Long-Term Ambient Concentrations of Total Suspended Particulates and Oxidants As Related to Incidence of Chronic Disease in California Seventh-Day Adventists

by David E. Abbey,* Paul K. Mills,* Floyd F. Petersen,* and W. Lawrence Beeson*

Cancer incidence and mortality in a cohort of 6000 nonsmoking California Seventh-Day Adventists were monitored for a 6-year period, and relationships with long-term cumulative ambient air pollution were observed. Total suspended particulates (TSP) and ozone were measured in terms of numbers of hours in excess of several threshold levels corresponding to national standards as well as mean concentration. For all malignant neoplasms among females, risk increased with increasing exceedance frequencies of all thresholds of TSP except the lowest one, and those increased risks were highly statistically significant. For respiratory cancers, increased risk was associated with only one threshold of ozone, and this result was of borderline significance.

Respiratory disease symptoms were assessed in 1977 and again in 1987 using the National Heart, Lung and Blood Institute respiratory symptoms questionnaire on a subcohort of 3914 individuals. Multivariate analyses which adjusted for past and passive smoking and occupational exposures indicated statistically significantly \( p < 0.05 \) elevated relative risks ranging up to 1.7 for incidence of asthma, definite symptoms of airway obstructive disease, and chronic bronchitis with TSP in excess of all thresholds except the lowest one but not for any thresholds of ozone. A trend association \( p = 0.056 \) was noted between the threshold of 10 ppbm ozone and incidence of asthma. These results are presented within the context of standards setting for these constituents of air pollution.

Introduction

Previous epidemiological studies of adverse health effects associated with long-term ambient air pollution have been difficult to conduct in most human populations due in large part to the confounding effects of cigarette smoking. However, several studies of air pollution and health have been completed using the Seventh-Day Adventist population of California, a nonsmoking population that experiences a wide degree of variation in exposure to several ambient air pollutants. For example, Hodgkin et al. demonstrated a statistically significant 15% increase in prevalence of symptoms of airway obstructive disease (AOD) in nonsmoking Adventists who had lived for 10 or more years in an area of high pollution (the South Coast Air Basin of California) compared to those residing 10 years or longer in less heavily polluted areas of the state \( I \). This result persisted in a multivariate analysis that controlled for age, sex, race, education, adverse occupational exposures, and past smoking history \( I \). Using this same population, Euler demonstrated statistically significant increased risk of AOD associated with both ambient levels of sulfur dioxide (SO\(_2\)) and total suspended particulates (TSP) \( 2 \). A later study also demonstrated statistically significant elevated AOD risk associated with ambient levels of total oxidants but not ambient levels of nitrogen dioxide \( 3 \).

These studies have been useful contributions in that they have demonstrated significant alterations in risk associated with long-term ambient concentrations of the pollutants in a nonsmoking population and have quantified that risk in reference to numbers of hours in excess of various thresholds of ambient air pollutants corresponding to state and national standards. However, they have been restricted to the analysis of the cross-sectional data then available in which respiratory symptoms data recorded by questionnaire at one point in time (1977) were correlated with ambient air pollutant levels during previous years. Longitudinal data are now available for this population for a 6-year period of follow-up (1977–1982) during which cancer incidence data and cardiovascular disease data were gathered in a prospective manner. Respiratory symptoms were ascertained on a subcohort in 1977 and again in 1987 enabling incidence of respiratory symptoms complexes to be ascertained. Mortality data are available for a 10-year follow-up period (1977–1986). Additionally, data on ambient levels of additional pollutants also have been collected (including SO\(_2\), SO\(_4\), and fine particulates less than 10 μm and less than 2.5 μm).
Recent papers describe the analysis of the longitudinal data regarding several thresholds of ambient levels of total suspended particulates (TSP) and ozone as they are related to definite symptoms of AOD, definite symptoms of chronic bronchitis, asthma, and cancer (Mills, manuscript submitted; Abbey, manuscript submitted). This paper summarizes those results and extends the disease outcomes to include cardiovascular disease and all natural-cause mortality.

