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Chronic Respiratory Disease Symptom Effects of Long-Term Cumulative Exposure to Ambient Levels of Total Suspended Particulates (TSP), Total Oxidants, Sulfur Dioxide and Nitrogen Dioxide in California

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I.
COPD Prevalence in Nonsmokers
in High and Low Photochemical Air Pollution Areas

II.
A Statistical Method for Assessing the Health Effects
of Long-term Environmental Exposures to Air Pollutants

III.
Chronic Respiratory Disease Symptom Effects of
Long-Term Cumulative Exposure to Ambient Levels of
Total Suspended Particulates, Total Oxidants, Sulfur
Dioxide and Nitrogen Dioxide in California

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David E. Abbey, Ph.D.
Professor of Biostatistics
School of Health
Loma Linda University
Loma Linda, CA 92350

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CHRONIC OBSTRUCTIVE PULMONARY DISEASE SYMPTOM EFFECTS OF LONG-TERM CUMULATIVE EXPOSURE TO AMBIENT LEVELS OF TOTAL SUSPENDED PARTICULATES TOTAL OXIDANTS, SULFUR DIOXIDE AND NITROGEN DIOXIDE IN CALIFORNIA

Gary L. Euler, Dr.P.H., RRT
Assistant Professor, Respiratory Therapy
School of Allied Health Professions
Loma Linda University
Loma Linda, California 92350

David E. Abbey, Ph.D.
Associate Professor Biostatistics
School of Health
Loma Linda University
Loma Linda, California 92350

John E. Hodgkin, M.D.
Clinical Professor of Medicine
University of California, Davis
Medical Director, Center for Health Promotion & Rehabilitation
Medical Director, Respiratory Care & Pulmonary Rehabilitation
St. Helena Hospital & Health Center
Deer Park, California 94576

Allan R. Magie, Ph.D.
Chairman-Professor, Environmental & Tropical Health
School of Health
Loma Linda University
Loma Linda, California 92350

Institution at which work was performed:
Department of Biostatistics and Epidemiology
School of Health
Loma Linda University
Loma Linda, California 92350

Address correspondence and requests for reprints to:
Gary L. Euler, Dr.P.H., RRT
Nichol Hall, Room, 1926
Loma Linda University
Loma Linda, California 92350
(714) 824-4932

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ABSTRACT

CHRONIC OBSTRUCTIVE PULMONARY DISEASE SYMPTOM EFFECTS OF LONG-TERM CUMULATIVE EXPOSURE TO AMBIENT LEVELS OF TOTAL SUSPENDED PARTICULATES TOTAL OXIDANTS, SULFER DIOXIDE AND NITROGEN DIOXIDE IN CALIFORNIA

Gary L. Euler, Dr.P.H., RRT, David E. Abbey, Ph.D.,
John E. Hodgkin, M.D., Allan R. Magie, Ph.D.
(Loma Linda University, Loma Linda, CA 92350)

To assess the risk of chronic obstructive pulmonary disease symptoms due to long-term exposure to ambient levels of total suspended particulates (TSP), total oxidants, sulfer dioxide (SO_2) and nitrogen dioxide (NO_2), symptoms were ascertained using the National Heart, Lung, and Blood Institute respiratory symptoms questionnaire (NHLBI) on 7,445 Seventh-day Adventist non-smokers, 25 years of age and older, who lived eleven years or longer in areas ranging from high to low photochemical air pollution in California. Participant cumulative exposures to each pollutant in excess of four thresholds were estimated using monthly residence zip code histories and interpolated dosages from state air-monitoring stations. Multiple logistic regression analyses were conducted for pollutants individually and together with eight covariables including passive smoking. Statistically significant associations with chronic symptoms were seen for 1) SO_2 exposure above 4 pphm, ($p = 0.03$), relative risk 1.18 for 500 h/yr of exposure; 2) total oxidants above 10 pphm, ($p < 0.004$), relative risk of 1.20 for 750 h/yr, and 3) total suspended

particulates (TSP) above 200 $\mu g/m^3$, ($p < 0.00001$), relative risk of 1.22 for 750 h/yr. When these pollutant exposures were entered together, TSP was the only one showing statistical significance, ($p < 0.01$). It appeared that TSP may be a surrogate measure of the mix of pollutants. Chronic respiratory disease symptoms were not found to be associated with the relatively low levels of NO_2 exposure in this population.

KEYWORDS

long-term exposure to ambient air-pollution

total suspended particulates

total oxidants

sulfur dioxide

nitrogen dioxide

symptoms of chronic obstructive pulmonary disease

multiple logistic regression

air quality standard setting

individual cumulative exceedance hours

Chronic Obstructive Pulmonary Disease Symptom Effects of Long-Term Cumulative Exposure to Ambient Levels of Total Suspended Particulates Total Oxidants, Sulfur Dioxide and Nitrogen Dioxide in California

INTRODUCTION

Toxic effects on the lungs and upper airways from inhalation of such specific ambient air pollutants as total suspended particulates (TSP) (1-5), total oxidants (OX) (6-13), sulfur dioxide (SO_2) (14-21), and nitrogen dioxide (NO_2) (22-28) have been demonstrated by experimental studies. Epidemiological studies published to date, however, have not been able to consistently demonstrate or quantify the risk of impairment, of otherwise normal respiratory health, due to long-term exposure to ambient concentrations of these specific pollutants regularly experienced in the most urbanized areas. (1,3,27,29-43) This may be in part because respiratory health in the adult is determined by many factors more influential than ambient air pollution exposure such as: genetic make-up (44,45), infant and childhood respiratory infections (46,47) tobacco smoke exposure--both active (48-55) and passive (56-63), and occupational (64,65) and indoor air pollution exposures. (27,66-70)

Studies to date have not been able to determine minimum safe levels of individual ambient pollutants, for example, that would produce no significant health effects in individuals if exposure continued for many years. Consequently, ambient air quality standards have had to be determined without substantial

METHODS

STUDY POPULATION

The study population was a subgroup of the National Cancer Institute funded Adventist Health Study (AHS), which in 1974 enrolled individuals of 36,805 Seventh-day Adventist (SDA) households in California, to study prospectively a wide variety of health effects possibly related to the SDA lifestyle, a lifestyle which generally incorporates abstainance from both tobacco smoking and drinking alcoholic beverages. SDA individuals 25 years of age or older, from the greater metropolitan areas of 1) Los Angeles and its' border counties, 2) San Francisco, and 3) San Diego and a random systematically selected sample of 862 from the rural areas of California, who had lived in their 1977 residential area for 10 years or longer were chosen for this study. For details concerning population distribution see a previous report. (71) The resulting population of 8,572 was identified by the letters AHSMOG representing Adventists, Health, and Smog.

In March 1977 these individuals were mailed a questionnarie which included the National Heart Lung and Blood Institute (NHLBI) questions on respiratory symptoms as well as additional questions to ascertain lifestyle factors pertaining to air pollution exposure such as smoking history, occupational history, residence history, etc. (71) Completed questionnaires were obtained from 7445 respondants representing an 87% response rate. The 109 who indicated they were presently smoking were excluded from the present analyses. Of those remaining 5539

(75.5%) had never smoked, while 1498 (20.4%) were past smokers. Past smoking histories were unknown for 299 (4.1%) individuals. Thirty percent had lived 10 or more years with a smoker and 18.5% had worked 10 or more years in a room with a smoker.

A respondant was defined as having symptoms of chronic obstruction pulmonary disease if they reported: 1) symptoms of cough and/or sputum production on most days, for at least three months per year, for two years or more or 2) having been told by their physician they had asthma as well as having a history of wheezing or 3) having been told by their physician they had emphysema as well as having shortness of breath when walking either normal paced or hurried. Fifteen percent of this population had these chronic respiratory symptoms. Age-adjusted sex-specific chronic bronchitis, emphysema, and asthma rates in never smokers in this population (71) were almost identical to those reported by Detels et al (35,37) when using comparable definitions.

MEASUREMENT OF AIR POLLUTION EXPOSURE

The AHSMOG study population resides in a geographic area within which the California Air Resources Board (ARB) maintains a network of 70 air quality monitoring stations. Hourly averages of total oxidants (OX), nitrogen dioxide (NO_2), sulfer dioxide (SO_2), and 24 hour averages of total suspended particulates (TSP) are recorded at these monitoring stations and stored on computer data tape. The methods of measuring each of these pollutants are described in ARB regularly published reports. (72)

In order to determine respiratory health effects due to

long-term exposure to concentrations of specific ambient air pollutants related to the state air quality standards we estimated each respondant's cumulative exposure to pollutant concentrations exceeding each threshold shown in table 1. For each of four pollutants four threshold concentrations were chosen from actually occuring ambient levels. Each set of four included at least one state standard. Two statistics were then calculated at each station: 1) total hours per month that concentrations at a station exceeded a threshold (exceedance hours) and 2) exceedance hours multiplied by each hourly concentration (exceedance dosage). These monthly, station specific, statistics were then interpolated to the center of each residential zip code of the study population from the three nearest monitoring stations using a $1/R^2$ (R = distance from station to center of zip code) interpolation method. (73)

The United States Environmental Protection Agency (EPA) has determined the distance from a monitoring station for which a measured value would be representative for each of the major ambient air pollutants. (74) Technology Service Corporation (TSC) of Santa Monica, California incorporated these distances in determining zip code areas for which relatively reliable concentration estimates could be obtained for a given pollutant. (73) For oxidants the distance from a station was 20 miles, for NO_2 10 miles, for SO_2 6 miles and for TSP it was 6 miles. Of the AHSMOG population excluding the small sample of 862 from rural areas, 99% lived within this area of relatively reliable concentration estimates for oxidants, 92% for NO_2, 62% for SO_2 and 70% for TSP.

With the 11 year monthly residential zip code history gained by questionnaire from each respondant and the monthly interpolated pollution values to each zip code, each individual's 11 year cumulative exceedance hours and exceedance dosage were then calculated for each threshold for each pollutant shown in table 1. Because of the high correlation between exceedance hours and exceedance dosage and because results of analyses were more easily interpretable for exceedance hours, only the results of analyses using the exceedance hours are reported here. Interpolated values since 1973 were felt to be more accurate as a much larger network of monitoring stations became operational in that year. Cumulations for participants' total oxidants exposure were thus done for two time periods--1966 through 1976 and 1973 through 1976 (prior to 1966 data were too scarce to merit interpolation). Analyses were run on both sets of data and close agreement was found between results based on the two time periods. To conserve space results for only the later time period are presented here.

STATISTICAL METHODS

Multiple logistic regression analyses were conducted to enable simultaneous statistical adjustment for confounding factors and other co-variate effects and to allow assessment of the singular effects of each exposure variable. Odds ratios obtained were adjusted to approximate relative risk. (Euler GL. Chronic Respiratory Disease Symptom Effects of Long-Term Cumulative Exposure to Passive Tobacco Smoke and to Ambient Levels of TSP, Oxidants, SO_2 and NO_2 in Southern California.

Dr.P.H. Dissertation, Loma Linda University, 1984.) Multiple logistic regression analysis is an appropriate technique when the outcome variable is incidence or prevalence of disease and one is seeking to estimate relative risks for various independent variables. (75)

Assessment of the goodness of fit of the multiple logistics model to the data was performed using a chi-square test between numbers of expected and observed cases for each decile of risk. (76) There were no statistically significant differences of cases by the regression equations which contained total suspended particulates (TSP) as the single ambient exposure variable; p-values from 0.35 to 0.68. The nitrogen dioxide (NO_2) regressions predicted observed cases with even better goodness of fit, p-values from 0.40 to 0.87. Oxidant regressions fit the observed distribution fairly well (p-values from 0.31 to 0.77) except for hours of exposure in excess of 15 pphm (p=0.01) and dosage in excess of 10 pphm (p=0.06). Sulfur dioxide (SO_2) regressions fit the observed distribution less well with p-values from 0.21 to 0.44 and the regression containing hours of SO_2 above 2 pphm does not fit well, p=0.06. In summary this multiple logistic model with these co-variables and confounders seems to fit the data moderately well with a few exceptions.

