variation in ambient air pollutants with asthma medication use and wheezing in school children.

72. Rondeau V, Berhane, K, Thomas, D.C. (submitted). A three level model for binary time-series data: the effects of air pollution on school absences in the Southern California Children's Health Study.

73. Li Y-F, Langholz B, Salam MT, Gilliland FD (submitted). Maternal and transgenerational smoking patterns are associated with early childhood asthma.

74. Salam, MT, Langholz BM, Gilliland FD (submitted). Maternal fish consumption during pregnancy and risk of childhood asthma.

75. Gauderman WJ, Avol E, Gilliland F, Vora H, Thomas D, Berhane K, McConnell R, Kuenzli N, Lurmann F, Rappaport E, Margolis H, Bates D (submitted) The effect of air pollution on lung function development in children aged 10 to 18 years.

MANUSCRIPTS IN PREPARATION

76. Thomas DC, Gauderman WJ, Lurmann F, Avol E. Exposure modeling for studies of the chronic effects of air pollution.

77. Berhane K, Molitor NT, et al. A Bayesian approach to functional based multi-level modeling of longitudinal data: with applications to environmental epidemiology.

78. Xie B, Gilliland FD, et al. Determinants of reproducibility of nutrient intakes and food consumption estimated by food frequency questionnaire in the Children's Health Study.

79. Gilliland FD, Y-F Li, W Tsai, L Dubeau, E Avol, and JM Peters. TNF α-308 genotype and ozone effects on asthma and wheezing: Results from the Children's Health Study.

80. Gauderman WJ, et al. Association between asthma and local exposure to nitrogen dioxide.

81. Gilliland FD, T Islam, K Berhane, WJ Gauderman, et al. GSTP1, sports, and incident asthma in schoolchildren.

82. Thomas DC, DV Conti, J Molitor, WJ Gauderman, K Berhane, F Gilliland, et al. Model selection, model averaging, and the use of prior covariates in the investigation of the health effects of multiple air pollutants.

83. Berhane K, et al. 8-year data analysis of sex-specific effects of asthma on lung function in children.

10. Glossary of Terms, Abbreviations, and Symbols

AIRS	Aerometric Information Retrieval System
AQMD	Air Quality Management District
ARB	California Air Resources Board
ATS	American Thoracic Society
BC	black carbon
BMI	body mass index
BTPS	body temperature, pressure, and saturation
CMB	chemical balance modeling
CHS	Children's Health Study
CI	confidence interval
CO	carbon monoxide
CO_2	carbon dioxide
COPD	chronic obstructive pulmonary disorder
CPC	condensation particle counter
EC	elemental carbon
EPA	Environmental Protection Agency (U.S.)
ETS	environmental tobacco smoke
FEF_{75}	forced expiratory flow at 75% of FVC
FEV_1	forced expiratory volume in one second
FVC	forced vital capacity
GC/MS	gas chromatography/mass spectrometry
GSTs	glutathione-s-transferase (genes)
GPXs	glutathione peroxidase (genes)
HCl	hydrochloric acid
HDV	high density volume
IEM	individual exposure model
LDV	low density volume
LRI	lower respiratory infection

MCMC	Markov Chain Monte Carlo
MMEF	maximum mid- expiratory flow
NAAQS	National Ambient Air Quality Standard
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NO	nitric oxide
NO_2	nitrogen dioxide
NO_x	oxides of nitrogen ($NO + NO_2$)
O_3	ozone
PAH	polycyclic aromatic hydrocarbons
PEFR	peak expiratory flow rate
PFT	pulmonary function test
PM	particulate matter
$PM_{2.5}$	particulate matter less than 2.5 μm in diameter
PM_{10}	particulate matter less than 10 μm in diameter
PPB	parts per billion
QA/QC	quality assurance/quality control
RELF	respiratory extracellular lining fluid
RI	respiratory illnesses
ROS	reactive oxygen species
SAPALDIA	Swiss Study on Air Pollution and Lung Diseases in Adults
SCAQMD	South Coast Air Quality Management District
Si	silicon
SoCAB	South Coast Air Basin
SODs	superoxide dismutase (genes)
SO_2	sulfur dioxide
SO_4	sulfate
STI	Sonoma Technology, Inc.
TD	traffic density
TNFα	tumor necrosis factor alpha
TWS	Two-week sampler

UCLA	University of California, Los Angeles
USC	University of Southern California
VOC	volatile organic compound
WHO	World Health Organization
XRF	X-ray fluorescence spectrometry

11. Appendix

(See separate document)