## Methods

This is a prospective epidemiological study involving approximately 6000 Seventh-Day Adventists living in California in 1976 who were participants in the Adventist Health Study (4) and who had resided within 5 miles of their current residence for at least 10 years. By church proscription, Adventists do not smoke, although some members of this cohort (36% males, 14% females) smoked prior to joining the church. In addition to completing a detailed lifestyle questionnaire in 1976, members of this cohort completed the National Heart, Lung and Blood Institute (NHLBI) respiratory symptoms questionnaire in April of 1977. This 1977 questionnaire also elicited detailed lifetime residential histories that were used to construct air pollution profiles for study participants. Measures of ambient concentrations of TSP and ozone in those areas of California inhabited by members of the cohort were provided by the California Air Resources Board for the period 1966–1987. In the earlier years of this time period, total oxidants were monitored. Between 1973 and 1980, ozone monitors replaced the total oxidant monitors. However, in a validation study conducted by Abbey (manuscript submitted), mean concentrations of total oxidants and ozone over a 2-year period were found to have a correlation of 0.94. Measurements of these pollutants were made at several hundred air monitoring stations throughout the state using methods satisfying the Environmental Protection Agency (EPA) standards in effect at the time of monitoring. For each study participant, levels of air pollutants at zip code centroids were estimated for each month of residence since 1966 by using data from the three nearest monitoring stations. An interpolation method was then used to create individual ambient air pollution profiles based on zip code by month residence histories. Details of how these data were generated and validation studies of the methods are described by Abbey (5; Abbey, manuscript submitted). Thus, each member of the study cohort had been carefully characterized as regards lifestyle habits, residential history, and ambient concentration of several air pollutants.

Between 1977 and 1982, the cohort was followed-up and monitored for newly diagnosed cancer and myocardial infarction. Details of the follow-up procedure have been described by Beeson et al. (4). Mortality follow-up of the cohort has been completed through 1986. The analyses presented in this report concern risk of cancer, myocardial infarction (1977–1982), and all natural-cause mortality (1977–1986) as they were related to long-term ambient concentrations of TSP and ozone. Moreover, the respiratory symptoms questionnaire was completed again in April of 1987 by approximately 85% of the surviving members of the 1977 cohort. Results of the analysis of TSP and ozone as regards incidence of definite symptoms of AOD, chronic bronchitis, and asthma (1977–1987) are also presented in this report. The size and nature of the various subcohorts discussed in this

| Cohort and disease endpoint | Questionnaire data obtained in | Period of follow-up | No. of persons | Person-years |
|----------------------------|--------------------------------|--------------------|---------------|--------------|
| Cancer and myocardial infarction, incidence population | 1976,1977 | 1977–1982 | 6303 | 34,431 |
| All natural-cause mortality population | 1976,1977 | 1977–1986 | 6303 | 56,567 |
| Respiratory symptoms population | 1976,1977,1978 | 1977–1987 | 3914 | —* |

*Person-years were not calculated for the respiratory symptoms cohort because date of onset of symptoms was not ascertained on the questionnaire and therefore person-time analyses were not feasible.

## Statistical Analysis

Frequency distributions of the pollutants inside and outside the South Coast Air Basin of California (SCAB) were examined in order to create cutpoints for the tertile categories used in preliminary age- and sex-adjusted stratified Mantel-Haenszel analysis. The cutpoint used in creating the lowest exposure category for both pollutants was taken to be that level experienced by 90% of the study population residing outside the SCAB. The middle and upper tertiles were then created by dichotomizing the remainder of the study population. After these tertiles were identified, age- and sex-adjusted relative risks and 95% confidence intervals were calculated for each level of the pollutant using the adaptation of the Mantel-Haenszel method for person-years data (6). Trend p-values were also calculated to determine the significance of dose-response relationships in the data. These preliminary stratified analyses were conducted as a check on the results of the final, more sophisticated multivariate models since they do not make any assumptions about linear or additive effects. Cox proportional hazards regression models were constructed which incorporated, in addition to age and sex, several other covariates that were deemed potentially confounding. The terms included in the final models depended on the disease outcome of interest. Examples of additional covariates include total years of past smoking, educational attainment, and exposure to passive smoke at home or work. The specific covariates included in each model are presented in the footnotes to the tables. For the stratified analyses and the multivariate analyses, various threshold levels as well as mean concentrations of TSP and ozone (1973–1977) were (separately) used as the main exposure variables in relation to risk of disease during the follow-up periods which commenced in April of 1977. As a check, however, the final Cox models were re-run using the time period 1966 through 1977 as the exposure variable for both pollutants. In no case were significant discrepancies in results noted. The time period 1973–1977 was used in preference to 1966–1977 as all study participants had lived 10 years or longer in their present neighborhoods, and it was felt that interpolations for the later
time would be more accurate due to a larger network of monitoring stations during later years.