The demographic profile of this population has been described in detail elsewhere. (71) The most unique characteristic of this group of adults is the high proportion of never smokers. While the entire population are non-smokers, 75.5% (5539) have never smoked tobacco.

RESULTS

Total Suspended Particulates (TSP)

In table 2 we see the effects of TSP exposure (in number of hours per year at concentrations above 200 $\mu g/m^3$) along with eight co-variates determined by stepwise discriminant analysis to be the most important of all those measured in this study. Coefficients of these eight co-variates were not altered significantly by any of the ambient exposure variables studied individually or in combination. Of these eight variables two exposure variables were consistently statistically significantly associated with chronic respiratory disease symptoms--"years lived with a smoker" and "years worked with a smoker".

Five percent of this population had 5 years or more of occupational air pollution exposure. As estimated in this study, this exposure was not statistically significantly associated with chronic symptoms in this population.

Past smoking history reported by questionnaire as a "yes/no" variable was not statistically significant, however, using supplementary data collected by the National Cancer Institute funded study we were able to ascertain maximum number of cigarettes smoked per day in the past, number of years smoked, and number of years since joining the church. Since non-smoking is a religious prescription of the church, years since joining the church would be an approximation, though underestimate of years since stopped smoking for those who have smoked in the past. Using these three variables, a ratio was constructed of years smoked times maximum number of cigarettes smoked divided by years since joined church. Since many of the respiratory

symptoms associated with smoking are reversible with time, it was felt that this ratio would be a more accurate reflection of possible effects of past smoking on present respiratory symptoms. When this past smoking ratio was entered into the multiple logistic regression, the relative risk for past smoking became statistically significant. The relative risks and level of statistical significance for the other exposure variables did not change substantially.

Varying Threshold Levels For TSP

Because exceedance hours above different thresholds are highly correlated, we ran four separate logistic regressions, one for each threshold level. The results are shown in table 3. The same set of covariables as indicated in table 2 were used for each run. Similar coefficients to those in table 2 were obtained for these other covariates not shown in table 3. Of the four thresholds, hours of exposure above 200 $\mu g/m^3$ was the most significantly associated with increased symptoms of chronic respiratory disease. When all four thresholds were entered into the same regression, 200 $\mu g/m^3$ remains the threshold above which exposure was by far the most significantly associated with chronic respiratory disease symptoms.

In table 3, as the threshold levels (above which hours per year of exposure were measured) increase, we see a consistant trend toward increased statistical significance with only the lowest threshold level not being significant. The relative risk estimates also increase comparing corresponding increment size from threshold to threshold. For example, 1000 h/yr above 60

$\mu g/m^3$ results in a relative risk estimate of 1.02, for 1000 h/yr above 100 $\mu g/m^3$ it is 1.04, for 1000 h/yr above 150 $\mu g/m^3$ is 1.11, and for 1000 h/yr above 200 $\mu g/m^3$ it is 1.28.

These results indicate that about one-quarter of this population are experiencing exposure to TSP at levels high enough and long enough over an eleven-year time frame to demonstrate association with an increase in risk toward developing chronic respiratory disease symptoms of 22 to 32 percent.

TOTAL OXIDANTS (OX)

In table 4, exposure above the lowest threshold of oxidant concentration, 10 pphm, is the most significantly associated with chronic respiratory disease symptom prevalence, suggesting that statistically significant effects begin at or below 10 pphm. To make sure this was not a statistical artifact due to correlations between thresholds, hours of exposure between the thresholds 10 and 15 pphm were entered together into the same logistic regression equation with hours above 15 pphm. This was repeated for hours between 10 and 20 pphm with hours above 20 pphm and then again for hours between 10 and 25 pphm with hours above 25 pphm. In each regression equation, hours between 10 and the upper threshold showed a more significant association with chronic respiratory disease symptoms than hours of exposure above the upper threshold.

As the concentration threshold increases in table 4, less and less hours per year are needed to increase the risk. The relative risk estimate of 1.07, for example, requires 250 h/yr above 10 pphm. Above 15 pphm only 125 h/yr are needed; above 20

pphm, 48 h/yr, and; above 25 pphm, 25 h/yr. Also as threshold concentrations increase exposure above those levels become less statistically significant because of higher variability due to smaller numbers at risk. The margin of error in the estimation of individual exposures has a much greater dilution effect on the individual estimates of hours per year above the threshold of 25 pphm (above which 45% of the population is exposed for only 6 h/yr) than above 10 pphm (above which 43% is exposed for 500 h/yr). It probably is this lack of sufficient exposure in our population to higher levels of oxidents that is causing the reduced statistical significance for the higher thresholds.

Fewer individuals in the population were exposed for 750 h/yr to concentrations of oxidants above the California 1-hour standard of 10 pphm, than, were exposed for 750 h/yr to concentrations of TSP above 200 $\mu g/m^3$, twice the concentration of the California 24-hour standard, 18% vs 25%. The risk increase is slightly higher and more statistically significant for TSP exposure, 22%, ($p < 0.00001$) versus 20%, ($p < 0.004$) for oxidant exposure.

SULFUR DIOXIDE (SO_2)

Sulfur dioxide exposure as shown by table 5 does not show significant association with symptoms of chronic respiratory disease until concentrations exceed 4 pphm--the former California 24-hour standard since revised upward to 5 pphm. At concentrations above 8 pphm the percent of the population exposed for a significant number of hours per year becomes very low. The margin of error dilution effect along with higher variability due

to smaller numbers at risk results in less statistical significance even though per hour per year the increase in risk is greater as concentrations increase above 4 pphm. Of our population, 13.3 percent are exposed to concentrations of SO_2 above 4 pphm for 500 hours per year resulting during eleven years of exposure in a significant association with an 18 percent increase in risk of developing symptoms of chronic respiratory disease, ($p = 0.03$).

NITROGEN DIOXIDE (NO_2)

A table depicting results of our multiple logistic regression analysis on ambient NO_2 exposure has not been included because we found no statistically significant association between hours of NO_2 exposure above any of the four threshold concentrations and symptoms of chronic respiratory disease. A large portion of the population had considerable exposure to levels in excess of the lowest threshold of 5 pphm; 80% being exposed for at least 1500 h/yr and 20% exposed for 4900 h/yr. For the next higher threshold of 15 pphm, exposure plummeted to where only the top 20% were exposed to 350 h/yr or more. For higher thresholds there was even less exposure; above 20 pphm the top 20% were exposed for 115 h/yr and above 25 pphm the top 20% were exposed for only 25 h/yr or more. It is possible that in our population insufficient numbers experienced high enough exposure to NO_2 to detect statistically significant associations with symptoms of chronic respiratory disease.

TSP, OX, SO_2, and NO_2 COMBINED

The pollutant/thresholds above which exposure was found to be most significantly associated with chronic respiratory disease symptoms were: TSP above 200 $\mu g/m^3$, TSP(200), oxidants above 10 pphm, OX(10), and SO_2 above 4 pphm, $SO_2(4)$. These were entered along with NO_2 at a threshold of 25 pphm and then again with a threshold of 5 pphm into one multiple logistic regression analysis incorporating the 8 co-variates shown in table 2. In the initial combined regression equations NO_2 again was not found to contribute in any consistent or significant manner. In addition, as stated above, none of the NO_2 threshold exposures were statistically associated with symptoms in the individual ambient logistic regression analyses. Consequently NO_2 was excluded from further logistic analyses.

In the three pollutant combined analyses TSP(200) exposure effects overshadowed the effects of OX(10) and $SO_2(4)$ and TSP(200) was the only pollutant/threshold where significant association with chronic respiratory disease symptoms was seen, ($p = 0.008$). The likelihood ratio statistic which can be used as a relative measure of the predictive power or "fit" of the model for this combined analysis was 60. This compares to likelihood ratio statistics for $SO_2(4)$ alone of 45, for OX(10) alone of 52 and $SO_2(4)$ and OX(10) together of 53. However, the likelihood ratio statistic was the highest when TSP(200) was entered alone, 63. This indicates that for these data, TSP(200) is the best predictor of chronic respiratory disease symptoms of the air pollutant/thresholds considered.

When we replaced TSP(200) in the above analysis with hours of TSP exposure above 100 $\mu g/m^3$, TSP(100), we found that the likelihood ratio statistic for TSP(100) alone was 51 and when combined with OX(10) and $SO_2(4)$ it was 53. This was not a statistically significant improvement in the likelihood ratio as indicated by the Chi-Square test. Thus OX(10) and $SO_2(4)$ do not significantly improve the fit of the model over TSP(100) alone.

To assess possible synergistic effects, interaction terms were developed by taking the product of hours in excess of a threshold for all possible combinations of two pollutants. All possible combinations were tried one at a time in the logistic regression equation with the three pollutant/thresholds. In no case did the interaction terms improve the likelihood ratio statistic by more than one indicating no significant improvement in the model. Neither did any of the terms have regression coefficients which approached statistical significance.

Because of the potential problems of multicolinearity in the above regressions, a set of multiple regression analyses were performed to determine what percent of the variation in each ambient pollutant threshold variable [TSP(200), OX(10), $SO_2(4)$, or $NO_2(25)$] was explained by the other three pollutant threshold variables as indicated by the multiple R^2. It was found that 80% of the variation in TSP(200) was explained by the other three, 74% of the variation of OX(10) by the other three, and 49% of the variation of $SO_2(4)$ by the other three. This would suggest that TSP(200) is presently the single best surrogate indicator of overall ambient air pollution exposure effects on chronic respiratory symptoms in Southern California.

DISCUSSION

PASSIVE SMOKE

Working in the same room with a smoker as compared to living with a smoker was found in this study to be more highly statistically significant and also to have a higher increase in risk. One possible explanation for this finding is that the work environment may be less conducive to modification to accommodate the non-smoker than that of the home environment.

The measures of passive tobacco smoke exposure at home and in the work place used in this analysis are only crude indicators of the actual exposure. However, because of the levels of increased health risk from passive smoke exposure indicated in other studies (69,77-80) and the relative size of the risk increases compared to that of ambient air pollution exposure shown in this study, passive smoke exposure, it seems, should be included as a covariable in future studies on the effects of ambient air pollution on the respiratory health of non-smokers.

OCCUPATIONAL AIR CONTAMINANTS

The relatively small numbers of study participants classified as having significant occupational exposure, the variety of occupations and varying levels of exposure to pollutants may account for this exposure lacking statistical significance in the multivariate analyses.

TOTAL SUSPENDED PARTICULATES (TSP)

When the results of the pollutant specific logistic regression analysis are compared, TSP exposure demonstrates the

strongest statistical association with chronic respiratory disease symptoms ($p < 0.00001$). In addition a greater percentage of the population were exposed for many more hours per year to TSP concentrations above state standards than for the other pollutants. More individuals were at the highest relative risks (shown in these tables) of chronic respiratory disease symptoms associated with TSP exposure than with exposure to any one of the other three pollutants. TSP exposure was the only exposure studied to show a consistant increase in strength of statistical association as the exceedance threshold concentrations increased. OX was of secondary importance to TSP according to the following characteristics--1) lower statistical significance, 2) smaller percentage of the population at the higher relative risks, and 3) fewer hours of exposure above the state standards. SO_2 was much less important and NO_2 was not statistically significant.