In the Cox models, for each of the disease outcomes except all natural-cause mortality, age was used as the time variable in the model because age is more closely related to risk of disease than time on study (6). However, since we have detected time trends in mortality probably due to a “healthy volunteer effect” in this data set (4), we used time on study as the time variable in the Cox models for the mortality analysis and incorporated age (as of April 1, 1977) as a covariate in the models.

As a check on the proportionality requirement of the Cox model, log-log plots were created, and the hazard function was examined across strata of covariates. In no case was there a crossover in the hazard function, indicating that the Cox model was an appropriate choice.

For the respiratory symptoms outcomes the multiple logistic regression model was used because date of incidence was not recorded. Stepwise procedures were used to select statistically significant covariates.

**Definition of Disease Outcomes**

Associations with ambient levels of TSP and ozone were made with several disease outcome categories including all malignant neoplasms (ICDO, 140–200) in males, all malignant neoplasms in females, respiratory cancer (ICDO, 160–165), definite myocardial infarction, and all natural-cause mortality (ICD9 000–799). The occurrence of incident myocardial infarction was documented by careful review of hospital records including cardiac enzymes and electrocardiographic readings by a cardiologist on the study staff. For the first four of these outcomes, incident events were considered for the time period April 1, 1977 through December 31, 1982. Since mortality ascertainment of the cohort had been extended through 1986 at the time this analysis was initiated, the follow-up period for the analysis of all natural-cause mortality included April 1, 1977 through December 31, 1982. To ascertain cumulative incidence of respiratory symptoms, the standardized NHLBI questionnaire was administered to study participants in April of 1977 and again in April of 1987. Computer algorithms were applied to the 21 respiratory symptoms questions on this questionnaire to classify individuals as having none, possible, or definite symptoms for each of chronic bronchitis, asthma, emphysema, or any or all of the above, which is termed AOD. An incident case for a particular respiratory symptoms complex was defined as having definite symptoms for that respiratory symptoms complex in 1987 but not having definite symptoms in 1977. To be classified as having “definite” chronic bronchitis, individuals must have had symptoms of cough, and/or sputum production on most days, for at least 3 months per year for 2 years or more. For a diagnosis of definite asthma, individuals must have been told by their physician that they had asthma, as well as having a history of wheezing. For emphysema, subjects must have been told by their physician that they had emphysema, as well as having shortness of breath when walking or exercising. Individuals not meeting the criteria for “definite” symptoms for a respiratory symptoms complex, but having some respiratory symptoms associated with that complex, were classified as “possible.” Due to an insufficient number of incident cases of emphysema to warrant separate analyses, emphysema was not analyzed as a separate outcome but it was included under AOD. Further details on the respiratory symptoms algorithms are provided by Abbey (7). Hodgkin (7) lists the respiratory symptoms that were used and gives the percentage of individuals having each symptom.

**Levels of TSP and Ozone in the Study Area**

Four threshold levels of TSP corresponding to state of California or national standards are graphically represented in Figure 1, which also shows the proportion of the study population that experienced several levels of hours in excess of these thresholds during the years 1973–1977. As expected, a relatively large proportion of the study population experienced several hundreds of hours in excess of the lowest threshold (THR60, i.e., 60 μg/m³ of TSP), whereas relatively few experienced many hours in excess of the highest threshold, THR200. However, it should be noted that 23% of the study population experienced 1000 hr or more in excess of THR200, which served as our primary threshold for analytic purposes.

In Figure 2, a similar pattern of hours in excess of several threshold levels of ozone is seen. In this case, our primary analytic threshold was OHR10 (i.e., 10 ppm [parts per hundred million] of ozone) and approximately 43% of the study population experienced 500 hr in excess of this level of ozone, 1973–1977. As regards mean concentration of TSP and ozone the distribution of these pollutants in the study population are graphically presented in Figures 3 and 4. It should be noted that in these figures individuals with more than 20% missing monthly values have been excluded and that the numeric values of the pollutants refer to the upper boundaries of the intervals.