When the exposure effects of TSP(200), OX(10), and SO_2(4) were studied simultaneously in one logistic regression analysis, TSP exposure was the only one of the three found to be significantly associated with chronic respiratory disease symptoms, ($p < 0.01$).

TSP concentrations ranging from 77 to 180 $\mu g/m^3$ have reportedly been associated in several studies with chronic respiratory illness. (1) In an excellent and critical review of the reported health effects of long-term TSP exposure, however, Holland et al (3) concludes the "weight of evidence . . . shows no measurable effect on health [due to TSP exposure

to annual mean concentrations] in the range of 80-130 $\mu g/m^3$," and that a minimum safe level might be 240 $\mu g/m^3$.

Although it would appear from our data that TSP (200) exposure is the pollutant exposure most strongly related to chronic respiratory disease symptoms in our population we cannot rule out the possibility that TSP (200) is a surrogate measure for the overall mix of pollutants.

TOTAL OXIDANTS (OX)

The Los Angeles area is felt to have the most severe known oxidant ambient air pollution in the United States. (33) Thus all the recent epidemiologic studies of the area residents have compared groups of people living in areas having relatively high to those living at low levels of oxidant exposure. (33-36,71) Chronic respiratory symptoms were not linked to increased oxidant exposure in several of the studies, (33-35,71) but in others an association was seen. (36) In all of the above references particulate levels were reported to be higher in the geographic locales with higher oxidant concentrations. Our data support this as we found a correlation of 0.79 between OX (10) and TSP (200). Because of this high correlation we cannot with certainty separate the effects of the two pollutants. Since 1983 the California Air Resources Board has defined the measurement of TSP into two components: coarse (10 to 2.5 microns) and fine (less than 2.5 microns). If the correlations of these components with oxidants is lower, separation of the effects may be possible for future studies.

By adjusting for passive smoking we may have controlled for the major indoor source of SO_2 and TSP air pollution. (81) However since oxidant levels are generally not as high indoors as they are outside, (82,83) exposure to oxidants as approximated by ambient residential levels would be less accurate for the individual who spent more time indoors. The fewer the hours per year of residential oxidant levels above a threshold the greater will be the resulting increased variablity in related exposure effects due to time spent indoors. This phenomenon along with the greater impact of interpolation error at higher threshold levels due to low hours of exposure may explain the trend toward decreasing statistical significance associated with increasing oxidant thresholds, shown in table 4.

SULFUR DIOXIDE (SO_2)

SO_2 air pollution is often studied along with TSP levels because both pollutants are usually found together in urban areas. For this reason, most studies in the past have found it very difficult to separate the effects of SO_2 exposure from TSP exposure. (32) We did not experience this difficulty with our long-term accumulation exposure data. The only threshold level of SO_2 showing statistical significance was $SO_2(4)$. The correlation coefficient of $SO_2(4)$ with TSP (200) was 0.3 indicating that less than 9% of the variation in $SO_2(4)$ is explained by TSP(200) thus making it possible to separate effects of the two pollutants. The levels of SO_2 experienced by the AHSMOG population however, are far below levels shown to produce significant acute respiratory effects (even in hyperreactive

individuals) from short term exposure. Linn et al (17) found no significant acute increases in respiratory symptoms or decrease in function in asthmatics exposed to concentrations as high as 50 pphm. By comparison 50% of those in AHSMOG were not exposed at all to concentrations of SO_2 any higher than 14 pphm in their residential area. Less than 2% were exposed for no more than 20 hours per year to levels above 14 pphm.

Several reports with conflicting findings do exist from studies of natural experimental conditions involving different pairs of two "similar" cities in which ambient SO_2 concentrations differed (38,40,41) In the studies where SO_2 concentrations occasionally reached 18 pphm no difference in lung function was noted (40,41) and with the exception of slightly more cough (41) no significant differences were seen in respiratory symptoms. In the study where SO_2 concentrations occasionally reached 30 pphm (38) symptoms of chronic bronchitis in men and the mean ratio of forced vital capacity to forced expiratory volume in one second were the only parameters statistically significantly worse in the higher SO_2 city.

In a study of the chronic effects of long-term exposure at yearly mean levels of SO_2 near 5 pphm Aubry et al (38) compared three communities in the greater Montreal region. They used discriminant analysis to adjust for a number of covariates and detected no statistically significant association of respiratory symptoms or function with yearly mean SO_2 levels higher than those experienced by the AHSMOG population--which were less than 3.2 pphm for those in our population with the highest exposure. (84,85,86)

Thus it appears likely that lack of statistical significance for the higher levels of SO_2 in our study is due to insufficient exposure in our population.

NITROGEN DIOXIDE (NO_2)

Historically it has been difficult to separate ambient NO_2 exposure effects from those of other pollutants because NO_2 also tends to occur in the presence of other pollutants. According to a review article by Dawson and Schenker (27), studies reporting on the respiratory effects of NO_2 exposure range from implicating mean concentrations as low as 5 pphm in children and 10 pphm in asthmatics to finding no effects in healthy adults from acute exposure to levels as high as 100 pphm. One study by Love and coworkers (30) found a reduction in acute respiratory illness rates associated with a drop in mean NO_2 concentrations. We are not aware of any studies to date which have determined the respiratory health effects in adults due to long-term exposure to commonly experienced ambient levels of NO_2, i.e. mean levels of 50 pphm and lower.

Yearly mean levels in residential areas of AHSMOG participants ranged only as high as 13.0 pphm. The mean of the station yearly mean levels was 5.2 pphm with a standard deviation (S.D.) of 4.3 pphm. We found no evidence in our population to support a link between this level of long-term exposure to NO_2 and chronic respiratory symptoms. Most likely these relatively low ambient NO_2 levels in Southern California do not directly contribute toward increased risk of development of chronic respiratory disease symptoms. However we did not adjust for

indoor NO_2 levels which may often be significantly elevated due to the use of gas cooking stoves and which have been reportedly associated in several studies with increased respiratory disease symptoms in children. (27) Childhood respiratory symptoms, in turn, have been associated with increased COPD in adulthood. (46,47)

STUDY LIMITATIONS

As in all cross-sectional studies of this type a number of biases due to the study design may be present. Our study population consists of a relatively stable population: a population that has lived for 11 years of longer at their 1977 residential area. Thus self selection factors could be present that might have altered the prevalence of chronic respiratory diseae symptoms in relationship to the level of ambient air pollution. There may be selective out migration of either sick people or healthy people from polluted areas resulting in an artificially produced relationship between chronic respiratory disease symptoms and ambient air pollution exposure. If individuals more sensitive to exposures likely to produce chronic respiratory disease symptoms tend to selectively move away from the more polluted areas and thus escape our study by having moved in the last 11 years, and if those with chronic respiratory disease symptoms in the lower pollution areas are less likely to move and therefore enter the study by having not moved in the last 11 years, then symptom rates due to self selection would be artifically higher in the low pollution areas. This would make a true positive relationship more difficult to detect. A self

selection bias in the opposite direction may exist due to disability induced immobility. A presently planned re-survey of the population will include those who have moved and could thus partially assess the migration effect.

Measurement bias may be introduced to the degree of inaccuracy that self reported symptoms of chronic respiratory disease actually measure the presence of these symptoms. The findings of the American Lung Association of Southern Florida in an unpublished report 1981 (Couch GB, Brimhall PN: Identification of chronic respiratory disease through self-reported as compared with pulmonary flow-volume loop screening. Prepared for the American Lung Association of Southeast Florida, October 1981. Unpublished.) indicate that when chronic symptoms of respiratory disorders are self-reported underreporting is much more common (47-54%) than overreporting (13%) as detected by medical examination and spirometry. If the same situation exists in this California population the group reporting chronic respiratory disease symptoms is more correctly defined than the group without reported chronic symptoms and the group not reporting chronic symptoms has poorer resiratory health than reported. This would result in the positions of the two groups on the discriminating variables being closer than in reality, producing a conservative bias. A non-conservative bias would result if those living in the higher pollution areas had less underreporting.

Self-reported prevalence of chronic respiratory disease symptoms measured even by a standardized questionnaire is not as valid or reliable as prevalence measured by a personal interview

with a physician or other trained interviewer. In addition, the use of spirometry and other pulmonary function tests may be helpful to detect early signs of chronic respiratory disease.

Another factor which could introduce large variability is the degree of inaccuracy involved in interpolating air monitoring station monthly statistics to residential zip codes to measure individual ambient air pollution exposure. According to the United States Environmental Protection Agency ambient pollutant concentrations monitored at a fixed monitoring station tend to be representative within a known radius (stated above) provided there are not physical barriers such as mountains present. (74) This has been confirmed by Technology Service Corporation for the Los Angeles Area. (73) Penalty boundary functions were thus used to avoid interpolation across the physical barriers present in the geographic area of the study population. (87) Multiple logistic regressions were repeated excluding those living outside the representative radius and similar results were obtained.

A number of additional variables, some of which are listed below, were measured by questionnaire to be used, if significant, to refine the cumulative exposure as measured by residential zip code history.

Weeks away from home during months of June-September

Hours per day during the work week/weekends spent on crowded roadway

Hours per week spent indoors/outdoors in vigorous exercise during the summer/rest of year

Hours per week spent outside of building during the summer/rest of year

Type of air-conditioning at home/work

Work location history if ever more than 5 miles from home

The above variables were initially included with the other 9 of table 2 in a discriminant analysis to determine if they made a statistically significant contribution. None did. Another way of incorporating these variables is to adjust exposure with an index composed of all the above variables. Such an adjustment formula would need to be determined using such devices as portable oxidant monitors on a sample of the study participants. We know of at least one large epidemiologic study by Ferris and coworkers on the "Effects of Sulfur oxides and Respirable Particles on Human Health" reported in the literature (89) that is doing elaborate individual and indoor air sampling. Their conclusions have not been published to date.

Certainly there are also limitations in statistically separating air-pollutants occuring in an ambient mixture. A more accurate way of assessing the effects of separate pollutants would be human gas chamber studies. These have been used to assess effects of short term acute exposures (89), however, they are not feasible for long-term cumulative exposures over many years. The statistically defined interaction terms used to assess possible synergistic effects in this study are not as valid as cumulated simultaneous exposure levels for pollutant combinations. This could be accomplished by computor using the existing recorded data which would allow for more accurate interpretation necessitating, however, considerable additional funds.

Indoor levels of air pollution were not measured in our study because of the large additional expense necessary for these measurements. TSP, SO_2 and NO_2 levels indoors may not correlate very well with ambient levels, because of several common indoor sources for these pollutants: tobacco smoking, gas cooking stoves, gas and wood burning fireplaces, etc. Indoor oxidant levels can be 60 to 80% of those outside if windows are open and/or outside air is rapidly circulated through the building (90,91). However indoor oxidant levels may rapidly drop from outside concentrations if little outside air is brought in (i.e., closed windows and doors). In 1973 Sabersky and coworkers (94) reported that within typical buildings located in photochemically smoggy areas ozone concentrations were found to be only a little less than corresponding outdoor concentrations. Because of this we felt outside levels of oxidants were representative of indoor levels and would serve as a valid surrogate measure of long-term cummulative exposure levels for comparison from individual to individual.

As a cross sectional study there are inherent possible biases that would be removed by a prospective appreach. We have maintained current files on this population. Future surveys will allow comparison between changes in chronic respiratory disease symptoms and changes in ambient pollution exposure levels over a period of years.