**TSP and Ozone As Related to Cancer Incidence, Myocardial Infarction, and All Natural-Cause Mortality**

In this section we review and summarize results concerning TSP and ozone as they were related to cancer incidence, myocardial infarction incidence, and all natural-cause mortality in the cancer incidence population. Rather than relying upon mean concentration of ambient air pollutants only, these analyses also evaluated numbers of hours in excess of several thresholds of ambient air pollutants as they were related to disease risk. These thresholds corresponded to various State of California and national standards. For TSP these thresholds were 60, 100, 150, and 200 mcg/m³. Table 2 summarizes relative risks for a 1000 hour per year average annual increase in ambient concentration above TSP200, the most statistically significant threshold. Our results indicated that, for all malignant neoplasms among females, statistically significant increases in cancer risk were associated with each threshold of TSP except for TSP60. For 1000 hr per year in excess of TSP200, the relative risk for this group was 1.37 (CI, 1.05, 1.80) (Table 2) (Mills, manuscript submitted). Risk was also elevated for the respiratory cancers, although this finding was not statistically significant for any of the thresholds.

For ozone, the thresholds included 10, 12, 15, 20, and 25 ppm. Table 2 summarizes the relative risks for a 500 hr per year average annual increase above OZ10. The relative risk for respiratory cancer for OZ10 was 2.25 for 500 hr per year in
excess of this threshold, which was of borderline statistical significance (CI, 0.96, 5.31). The results of the analysis of mean concentration of TSP and ozone were also elevated but were not statistically significant.

When risk of myocardial infarction was evaluated in relation to ambient TSP levels, there was a slight increase in risk associated with TSP60, which was of borderline statistical significance. This increase was observed in both the stratified analysis and the regression analysis. However, none of the other threshold levels were associated with increased risk nor was there increased risk associated with mean concentration of TSP.

Ambient levels of oxidants were not associated with altered risk of myocardial infarction in regard to any threshold level of ozone or of mean concentration of ozone. For 500 hr in excess of OZ10, the multivariate adjusted relative risk for myocardial infarction was 1.06 (CI, 0.69–1.61) (Table 2).

The relationship between all natural-cause mortality (1977–1986) and ambient levels of TSP and ozone was examined, and
no alterations in risk emerged either when various threshold levels of TSP and ozone were examined nor when mean concentration was examined (Table 2). For 1000 hr in excess of TSP200, the relative risk for all natural-cause mortality was 0.99; for 500 hr in excess of OZ10 the relative risk was unity (Table 2).

**TSP and Ozone As Related to Respiratory Symptoms**

Incidence of definite symptoms of AOD and chronic bronchitis were statistically significantly ($p < 0.05$) elevated for average annual hours in excess of 100, 150, and 200 $\mu g/m^3$ and mean concentrations of TSP but not for 60 $\mu g/m^3$. For incidence of asthma, there was significantly elevated risks only for average annual hours above thresholds of 150, and 200 mcg/m³. Table 2 shows the relative risk for 1000 hr per year in excess of TSP200 for AOD and chronic bronchitis. Neither mean concentration nor any of the thresholds of ozone were statistically significantly associated with cumulative incidence of any of the respiratory symptoms outcomes, though a trend association ($p = 0.056$) was noted between OZ10 and cumulative incidence of asthma. The point estimate of relative risk for asthma was 1.40 (95% CI, 0.99–2.34). See Table 2.

**Discussion**

The pertinent results from this study indicate that risk of all malignant neoplasms among females, definite symptoms of AOD and chronic bronchitis, as well as asthma, are all significantly associated with ambient concentrations of TSP for thresholds of 100 $\mu g/m^3$ and higher and for asthma a threshold of 150 $\mu g/m^3$ and higher. Moreover, there is suggestive evidence that risk of respiratory cancer and asthma may be associated with elevated levels of ambient ozone at a threshold of 10 ppbm.