SUMMARY

The purpose of this study was to determine the association of symptoms of chronic obstructive pulmonary disease with long-term ambient air pollutant exposures above threshold levels for specific pollutants. Since a number of individual pollutants exist in combination in the ambient air, assessment of health effects of one pollutant must include adjustments for the effects of the associated major air pollutants in the mix of ambient air as well as exposure to other airborne contaminants. In this study we sought to statistically separate the effects of TSP, total oxidants, SO_2 and NO_2 as well as exposure to passive cigarette smoke and occupational pollutants. The results of the multiple regression analyses seem to indicate that the most statistically significant ambient air pollutant and threshold of those we investigated to be TSP of 200 $\mu g/m^3$. In the presence of this variable, other pollutants do not show statistical significance in the regression equation nor do they improve the fit of the multiple logistics regression model. It did not appear that NO_2 or SO_2 had a strong relationship with symptoms at the levels experienced in our study population. Our findings would be consistent with the hypothesis that cumulative exposure to total suspended particulates in excess of 200 $\mu g/m^3$ had the strongest relationship with chronic respiratory disease symptoms among those pollutants we studied. However, another possibility which cannot be discounted is that TSP(200) may simply be the best single surrogate indicator of the chronic respiratory symptom exposure effects of the ambient pollution mixture in Southern California. The measurement methods begun by California

ARB on July 1, 1983 which separate TSP into two components, coarse (10 to 2.5 microns) and fine (less than 2.5 microns), (85) will enable further assessment of these possibilities.

It is hoped that the findings presented here will provide new insight and support for past and future air quality standard setting and that future assessment of the adequacy of these standards will find the application of the technical and statistical methods illustrated useful.

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TABLE 1

CONCENTRATION THRESHOLD LEVELS

Pollutant	Concentration Threshold 1st Level	2nd Level	3rd Level	4th Level
OX	10 pphm (Calif. std.)	15 pphm	20 pphm (1st stage alert)	25 pphm
NO_2	5 pphm (primary 1 yr. std.)	15 pphm	20 pphm	25 pphm (Calif. 1-Hr. std.)
SO_2	2 pphm	4 pphm* (Calif. 24-Hr. std.)	8 pphm	14 pphm (primary 24-Hr. std.)
TSP	60 mcg/m^3 (Calif. 1 yr. std.)	100 mcg/m^3 (Calif. 24-Hr. std.)	150 mcg/m^3 (secondary 1 yr. std.)	200 mcg/m^3

*The Calif. 24-Hr. std. for SO_2 has since been revised upward to 5 pphm.

TABLE 2

Independent estimates of chronic obstructive pulmonary disease symptom risk for selected exposure and demographic variables by multiple logistic analysis: Southern California SDA residents 25 years of age and older, 1966-1976

n = 6472
cases = 1023

Variable	Logistic Coefficient*	Increment	Relative Risk Estimate	p-value
Hours TSP(200) Exposure	0.00008	750 hrs/yr†	1.22	<0.00001
Occupational Exposure	0.23069	(No; Yes)	1.22	0.11
Years lived with smoker	0.00790	10 yrs.	1.07	<0.01
Years worked with smoker	0.01207	10 yrs.	1.11	<0.001
Past smoker	0.14454	(No; Yes)	1.13	0.10
Sex	0.07183	(Female; Male)	1.06	0.36
Age	0.00395	30 yrs.	1.11	0.13
Race	0.16567	(Non white; white)	1.16	0.15
Education	0.01254	4 yrs.	1.04	0.65

*Per one unit, i.e., 1 hr. or 1 yr.
†Spanning four years (1973-1976)

TABLE 3

Independent estimates of chronic obstructive pulmonary disease symptom risk for hour thresholds by multiple logistic analysis: Southern California SDA residents 25 years of age and older, 1966-1976*
n = 6472
cases = 1023

Hours TSP Exposure	Percent Population Exposed	Increment Size	Relative† Risk Estimate	p-value‡
Above 60 mcg/m^3	27	7500 hrs/yr	1.16	
	78	3500 hrs/yr	1.07	0.12
	91	1000 hrs/yr	1.02	
Above 100 mcg/m^3	24	5000 hrs/yr	1.23	
	67	2500 hrs/yr	1.11	0.006
	77	1000 hrs/yr	1.04	
Above 150 mcg/m^3	24	2500 hrs/yr	1.32	
	60	1000 hrs/yr	1.11	<0.0001
	69	500 hrs/yr	1.05	
Above 200 mcg/m^3	23	1000 hrs/yr	1.30	
	25	750 hrs/yr	1.22	<.00001
	28	500 hrs/yr	1.14	
	55	250 hrs/yr	1.07	

*Exposure time period was 1966-1976, however, 1973-1976 air monitoring data was used for the analysis represented in this table. See text for rationale.

† The relative risk estimate is a function of the regression coefficient and the increment size.

‡ The p-value is determined by the regression coefficient and is the same for all relative risk estimates for a given threshold.

TABLE 4

Independent estimate of chronic obstructive pulmonary disease symptom risk for hour thresholds by multiple logistic analysis: Southern California SDA residents 25 years of age and older, 1966-1976*
n = 6482
cases = 1026

Hours Oxidant Exposure	Percent Population Exposed	Increment Size	Relative† Risk Estimate	p-valve‡
Above 10 pphm	18	750 hrs/yr	1.20	
	43	500 hrs/yr	1.13	<0.004
	50	250 hrs/yr	1.07	
Above 15 pphm	23	250 hrs/yr	1.15	
	45	125 hrs/yr	1.07	<0.005
	49	75 hrs/yr	1.04	
Above 20 pphm	16	96 hrs/yr	1.13	
	40	48 hrs/yr	1.07	<0.02
	45	24 hrs/yr	1.03	
Above 25 pphm	16	24 hrs/yr	1.07	
	33	12 hrs/yr	1.03	0.11
	45	6 hrs/yr	1.02	

*Exposure time period was 1966-1976, however, 1973-1976 air monitoring data was used for the analysis represented in this table. See text for rationale.

† The relative risk estimate is a function of the regression coefficient and the increment size.

‡ The p-value is determined by the regression coefficient and is the same for all relative risk estimates for a given threshold.

TABLE 5

Independent estimates of chronic obstructive pulmonary disease symptom risk for hour thresholds by multiple logistic analysis: Southern California SDA residents 25 years of age and older, 1966-1976*
n = 6350
cases = 1003

Hours SO_2 Exposure	Percent Population Exposed	Increment Size	Relative † Risk Estimate	p-value ‡
Above 2 pphm	16	2000 hrs/yr	1.09	
	62	1000 hrs/yr	1.04	0.24
	80	500 hrs/yr	1.03	
Above 4 pphm	13	500 hrs/yr	1.18	
	31	250 hrs/yr	1.09	0.03
	77	100 hrs/yr	1.03	
Above 8 pphm	23	60 hrs/yr	1.07	
	37	30 hrs/yr	1.03	0.18
	43	15 hrs/yr	1.02	
Above 14 pphm	17	10 hrs/yr	1.03	
	26	5 hrs/yr	1.01	0.58
	45	1 hrs/yr	1.00	

*Exposure time period was 1966-1976, however, 1973-1976 air monitoring data was used for the analysis represented in this table. See text for rationale.

† The relative risk estimate is a function of the regression coefficient and the increment size.

‡ The p-value is determined by the regression coefficient and is the same for all relative risk estimates for a given threshold.

COPD Prevalence in Nonsmokers in High and Low Photochemical Air Pollution Areas*

John E. Hodgkin, M.D., F.C.C.P.;† David E. Abbey, Ph.D.,‡ Gary L. Euler, Dr.P.H., R.R.T.;§ and Allan R. Magie, Ph.D.‖

The prevalence of respiratory symptoms, as ascertained by questionnaire, was evaluated in 6,666 nonsmokers who had lived for at least 11 years in either a high photochemical pollution area (4,379 individuals) or a low photochemical pollution area (2,287 individuals). Of these, 5,178 had never smoked, and none was currently smoking. The risk estimate for "definite" COPD, as defined in this study, was 15 percent higher in the high pollution area ($p = 0.03$), after adjusting for sex, age, race, education, occupational exposure, and past smoking history. Past smokers had a risk estimate 22 percent higher than never smokers ($p = 0.01$). Multivariate analysis showed a significant effect of air pollution on the prevalence of "definite" COPD which univariate analysis failed to demonstrate.

From studies published to date, there is conflicting evidence regarding the effects of long-term exposure to ambient levels of photochemical air pollutants on respiratory symptoms and lung function.[1-4] Even less clear is the evidence linking chronic obstructive pulmonary disease (COPD) to photochemical air pollution exposure. It is possible that at least some of the conflicting evidence is due to overwhelming effects of confounding factors such as smoking. We therefore set out to evaluate the effect of long-term exposure to photochemical air pollution on respiratory symptoms and COPD in a stable, homogenous group of California nonsmokers.

Materials and Methods

Such a group of nonsmokers became available through the National Cancer Institute funded Adventist Health Study. This prospective Adventist Health Study enrolled individuals in 36,805 Seventh-day Adventist (SDA) households in California in 1974, to study a wide variety of health effects possibly related to the SDA unique lifestyle. Those individuals enumerated in the census questionnaires who were 25 years or older were mailed a detailed lifestyle questionnaire in August 1976. Annual follow-up has been conducted in the study population to ascertain hospital and address changes.

A subgroup of this population who had lived 11 years or longer in either a high pollution or a low pollution area was selected for further study. This substudy was tagged AHSMOG for Adventist Health Smog. A portion of the South Coast Air Basin was selected for the high-pollution study area. The boundaries for this area were defined using individual monitoring station data to include a portion of the Southeast Desert Air Basin known to have significant levels of oxidants and to exclude the southern edge of the South Coast Air Basin where oxidant levels and population density were much lower than the rest of the area (Fig 1). Two low pollution urban areas were selected for the study—San Francisco and San Diego. The geographic boundaries of the study population for San Francisco were defined by zip code using population density maps so as to include the surrounding metropolitan area (Fig 2). A similar procedure was used to define the boundaries of the San Diego Metropolitan Study Area (Fig 3).

In addition to these three urban areas selected for the study, a sample of 862 individuals was selected from the rest of the Adventist Health Study who met the 11 year residence criteria. This was done to provide a low exposure rural group, as well as to provide a more random sample for estimating COPD prevalence for the Adventist Health Study. They were selected according to a systematic random

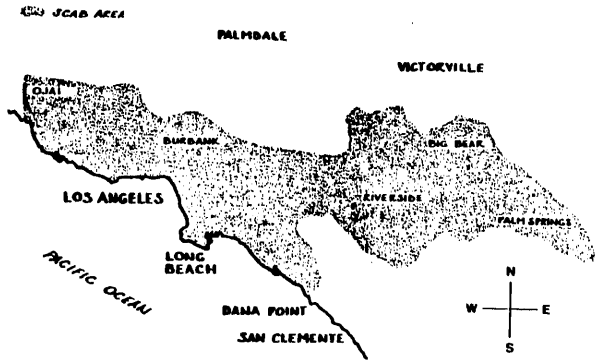

FIGURE 1. Geographic boundaries for South Coast Air Basin (SCAB).

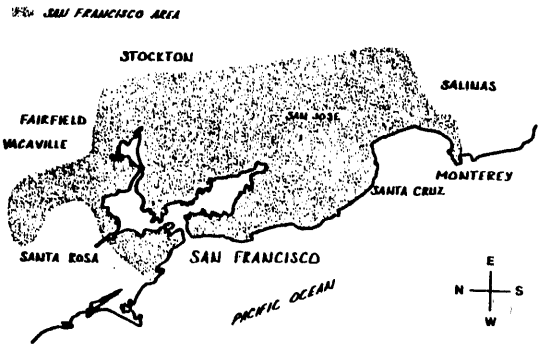

FIGURE 2. Geographic boundaries for San Francisco.

*From the University of California at Davis; the Center for Health Promotion and Rehabilitation, St. Helena Hospital and Health Center, St. Helena; and the School of Allied Health Professions and School of Health, Loma Linda University, Loma Linda, CA.
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†Clinical Professor of Medicine.
‡Associate Professor, Biostatistics.
§Assistant Professor.
‖Chairman-Professor, Environment and Tropical Health.
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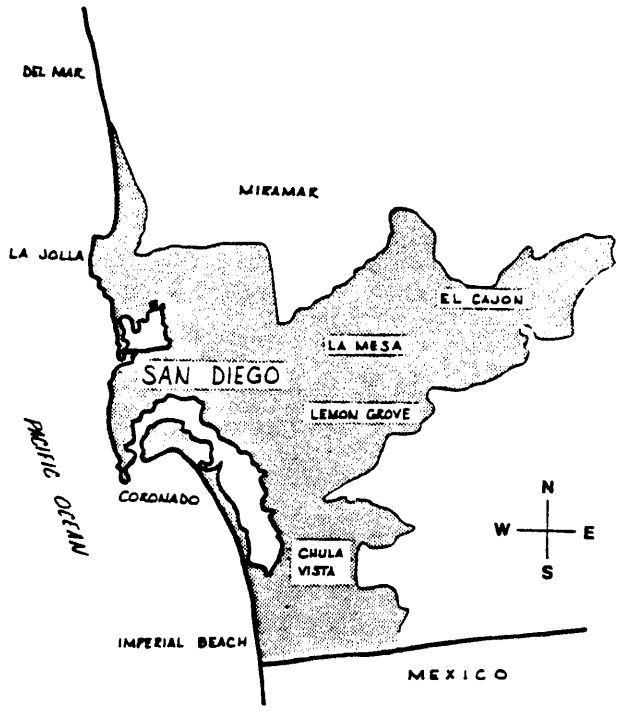

FIGURE 3. Geographic boundaries for San Diego.

sample, with all of the population ordered by zip code, to assure a wide geographic spread. All of these 862 individuals were in areas which were low in air pollution levels as compared to the South Coast Air Basin.

An additional questionnaire was mailed out in March 1977 to the 8,572 individuals selected for further study. This questionnaire included the National Heart, Lung and Blood Institute Respiratory Symptoms Questionnaire to which were added questions to ascertain lifestyle factors pertaining to relative air pollution exposure, residence history, occupational history, and smoking history. Completed questionnaires were obtained from 7,267 individuals, giving an overall response rate of 85 percent. The response rates were similar in each of the four areas: South Coast Air Basin, 85.7 percent; San Diego, 88.4 percent; San Francisco, 89.4 percent; and 89.6 percent in the rural areas.

One-hundred and nine of the respondents indicated they were presently smoking. These individuals were excluded from the present analyses. Four-hundred ninety-two of the individuals were discovered to have lived for a portion of the previous 11 years outside of the designated areas so were also excluded from analysis. The exclusion of these 601 individuals left 6,666 individuals available for analysis.

A total of 2,287 individuals lived in the low-pollution areas, and 4,379 in the high pollution area. Five-thousand one-hundred seventy-eight (77.7 percent) of those studied had never smoked, while 1,482 (22.2 percent) were past smokers. The past smoking history was unknown for six individuals. Three-hundred sixty-four subjects (5.5 percent) were felt to have a significant occupational exposure, as defined by at least a five-year exposure to pollutants such as welding fumes, rock dust, and silica.

Significant occupational exposure was defined as five or more years of occupational exposure to a pollutant thought to predispose an individual toward development of COPD. Respondents reported their main occupation and major duties and whether or not they had ever been employed where they were exposed to contaminants such as chemical fumes, paint fumes, welding fumes or dust, wood dust, rock dust, etc. They also reported the number of years of exposure, type of work performed, and specific types of contaminant exposure. Reported occupations with adverse exposure in this population were as follows:

Heavy equipment/bulldozer operator
Automobile body repairman
Carpenter, woodshop furniture maker, lumbermill worker
Road construction worker
Painter
Welder, boilermaker
Foundry worker
Masonry worker, cement worker, quarry worker
Miner (underground)
Textile operator, sewer worker, spinner, knitter

When the respondent reported one of the occupations listed above or five years or more of exposure to one of the contaminants listed below, the respondent was considered to have a significant occupational exposure: welding fumes, silica dust, wood dust, other plastic dust, cotton dust, paint thinner fumes, glass dust, rock dust, fiber glass dust, asbestos fibers, and paint fumes.

Comparison between pollution levels among the three air basins are shown in Table 1. The data in Table 1, Section A, were tabulated from the State of California Air Resources Board (ARB) air monitoring station data summary tapes.[5,6] Because of the variability in number of months reported between stations during the four years, comparisons between air basins were made by using the units station months explained in Table 1. The data in Table 1, Section B were calculated from the State of California ARB 1973 to 1975 Three Year Summary[7] and from the State of California ARB 1976 Annual Summary[8] and represents only approximations to be used for general comparison between these three basins. The South Coast Air Basin had many more hours above the threshold levels of all six air pollutants compared to San Francisco and San Diego Air Basins between 1973 and 1976. The greatest differences are seen between South Coast and the other two basins in oxidants, nitrogen dioxide and total suspended particulates hours in excess of the threshold level. The components of TSP most likely to harm the lungs are nitrates and sulfates, and the 1977 to 1982 average of the annual average combined percentage of these two components out of the total ranged from 24.4 percent in the South Coast Air Basin to 19.2 percent in San Diego, and 16.6 percent in San Francisco.[9] By studying the distribution of our own population according to monitoring stations, we found that 83 percent in the South Coast Air Basin experienced levels of oxidant air pollution exposure higher than any exposure experienced by our population in the areas outside of the South Coast Air Basin.

RESULTS

A summary of pertinent responses for selected items of the AHSMOG Respiratory Symptoms and Residence History questionnaire used in these analyses are shown separately for the high and low pollution areas in Table 2. Questions dealing with respiratory symptoms were taken from the standard NHLBI questionnaire. Based on questionnaire responses, patients were classified as having chronic bronchitis, asthma, or emphysema.

Criteria were developed for what would be considered as "definite" chronic bronchitis, "definite" emphysema, or "definite" asthma. Individuals meeting the criteria for one of these three diagnoses were classified as having "definite" COPD. 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 three months per

Table 1—*Total Hours in Excess of Threshold 1973-1976*

Pollutant Threshold		South Coast Air Basin	San Francisco Air Basin	San Diego Air Basin
		Section A		
Oxidants ≥20 pphm (Calif 1st Stage Alert)	Sum[a]	10,490	9	25
	N[b]	1,440	1,084	271
	Mean[c]	7.28	0.01	0.09
	SD[d]	18.94	0.14	0.53
	Min[e]	0	0	0
	Max[f]	167	3	5
NO_2 ≥25 pphm (Calif 1 hr Standard)	Sum[a]	2,419	43	30
	N[b]	960	701	223
	Mean[c]	2.52	0.06	0.13
	SD[d]	6.82	0.69	0.78
	Min[e]	0	0	0
	Max[f]	64	14	7
SO_2 ≥4 pphm (Calif 24 hr Standard)	Sum[a]	30,807	3,676	31
	N[b]	816	390	101
	Mean[c]	37.75	9.43	0.31
	SD[d]	46.99	17.91	1.07
	Min[e]	0	0	0
	Max[f]	334	148	7
CO ≥10 ppm (Calif 12 hr Standard)	Sum[a]	32,740	2,657	703
	N[b]	1,248	735	224
	Mean[c]	26.23	3.61	3.14
	SD[d]	54.75	13.61	8.40
	Min[e]	0	0	0
	Max[f]	334	204	52
		Section B		
TSP* ≥100 ug/m³ (Calif 24 hr Standard)	Sum[a]	344,492	10,728	9,048
	N[b]	1,104	761	239
	Mean[c]	312.04	14.10	37.86
	SD[d]	232.93	10.44	36.93
	Min[e]	0	0	0.89
	Max[f]	744	45	120
			(Year 1976 only†)	(Year 1976 only†)
SO_4 ≥25 μg/m³ (Calif 24 hr Standard)	Sum[a]	22,227	0	0
	N[b]	336	102	16
	Mean[c]	66.15	0	0
	SD[d]	110.56	0	0
	Min[e]	0	0	0
	Max[f]	529	0	0

[a]Sum, Total hours in excess of threshold
[b]N, Number of station months‡
[c]Mean, Sum/N Mean hours in excess per station month
[d]SD, Standard deviation of total hours 1973-1976 in excess of the threshold per station month
[e]Min, [f]Max, Range of total hours 1973-1976 in excess of threshold per station month
*Measured by the high volume method
†Data not available for years 1973-1975
‡Station month represents a month in which a station had a reported value listed. For example, four stations in a basin listing a reported value for the month of May would represent four station months.

year, for two 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 these criteria, but having some respiratory symptoms,

Table 2—*Respiratory Symptom Percentages by Area of Residence*

Symptom	Percentages: Low Smog (n = 2287)	Percentages: High Smog (n = 4379)
Cough first thing in the morning	8.3	9.2
Cough at other times	13.0	15.0
Cough on most days for three months or more*	8.3	9.8
Cough for two or more years	12.1	12.6
Bring up sputum first thing in morning	12.5	13.4
Bring up sputum at other times	10.6	11.4
Bring up sputum on most days for three months or more	10.5	11.8
Brought up sputum for two or more years	12.4	13.3
Breathing is ever wheezy or whistling	13.2	13.0
Shortness of breath with wheezing (ever had)	9.7	11.1
Shortness of breath when hurrying on level ground*	29.2	32.6
Shortness of breath when walking at normal pace†	7.4	9.3
Unable to perform usual activities because of chest illness during past year	23.5	24.8
Ever thought they had asthma, bronchial condition, or emphysema	20.1	21.4
Ever told by doctor they had asthma	6.4	6.7
Ever told by doctor they had a bronchial condition	10.6	11.2
Ever told by doctor they had emphysema†	1.2	2.0
Stuffy nose or post-nasal drip six or more days per month during summer*	27.8	44.3
Stuffy nose or post-nasal drip six or more days per month during winter*	32.0	54.1
Had head cold two or more times during past year	27.9	26.9
Had chest cold two or more times during past year	6.7	6.9
Had pneumonia one or more times during past year	2.7	2.7

*$p<0.01$
†$p<0.05 \geq 0.01$

were classified as "possible COPD."

Univariate Analysis

We initially looked at the prevalence rates or respiratory symptoms related to several key factors, without adjusting for covariate effects. Along with the crude prevalence rates, we have included the p values from the simple chi square test as shown in Table 3. There was a significantly greater percentage of "definite" COPD in past smokers vs never smokers ($p<0.001$). While there was a trend toward increased prevalence of COPD in those with an adverse occupational exposure (as compared to those with no such exposure) ($p=0.054$) and in high pollution exposure vs low pollution exposure ($p=0.11$), these were not statistically significant.

We also compared the prevalence of reporting of any respiratory symptom, regardless of its duration. There was a significantly greater prevalence of respiratory symptoms in those in the high pollution area, 32.6 percent vs 30.1 percent ($p=0.04$). Adverse occupational exposure (AOE) showed an even greater effect on the prevalence of any respiratory symptoms, 37.0 percent in those with AOE versus 31.4 percent in those without AOE ($p=0.03$), and past smoking showed the greatest effect, 38.9 percent in past smokers, vs 29.7 percent in never smokers ($p<0.0001$).