Several considerations, however, need to be taken into account in interpreting these findings. Although the study has numerous strengths that have been lacking in previous studies including the fact that it is a prospective study involving only nonsmokers who were geographically stable for a period of at least 10 years prior to the beginning of follow-up, certain limitations in the study design should be noted.

Estimates of air pollution exposure used in this study were estimates of ambient concentrations only. Studying the associations between adverse health effects and ambient concentrations is useful, since ambient concentrations are monitored, and air quality standards are based on them. Future analyses of these data, however, will attempt to model subjects' exposure more accurately by use of adjustment factors obtained in other human exposure modeling studies. The lack of incorporation of such factors in the present analyses are likely to make statistically significant associations more difficult to demonstrate as long as they are
not systematically biased due to an increase in uncontrolled variability (8).

Measurement error in cumulative ambient concentrations may have resulted from our use of interpolations from fixed site monitoring stations. A validation study, which compared concentrations at monitoring stations with those interpolated by surrounding stations indicated a correlation of 0.83 for mean concentration of TSP and in excess of 0.80 for mean concentrations of ozone (2; Abbey, manuscript submitted). Sensitivity analyses of these data were conducted which restricted individuals to those living within distances from monitoring stations regarded as having acceptable quality by EPA. The results of these sensitivity analyses indicate concurrence with the results described above (2; Mills, manuscript submitted).

Another weakness in the present study is that the respiratory cancer analysis was based on only 17 cases. In the future we plan to extend follow-up and to conduct a nested case-control study within the cohort with a larger number of respiratory cancer cases and an appropriate reference group.

It is difficult to explain the higher cancer incidence risk in females associated with TSP. Much smaller percentages of the females had been exposed to tobacco smoke and occupational fumes and dust. Only 14% of the females had a history of past smoking, compared to 36% of the males. There is some evidence that the increased risk of lung cancer associated with urban living is more apparent in nonsmokers than smokers (9-11). This is consistent with females' stronger relationship between TSP exposure and cancer incidence in this study.

Particulate matter in ambient air is known to contain substances that exhibit carcinogenic activity in experimental systems (12). The polycyclic aromatic hydrocarbons have received the most attention; several are known to be carcinogens in both animals and humans (13). A direct relationship between increasing exposure to TSP and increasing cancer incidence and mortality rates would therefore be expected.

Although the majority of studies attempting to evaluate the air pollution-cancer relationship have focused on lung cancer (14), several studies have investigated relationships with cancer and at all site and nonrespiratory tract cancers. For example, Winkelstein and Kantor found that both stomach and prostate cancer mortality rates were higher in the area of Buffalo, New York, with higher TSP pollution than in the less polluted areas (15,16). Other investigators noted significantly higher mortality rates for cancers of the stomach, esophagus, and bladder in more highly polluted areas of Nashville, Tennessee, than in less polluted areas (17). In the present study, large increases in risk of respiratory cancer were observed for elevated TSP ambient concentrations, yet increased risks for all malignant neoplasms were also observed, especially in females. These increased risks suggest that high ambient levels of TSP may have both local and systemic effects on cancer induction. Tobacco smoke exhibits similar effects. It greatly enhances the risk of tumors arising in the bronchial lining of the lung, which has a direct, intimate contact with the smoke, but also enhances the risk of cancers in the pancreas and bladder, which are exposed to carcinogenic metabolites of various tobacco constituents (18).

Only one case-control study of air pollution and lung cancer has been reported to date (19). In that study of white males, cases (n = 417) and controls (n = 752) were selected from residents of areas of high, medium, or low TSP levels (the maximum level was 200 µg/m²). The authors reported a nonsignificant odds ratio of 1.26 for residence in the high pollution area. Despite these findings, the authors pointed out that there was increased lung cancer risk from smoking and occupational exposure if there was also long-term exposure to air pollution.

In this study, no association between ambient levels of TSP or ozone and definite myocardial infarction was found. We also evaluated other cardiovascular disease outcomes including definite coronary heart disease death and sudden death but observed no relationships between these outcomes and ambient concentrations of TSP or ozone.

Most previous studies of air pollution and cardiovascular disease have focused on the role of carbon monoxide (CO). There does seem to be good evidence that exposure to elevated levels of atmospheric CO enhances the onset of angina in persons with pre-existing cardiovascular disease (20) and that the case-fatality rate from myocardial infarction is higher in highly polluted areas during periods of relatively increased CO pollution (21). The number of our study subjects living close enough to monitoring stations to enable ambient CO estimates was too small to warrant analyses.