Individuals were also asked to report how many times they had head colds, chest colds, and pneumonia during the past year. There was no significant association between air pollution exposure and reporting of head colds or pneumonia, but there was a highly significant association between the reporting of chest colds and air pollution exposure ($p<0.001$). Of those in the high pollution area, 28.6 percent reported having one or more chest colds in the past year compared to 24.3 percent in the low pollution areas.

Since univariate techniques do not take into account various confounding factors, we proceeded to analyze these data using multivariate techniques. For the multivariate analyses, we restricted the definition of COPD to the presence of definite COPD symptoms.

Multivariate Analysis

We compared the high and low pollution areas on the distribution of a number of possible confounders. We then removed the effects of these confounders with multivariate analysis. The comparisons are given below.

Table 4 shows the sex-age distribution of the population compared to the 1970 California population according to ten-year age intervals. It can be seen that the AHSMOG population tends to be older than the general California population. This is partially due to the screening criteria of having to live 11 years or longer in the present neighborhood and also the fact that the Adventist Health Study population is older. Table 5 shows that the sex-age distribution was statistically significantly different between the high and low pollution areas.

The racial distribution in the high pollution area was not significantly different ($p=0.42$) from the combined low pollution areas in the male population for blacks, hispanics, orientals, whites, and all others. In the females, however, there was a slightly higher percentage of hispanics (3.5 percent vs 2.1 percent) and slightly lower percentage of blacks (4.1 percent vs 6.2 percent)

Table 3—*Prevalence of COPD According to Past Smoking, Occupation and Air Pollution Exposure**

	COPD				
	None	Possible	Definite	n	p-value†
Effect of smoking					
Past smokers	61.1%	19.6%	19.3%	1,427	p<0.0001
Never smokers	70.3%	14.7%	15.0%	4,990	
Effect of occupational exposure					
Significant exposure	63.0%	16.9%	20.1%	354	p=0.054
No significant exposure	68.6%	15.7%	15.7%	6,067	
Effect of air pollution					
High pollution	67.4%	16.1%	16.5%	4,219	p=0.11
Low pollution	69.9%	15.2%	14.9%	2,202	

*Non sex-age adjusted crude prevalence rates.
†p values as ascertained by univariate chi-square test.

Table 4—*Sex-Age Distribution (Percent) for AHSMOG Population Compared to California Population as Given by 1970 Census*

		Age							Total	
Sex	Population	25-34	35-44	45-54	55-64	65-74	75+	M*	Percent	Frequency
Male	AHSMOG	5.6	15.2	26.8	26.0	16.8	9.2	0.4	100.0	2,352
	California	25.5	22.6	21.8	15.7	9.3	5.1	—	100.0	5,205,202
Female	AHSMOG	7.0	15.3	22.9	25.3	18.1	11.0	0.4	100.0	4,314
	California	23.5	21.1	21.0	15.8	11.0	7.6	—	100.0	5,670,781

*Missing.

Table 5—*Sex-Age Distribution of AHSMOG Population According to Three Age Groupings by Pollution Area (n=6,666)**

	Age							
	Male			Female			Total	
Pollution Area	25-54	55-74	75+	25-54	55-74	75+	Percent	Frequency
High	16.4%	15.7%	3.1%	28.4%	28.4%	7.9%	65.7%	4363 (16)†
Low	17.7%	14.1%	3.5%	31.1%	27.8%	5.8%	34.3%	2275 (12)†

*Sex-age distribution according to chi square (p=0.003).
†Missing.

in the high versus low pollution areas (p<0.002). These small differences, though statistically significant because of the large sample size, are not likely to confound basin comparisons. A simple comparison of the white vs nonwhite distribution showed no significant difference between high and low pollution areas.

The respondents in the high pollution area were compared to those in the low pollution areas by educational distribution (Table 6). Male and female subjects in the high pollution area reported significantly more education than in the low pollution areas (p<0.0001).

There was a slightly higher percentage of past smokers in the combined low pollution areas (22.9 percent) compared to the high pollution area (19.2 percent), (p<0.0003). This may represent a conservative bias tending to obscure observation of any real higher COPD prevalence due to high pollution residence.

There was a higher percentage of individuals with significant occupational exposure in the combined low pollution areas (6.6 percent) compared to the high pollution area (4.9 percent) (p<0.004), also representing a conservative bias. The percentage of past smokers was higher in the individuals with significant

Table 6—*Distribution of Education by Pollution Area (n=6,666)*

Education	Combined Low Pollution Areas (%)	High Pollution Area (%)
Eighth grade or less	10.5	8.6
Some high school	13.8	11.4
High school graduate	17.3	13.5
Some college or trade school	38.6	36.9
College graduate	11.5	14.6
Master's or Doctoral degree	6.6	12.4
Unknown	1.7	2.5

Table 7—*Percentage of Increase in Risk Estimates Obtained from Multiple Logistic Regression Analysis for Prevalence of "Definite" COPD (n = 6066)**

Covariate	Percentage of Increase In Risk Estimate	Significance Level
1. Smog (outside SCAB/ inside SCAB)	15	p = 0.03
2. Past smoker (no/yes)	22	p = 0.01
3. Adverse occupational exposure (no/yes)	21†	(p = 0.15)‡
4. Race (nonwhite; white)	19†	(p = 0.08)‡
5. Sex (female/male)	3	(p = 0.70)‡
6. Age (30 yr interval)§	12	(p = 0.10)‡
7. Years of education (4 yr interval)§	2	(p = 1.0)‡

*Excludes persons with missing data.
†The higher percentage increases which are not statistically significant such as "21%" and "19%" are so because of their high variability due to smaller numbers at risk.
‡Not statistically significant.
§The number of years resulting in the percent increase in risk.

occupational exposure (43.7 percent), compared to those with no significant occupational exposure (19.1 percent) ($p<0.001$). Thus, past smoking does seem to have a confounding effect on occupational exposure. Because of this confounding with past smoking, the multivariate analysis was repeated on those who had never smoked.

The multivariate analysis of choice for these data is the multiple logistic regression. This technique is appropriate when the outcome variable is incidence or prevalence of disease and one is seeking to estimate relative risk for various independent variables.[10]

In Table 7, the results of the multiple logistic analysis are shown, in which the effects of the above covariates were simultaneously adjusted for in order to assess COPD risk due to long-term exposure to southern California ambient air pollution. After adjusting for the covariates, the risk toward development of "definite" COPD due to ambient air pollution exposure was shown to be 15 percent greater inside the South Coast Air Basin than outside the Air Basin, ($p = 0.03$), with a 2 percent to 32 percent 95 percent confidence interval (CI). Past smokers had a risk estimate for "definite" COPD 22 percent higher than for never smokers, ($p = 0.01$), with a 5 percent to 43 percent 95 percent CI. Multivariate analysis showed the effect of adverse occupational exposure in this population on the prevalence of "definite" COPD to be insignificant. When the analysis was repeated, excluding past smokers, risk estimates for the exposure factors other than smoking were similar to those obtained in the analysis on the entire group.

Discussion

Chronic obstructive pulmonary disease has shown an apparent increase in the United States. In the years 1958 through 1967, the death rate from bronchitis increased 80 percent and from emphysema, 172 percent.[11] More recently, during the one year time span from 1979 to 1980, age adjusted death rates for COPD and allied conditions increased 9.5 percent.[12]

Mortality statistics do not, however, tell the whole story. Chronic obstructive pulmonary disease is noted more for its being a source of morbidity than a cause of mortality. Hence, incidence and prevalence may be more useful measures than mortality. In 1965, the incidence rate for COPD was estimated at 300 per 100,000 persons.[13] The National Health Evaluational Survey[14] estimated in 1979 that the prevalence of chronic bronchitis, emphysema, and asthma in the United States was about 3.5 percent, 1.0 percent, and 3.0 percent, respectively, of the total population.

Epidemiologic studies have successfully used several simple questions as instruments to screen for the presence of chronic bronchitis and emphysema.[15,16] This method, although not as sensitive as lung function tests in detecting early disease, correlates fairly well with the results of lung function testing. However, a disparity between reported respiratory symptoms and lung function abnormalities has been observed in some studies.

Smoking seems to be the primary cause of COPD.[14,17-19] Whether or not exposure to the present ambient levels of photochemical air pollutants significantly contributes in addition to the development of COPD is of major interest. Results of studies to date appear contradictory.

One of the major sources of photochemical air pollutants is auto emissions which has been linked to increased acute respiratory symptoms.[20,21] Acute symptoms[1,4] and chronic symptoms[4] have also been linked by some studies to exposure to ambient levels of photochemical air pollution. However, other investigations have suggested no significant increase in chronic respiratory problems due to exposure to automobile exhaust,[22,23] or due to employment[1] in high vs low photochemical air pollution areas.

Cohen et al,[2] in comparing 430 nonsmoking Seventh-day Adventist adult residents of San Gabriel and San Diego, found no significant difference between the two areas for any of the pulmonary parameters tested (all mean values were within normal ranges) or for any of the respiratory symptom complexes ascertained with a standardized respiratory symptom questionnaire. For the years 1963 to 1967, the number of days when the daily minimum hourly average equaled or exceeded 0.15 ppm for oxidants was more than seven times greater in San Gabriel than in San Diego, while the annual mean values for all hourly oxidant concentrations were almost identical. The mean annual concentrations of the other major gaseous pollutants were in general greater in San Gabriel, although occasion-

ally peak values were higher in San Diego. Several possible reasons Cohen and coworkers' results did not show a significant association between respiratory function and air pollution exposure, in contrast to our results, are as follows: (1) the differences in pollution exposure may not have been as large, since their mean air pollution levels were the same between the high and low pollution areas; (2) their population was much smaller, 430 vs 6,666; and (3) they did not control for significant covariates through the use of multivariate techniques.

Detels et al[3] compared 3,528 residents in high oxidant pollution Burbank, California and 5,350 in low oxidant pollution Lancaster, California, using lung function tests and the NHLBI questionnaire to detect differences in lung function and reported related symptoms. In general, although lung function was better, the prevalence of reported respiratory symptoms was higher in Lancaster, the low pollution area. These low oxidant area residents may be more symptom conscious or, in other words, have lower symptom thresholds than the residents of the higher oxidant area. Since out migration cannot be measured in this design, out migration due to high pollution may partially explain this distribution of reported symptoms.[24] This study also did not adjust for differences in past residential history in the statistical analysis which could introduce considerable variability in cumulative exposure, thus destroying the possibility of showing statistical significance.

Another possible explanation for the conflicting results seen between symptoms and function in the study by Detels et al[3] may be related to the phenomenon pointed to by van der Lende et al,[25] where short periods of air pollution exposure can affect the results of pulmonary function measurements without influencing the reported prevalence of chronic respiratory symptoms by standardized questionnaires. Although Detels et al[3] attempted to control for effects from acute exposure by doing lung function testing on low pollution days, it is possible that effects of other covariates such as passive exposure to tobacco smoke, in-transit exposure to traffic emissions, etc, may have caused the phenomenon mentioned above.

Additional covariates that should be measured in studies of this type are each respondent's history of residential air pollution levels and history of significant passive exposure to tobacco smoke, *ie*, living or working regularly with a tobacco smoker. Because the measureable effects of chronic long-term exposure to ambient air pollution are likely to be overshadowed by a variety of covariate exposures, it seems necessary to use multivariate techniques to control simultaneously for each of the more significant effects. When relatively large differences exist in air pollution exposure between residents in different areas, these covariate effects are overshadowed by the effects of air pollution exposure. In a later report by Detels et al,[4] this is demonstrated.