In the Nashville air pollution study, cardiovascular disease morbidity was associated with increasing levels of a soiling index although particulates measured by a high volume sampler showed an inverse association with cardiovascular morbidity among white males greater than 55 years of age (17). White females, however, showed direct positive relationships with all pollutants measured in that study (22). Although it appears that data on social class and race were obtained, no adjustments were made for these factors nor were smoking habits evaluated. A subsequent report from the same study restricted the analysis to middle class participants only and reported a "consistent pattern of direct relationships of increasing cardiovascular disease mortality . . . for suspended particulate matter as measured by the soiling index." Again, however, it does not appear that the results were race or smoking history adjusted (23).

We did not detect any relationships between ambient levels of TSP or ozone and all natural-cause mortality in our population. Previous work has shown a relationship between ambient sulfates and particulates in relation to total mortality among 117 standardized metropolitan statistical areas in the United States (24). These earlier results may have been due to concomitant exposure to high levels of sulfates or to other unmeasured variables that may have produced spurious results. It should be noted that such high levels of sulfates do not exist in California. However, our inability to detect elevated mortality rates at 1000 hr in excess of TSP200 is in general agreement with recent efforts to identify a "no effects observable level" which concludes that there are no effects on mortality below 150 µg/m³ mean concentration of TSP (25). Ostro, on the other hand, argues that there is not sufficient evidence to support a no observable effects level at 150 µg/m³ of British smoke, for example (26). It can be seen in our data (Fig. 3) that there were insufficient numbers of study subjects above 150 µg/m³ of TSP mean concentration to adequately assess health effects at those levels.

By definition, incidence for the respiratory symptoms complexes excluded those individuals who had definite symptoms in 1977. These individuals may be the ones most susceptible to
respiratory effects as a result of high levels of ambient concentrations of TSP and ozone. To assess this possibility, a respiratory symptoms severity score was developed for each of AOD, chronic bronchitis, and asthma (7). Analyses for TSP and ozone were repeated, incorporating those individuals who had definite symptoms in 1977 and using multiple linear regression models to relate change in score 1977–1987 to pollutant thresholds and mean concentration. The results of these analyses are reported by Abbey (manuscript submitted) in general concurrence with the incidence results described above with the following exceptions: Mean concentration of ozone (1987–1987) and the 1977–1987 average annual hours in excess of thresholds 10 ppb and 12 ppbm of ozone showed statistically significant (p < 0.05) associations with change in the asthma severity score. When change in symptoms score rather than incidence was used for chronic bronchitis, no statistical significance was detected for the threshold of 100 μg/m³ of TSP, although statistical significance was still achieved for higher thresholds. These results suggest that asthmatics may be especially sensitive to continued elevated levels of ambient concentrations of ozone.

Although analyses of these health outcomes with SO2 have not yet been completed, it is unlikely that SO2 is confounding our results as average annual levels of SO2 in all of our study areas are below 25 μg/m³ which is low in comparison with other studies of the health effects of ambient air pollutants (27).

The findings of our study are consistent with those of the University of California–Los Angeles (UCLA), population studies of chronic obstructive pulmonary disease that were conducted on subjects in areas of high versus low oxidant air pollution of Southern California (28,29). The UCLA studies failed to show significant associations of oxidant air pollution with incidence of respiratory symptoms, but did show statistically significant associations of oxidant air pollution with declines in lung function.

The general conclusion of a number of recent review articles is that elevated concentrations of total suspended particulates contribute to respiratory morbidity over and above the effects due to cigarette smoking (27,30). Our findings relating elevated ambient levels of TSP to incidence of respiratory symptoms in non-smokers are consistent with this.

Results of our analyses pertaining to incidence of respiratory symptoms is in close agreement with previous reports on associations of TSP with prevalence of respiratory symptoms in this population (2). However, previous analyses of prevalence of definite AOD symptoms showed statistically significant associations with total oxidants, whereas our current analyses failed to show any statistically significant associations between cumulative 10-year incidence of AOD and total oxidants/ozone (3).

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