They compared reported symptoms and lung function in 3,192 low pollution area residents, ages 24 to 59, in Lancaster, California, to 2,369 high pollution area residents of Glendora, California. Glendora is located in the center of the highest photochemical oxidant concentration area of Southern California, resulting in a greater difference in pollution levels between the low and high exposure populations than when Burbank[3] was used as the high exposure area—Burbank levels being somewhat lower than Glendora. In Glendora residents, both the prevalence of symptoms and the majority of lung function tests were worse than those of the Lancaster residents. In these studies by Detels et al,[3,4] questionnaire results correlated much more closely with lung function tests and symptoms were higher in the high pollution area when air pollution exposure differences were greater between the two populations being studied.

The rates for COPD shown in Table 3 are higher than the rates reported in the National Health Educational Survey in 1979[14] for at least two reasons, as follows: (1) our population was restricted to persons of age 25 years and older, and (2) we used a more "liberal" definition for the chronic bronchitis component of COPD. As stated earlier, we defined "definite" chronic bronchitis as the presence, on most days during three months, for two years in a row, of either cough or sputum. For comparison with other reports, we determined prevalence using the more traditional definition which includes the same occurrence frequency noted above, but is limited to the presence of both sputum and cough. We then compared our rates to those reported by Detels et al.[3,4] We sex-age adjusted to the same reference population and used only never smokers (as they were the most comparable and represented 78 percent of our population). Our resulting rates for males and females, respectively, were as follows: for chronic bronchitis, 3.3 percent and 3.6 percent, for emphysema, 0.5 percent and 0.7 percent; and for asthma, 5.6 percent and 5.6 percent. These are very similar to those reported by Detels et al[3,4] who also used the NHLBI questionnaire and whose population also resided within the geographic boundaries defining our population.

In the population studied by Bouhuys et al,[26] textile dust exposure and smoking effects on lung function appeared to be additive. This additive effect is supported by Cohen et al[27] who found that cigarette smokers retained five times more dust than nonsmokers over one year in an experimental study population of three heavy smokers and nine nonsmokers. This suggests the higher retention of other dusts such as toxic occupational and urban dusts which

may contribute to the higher incidence of lung diseases in cigarette smokers.

Office workers, 441 in low oxidant San Francisco and 206 in high oxidant Los Angeles, were compared using lung function tests and the NHLBI questionnaire to detect differences in lung function and reported related symptoms.[1] Most of the results were not significantly different between the two cities. Acute symptoms, nonpersistent cough, and phlegm were more often reported by Los Angeles women than by San Francisco women. This may be related to peaks in Los Angeles oxidant concentrations. However, smokers in both cities showed increased functional abnormalities. Reporting these results in 1976, Linn et al[1] concluded that Los Angeles oxidant exposure is far less significant than smoking as a risk factor in development of chronic respiratory disease in sedentary indoor workers in good general health. This study again points to the need for studies on nonsmokers so that air pollution exposure effects are not overwhelmed.

In summary, in the studies to date, there is conflicting evidence regarding the effects of urban photochemical air pollutants on the respiratory system. Possible reasons for these conflicting findings would include the lack of any prospective studies with repeated measurements of lung function on the same individuals over a long period of exposure, lack of long-term residence history and calculated long-term cumulative exposure, presence of too many confounding and covariate factors which were not measured in the studies, and a lack of multivariate analysis techniques to control for such effects.

Another possible confounding factor in studies in differing geographically located populations could be interactions between different levels of pollutants. For example, areas low in one pollutant may be high in another pollutant which also has effects on lung function; thus, differences between the areas when examining one pollutant at a time are not apparent.

The present report describes the findings of a cross sectional prevalence study and makes comparisons between subjects in a high photochemical pollution area (South Coast Air Basin) and in low photochemical pollution areas (San Francisco and San Diego areas). Following our initial univariate analysis, it appeared that while past smoking had a significant effect on the prevalence of "definite" COPD ($p<0.0001$), the effect of air pollution on "definite" COPD was insignificant ($p=0.11$). However, the reporting of any respiratory symptoms was significantly higher in the high pollution area ($p=0.04$). It seemed that the effect of adverse occupational exposure in this population on "definite" COPD was of marginal significance ($p=0.054$).

When the effects of the covariates of age, sex, race, adverse occupational exposure, and past smoking were controlled for through multivariate analysis, long-term exposure to ambient air pollution was shown to increase the risk of "definite" COPD by 15 percent ($p=0.03$). Individuals with a history of past smoking had their risk of "definite" COPD increased by 22 percent ($p=0.01$). With multivariate analysis, the effect of adverse occupational exposure in our population on the risk of "definite" COPD was not statistically significant.

There were some limitations of this study. This study fails to isolate the effects of ambient air pollution exposure from indoor types of air pollution such as passive tobacco smoke and nitrogen dioxide from gas cooking stoves. Occupational exposure may not be high enough in this population or may not be measured finely enough to detect a real association with COPD. The self-reporting of respiratory disease symptoms in a standardized questionnaire is not as valid or reliable as, for example, a detailed history illicited by a trained interviewer or physician. Selective out migration may have biased the results; however, individuals most likely to move from high smog areas may be those most sensitive to smog and thereby most likely to have or develop COPD. If so, it would be more difficult with this design to detect a real association between COPD and smog. Further data collection and analyses are currently planned to deal with these limitations.

In conclusion, multivariate techniques of analysis were able to demonstrate a significant effect of photochemical air pollution on the prevalence of "definite" COPD, while univariate techniques of analysis failed to show this adverse effect.

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A Statistical Method for Assessing the Health Effects of Long-term Environmental Exposures to Air Pollutants

David E. Abbey, Ph.D.
Professor, Biostatistics and Epidemiology
School of Health
Loma Linda University
Loma Linda, California 92350

Gary L. Euler, Dr.P.H.
Assistant Professor, Respiratory Therapy
School of Allied Health Professions
Loma Linda University
Loma Linda, California 92350

Allan R. Magie, Ph.D.
Chairman-Professor, Environmental & Tropical Health
School of Health
Loma Linda University
Loma Linda, California 92350

John E. Hodgkin, M.D.
Clinical Professor of Medicine
University of California, Davis
Medical Director, Center for Health Promotion & Rehabilitation
Medical Director, Respiratory Care & Pulmonary Rehabilitation
St. Helena Hospital & Health Center
Deer Park, California 94576

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A Statistical Method for Assessing the Health Effects of Long-term Environmental Exposures to Air Pollutants

by David E. Abbey, Ph.D.
Loma Linda University

Abstract--A method for assessing the health effects of long term cumulative exposures to air pollutants or other environmental exposures is proposed and illustrated using self-reported symptoms of Chronic Obstructive Pulmonary Disease for a population of 7,343 non-smokers. Using zip code by month residence histories and interpolated exposure estimates from the network of California air monitoring stations. Two alternative exposure indices were calculated to estimate cumulative exposure over an 11-year period above different threshold levels for each of four pollutants. The indices were used with multiple logistics regression models to form dose response curves for relative risks adjusting for covariates. The dose response curves are used to illustrate how a determination of at what exposure amounts and threshold levels health effects which are biologically and statistically significant begin to occur. Statistically significant effects were noted for total suspended particulates, total oxidants, sulfur dioxide, past and passive smoking.

A Statistical Method for Assessing the Health Effects of Long-term Environmental Exposures to Air Pollutants

Introduction

The "safeness" of existing standards for air pollutants is a matter of considerable controversy. Existing standards for exposure are based primarily on estimates of health effects obtained from animal studies in which high level exposures are used and dose response curves are extrapolated to lower levels, or from human chamber studies where acute short term effects of specific mixes of pollutants are measured. Neither of these methods are adequate or feasible to assess what levels of air pollutants are safe for long-term human exposure.

Over the past decade the quality of air pollution measuring and monitoring has increased greatly. For example, the California Air Resources Board now maintains a network of 41 air monitoring stations in the South Coast Air Basin, 22 in the San Francisco Air Basin, and 7 in the San Diego Air Basin. These monitoring stations record levels for gaseous pollutants on an hourly basis and particulate pollutants on a daily basis. All data is stored on magnetic computer tape and is available for statistical analysis. A methodology is needed which can utilize this existing wealth of data to study possible health effects on resident human populations and in a manner which would substantiate what levels for human exposure are safe. In this paper we propose two alternative methods for utilizing this data to estimate long-term cumulative human exposure to specific air pollutants above different threshold levels and illustrate their usage by applying them to an epidemiological data base.

The multiple logistic regression technique is used to remove effects of spurious lifestyle and other factors, and methods are developed for estimating relative risks for specific air pollutants in a manner to indicate at what threshold level health effects which are statistically and biologically significant might begin to occur.

Though the applications in this paper are limited to air pollution, it would seem that the techniques developed might be applicable to other environmental hazards such as radiation exposure, occupational exposure to various chemicals, levels of food additives, etc.

Description of Cumulative Exposure Indices

In forming long-term cumulative exposure indices it is desirable that they be pollutant specific and be able to be used to assess above which levels significant health effects begin to occur so that they can be used to assess the adequacy of existing air quality standards. Two indices are proposed: 1) exceedance frequency which is the number of hours in excess of a threshold for a specific pollutant; 2) excess dosage which is the integrated function of parts per million hours in excess of a threshold.

The threshold levels for each pollutant used in this study are indicated in Table 1. The pollutants carbon monoxide and sulfates (SO_4) were also considered but were not included due to the limited interpolation range of carbon monoxide and the unavailability of SO_4 data (available only for the last year of the study period). Threshold levels in Table 1 were determined

by taking existing standards and inserting intermediate levels or levels that were above or below.

Total suspended particulates are sampled every sixth day for a 24-hour period. The other pollutants are sampled hourly, 24-hours a day, 7 days a week. All of the data is stored on computer tape. The details of measurement method for each of the pollutants are described in California Air Resources Board regularly published reports [1].

For each threshold of each pollutant, the two statistics, exceedance frequency and excess dosage, were first calculated at each monitoring station for each month for the time period 1966 through 1976. Calculation of statistics was facilitated using a low computer algorithm developed by Technical Services Corporation of Santa Monica. First a cumulative distribution of pollutant concentration versus hours at each monitoring station was formed. Then the hours or dosage in excess of a threshold was determined by the intersection of the concentration line with a cumulative distribution curve. In order to apply monitoring station values to a free-living population, who over past years may have lived in different areas, statistics were interpolated on a monthly basis to zip code centroids using a $1/R^2$ interpolation from surrounding monitoring stations. Penalty boundary functions were used for geographic obstructions of 1,000 feet of elevation or more. These boundary functions allowed no interpolation across them.

Application of Methods to Epidemiological Data

In March of 1977 a subgroup of 7,343 members of the National Cancer Institute-funded Adventist Health Study were enrolled for

the primary purpose of studying the health effects of air pollution. By religious prescription SDA's neither smoke nor drink alcoholic beverages but do experience widely differing levels of air pollution exposure. To be included in the study, individuals must have met the following criteria:

1. Lived ten years or longer within five miles of present residence.

2. Resided in one of the three metropolitan areas--San Francisco, South Coast Air Basin, or San Diego, or a sample of 600 from the rest of California.

Individuals meeting these criteria were mailed a baseline questionnaire which ascertained their residence history by month and zip code since 1960 as well as lifestyle habits pertinent to relative air pollution exposure such as work location, hours driving on crowded freeways, percent of time indoors/outdoors, etc. They also completed the National Heart Lung and Blood Institute Respiratory Symptoms questionnaire which was used to ascertain self-reported symptoms of chronic respiratory disease. A wide range of other lifestyle data was already available on these individuals as part of the Adventist Health Study data base. Sixty-six percent of the population lived in the South Coast Air Basin; 65% were female, 85% were white. All were not currently smoking, although 20% had smoked in the past. Individuals reported the number of years they had lived with a smoker and the number of years they had worked with a smoker. Thirty percent had lived 10 or more years with a smoker, and 18.5% had worked 10 or more years with a smoker. Five and a half

percent were exposed for 5 or more years to airborne pollutants at the workplace and were termed to have hazardous occupational exposure. This classification was made on the basis of occupation and contaminants to which a worker was exposed. The reported occupations with adverse exposure in this population were:

Heavy equipment/bulldozer operator
Automobile body repairman
Carpenter, woodshop furniture maker, lumbermill worker
Road construction worker
Painter
Welder, boilermaker
Foundry worker
Masonry worker, cement worker, quarry worker
Miner (underground)
Textile operator, sewer worker, spinner, knitter

The occupational contaminants to which study participants were exposed were:

Welding fumes
Silica dust
Wood dust
Other plastic dust
Cotton dust
Paint thinner fumes
Glass dust
Rock dust
Fiber glass dust
Asbestos fibers
Paint fumes

Excluding 862 individuals who lived in rural low pollution areas of California, the distribution of the study population with respect to distance from the nearest monitoring station was as follows: 97% lived within 10 miles of a monitoring station, 67% within 5 miles, and 25% within 3 miles. Technical Services Corporation has determined that reliable estimates of concentration can be obtained by interpolation for oxidants within a 20-mile radius, NO_2 within a 10-mile radius, and SO_2 and total

suspended particulates within a 6-mile radius [2]. Thus 99% lived within this area of relatively reliable concentration estimates for oxidants, 92% for NO_2, 62% for SO_2 and 70% for TSP.

The primary health outcome variable which we will use to illustrate the methods in this paper is the presence or absence of self-reported definite symptoms of chronic respiratory disease. Definite symptoms were defined as:

1. Symptoms of cough and/or sputum production on most days for at least three months for two years or more.

2. Having been told by their physician that they had asthma as well as having a history of wheezing.

3. Having been told by their physician that they had emphysema as well as having shortness of breath when walking either normal paced or hurried.

Discussion of this definition is given by Hodgkin, et. al. [3]. Fifteen percent had definite symptoms according to this definition.

For statistical analysis purposes cumulative exposure for individuals was estimated for two time periods--1966 through 1976 and 1973 through 1976. Prior to 1966 air pollution data is too scarce to merit interpolation. From 1973 on, many more monitoring stations were on-line making the interpolation data much better than for the time period prior to 1973. The main statistical analyses below were repeated for both time periods. Similar results were obtained. Hence, only those results for the latter time period will be illustrated.

An appropriate multivariate model for this type of data is a multiple logistic regression model where the probability of an

event, y, is modeled by

1) $$y = \frac{1}{1 + e^{-(\alpha + \beta_1 x_1 + \beta_2 x_2 + \cdots)}}$$

The odds of an event is given by

2) $$\frac{y}{1-y} = e^{\alpha + \beta_1 x_1 + \beta_2 x_2 + \cdots}$$

The odds ratio or relative odds for a specific variable, say x_1, is given by e^{β_1}. The estimated odds ratio for a k-unit increase in x_1 has been shown by Kahn [4] to be equal to $e^{k\beta_1}$. It is more meaningful to talk about relative risk rather than relative odds. The relative odds for a k-unit increase can be converted to relative risk using the formula

3) $$\text{Relative Risk for k-unit increase in } x_1 = \frac{e^{k\beta_1}}{1 - P_0 + P_0 e^{k\beta_1}}$$

where P_0 = Probability of event given no exposure to x_1

The derivation for this is given in the appendix. Note that P_o can be estimated from the sample data using the number of cases of the event occurring at zero level exposure to x_1 divided by the number of population at zero level exposure to x_1.

As our first approximation, we will treat air pollution simply as a dichotomous variable with high exposure being defined as living the entire ten year period within the South Coast Air Basin and low exposure living the entire ten year period outside the South Coast Air Basin. The results of the multiple logistics regression are shown in Table 2. The Duncan/Walker technique of maximum likelihood estimation was used to fit multiple logistic regression models to the data. The Hosmer/Lemeshow goodness of fit test [5] was made for multiple logistic analyses. Unless otherwise noted, no statistically significant differences were

found between the predicted and observed values indicating that the model fit the data well.

The statistically significant relative risks in this multiple logistic regression were: smog exposure, years lived with a smoker, and years worked with a smoker. Note that whether or not an individual had smoked in the past has a larger relative risk estimate than either of the passive smoking variables but is not statistically significant. This is likely due to the higher variability due to less precision of measurement.

Using supplementary data collected by the National Cancer Institute funded study we were able to ascertain maximum number of cigarettes smoked in the past, number of years smoked, and number of years since joining the church. Since non-smoking is a religious prescription of the church, years since joining the church would be an approximate, though underestimate, of years since stopped smoking for those who have smoked in the past. Using these three variables, a ratio was constructed of years smoked times maximum number of cigarettes smoked divided by years since joined church. Since many of the respiratory symptoms of smoking are reversible with time, it was felt that this ratio would be a more accurate reflection of possible effects of past smoking on present respiratory symptoms. When this past smoking ratio was entered into the multiple logistic regression, the relative risk for past smoking became statistically significant. The relative risks and level of statistical significance for the other exposure variables did not change substantially.

Univariate statistical analysis revealed evidence of confounding between passive and past smoking. So the multiple

logistic analysis was repeated including only individuals who had never smoked. Similar results were obtained. In fact, relative risks for the exposure variables do not differ by more than 1%.

In order to relate cumulative pollution exposure to threshold levels and to provide a finer measure of exposure, we next used the two cumulative exposure measures--exceedance frequency and excess dosage. We found the two statistics to be highly correlated. Correlations were Ø.9 or greater for all thresholds of each pollutant with exception of SO_2, which had a correlation of Ø.8 for the level 2 pphm. Multiple logistic analyses were repeated using excess dosage as well as exceedance frequency, and as might be expected, very similar results were obtained. Exceedance frequency is an easier statistic to interpret, so we will present the results for this statistic only. As mentioned previously, cumulative exposure was computed for two timeperiods--1966-1976 and 1973-1976. We will present the analyses for the later cumulation only as we feel that it is a more accurate measure due to a greater number of monitoring stations. Again, key analyses were repeated using the 1966-1976 cumulative exposure and very similar results were obtained.

Let us illustrate how exceedance frequency can be used to determine the threshold levels at which relative risks which are significant both statistically and biologically begin to occur. We will do this first for total oxidants. We note from Table 3 that there is a high degree of confounding between threshold levels for the same pollutant. Even when the statistics are made mathematically independent by correlating hours between

thresholds as shown for oxidants in Table 4, there are still large correlations between thresholds. We therefore ran a separate multiple logistic regression analysis for each threshold level. The results are given in Table 5. The variables other than oxidant exposure were kept the same as in Table 2 for all subsequent multiple logistic regression analyses. For all of the subsequent regressions, the coefficients for the other variables changed very little from that shown in Table 2.

For each threshold level in Table 5 the relative risk was estimated for three different increment sizes using equation 3. To avoid extrapolation we limited the largest increment size to an amount for which at least 15% of the population was exposed above a one-step increase. By varying the increment sizes, one can estimate at what average annual exposure relative risks become large enough to warrant legislative intervention. Thus if one were to determine that a 20% increase in relative risk of developing Chronic Obstructive Pulmonary Disease symptoms was the maximum allowable relative risk considered to be "safe" for the population, then the legislature would not want to allow levels to exceed 10 pphm of oxidant exposure more than 750 hours per year. Note that "allowable" relative risks would be a function of the prevalence of a disease as well as the seriousness, in terms of cost to society. For example a 10% increase in relative risk might be meaningful for a disease with a prevalence of 15%, meaning a 1.5% increase in prevalence, whereas it might not be meaningful for a disease which had a prevalence of only 1%, unless the latter disease had very serious consequences and a high cost to society. The prevalence of symptoms in this study

was 15%. Thus relative risks as small as 10% may have legislative importance. Thus we see that by varying increment size, we can study, for a particular threshold level, what annual maximum exposure might be considered allowable for a population.

Let us now determine how we might ascertain at what threshold level effects which are statistically and biologically significant begin to occur. In Table 5 we note that the lowest threshold level used in analysis, 10 pphm, is highly statistically significant. It would have been desirable to use an even lower threshold level, such as 5 pphm to see if statistical significance was obtained. For the highest threshold, 25 pphm, the regression coefficient is not statistically significant, indicating that it could be 0. The decrease in statistical significance for higher threshold levels may be due to lack of sufficient exposure above higher threshold levels in this population. Note that only 16% of the population is exposed for 24 hours per year or more above 25 pphm. This small amount of annual exposure is subject to large variability due to errors in interpolation. Note that the relationship between relative risks and increment size is consistent with the hypothesis that higher threshold levels would entail greater relative risks with less exposure. From Table 5 we see that a relative risk of 1.07 is achieved for 250 hours per year exposure above 10 pphm, 125 hours per year above 15 pphm, 48 hours per year above 20 pphm, and 12 hours per year above 25 pphm. In setting a standard then, it becomes obvious that both threshold level and hours exposure above that threshold level must be taken into consideration.

Another way of determining at which threshold level biologically significant effects begin to occur is to plot relative risk as a function of threshold, holding hours annual exposure constant. This was done for four different exposure levels in Figure 1. The point at which a significant relative risk begins to occur could be taken as the point at which the relative risk begins to increase most rapidly which is the point at which the rate of change of the slope of the curves in Figure 1 is maximized. By visual inspection we see that this point would be between 10 and 15 pphm, tending towards 10 pphm for 250 hours annual exposure and towards 15 for 30 hours annual exposure.

Total Suspended Particulates

Table 6 shows the results for total suspended particulates. Statistically significant effects did not occur here until the second threshold level, 100 micrograms per cubic meter. Statistical significance increased for the higher threshold levels. Note that there was much greater population exposure at the higher levels for total suspended particulates than for total oxidants. Figure 2 plots relative risk as a function of increasing threshold level. Visual inspection would indicate a maximum rate of increase in relative risk between 100 and 150 micrograms per cubic meter. This data and that of Table 6 might suggest a legislative standard of less than 2500 hours per year in excess of 100 micrograms per cubic meter or 1000 hours per year in excess of 150 micrograms per cubic meter if a 10% relative risk were deemed "safe".

Sulfur Dioxide

Table 7 shows the results for sulfur dioxide. Statistical significance occurs for the level 4 pphm. Here again we have the problem of insufficient exposure in this population at higher threshold levels to enable ascertainment of statistically significant effects.

Nitrogen Dioxide

Multiple logistic analyses for nitrogen dioxide failed to show statistical significance for any of the threshold levels. The top 20% of the population were exposed to 4900 hours per year or less in excess of 5 pphm, 350 hours per year or less in excess of 15 pphm, 115 hours per year or less in excess of 20 pphm, and 25 hours per year or less in excess of 25 pphm. Thus insufficient exposure may again account for lack of statistical significance for the two higher thresholds, but there would appear to be enough exposure to the two lower levels to show statistical significance. It is possible that indoor sources of NO_2 contamination such as gas stoves may be introducing too much variability here.

TSP, OX, SO_2, and NO_2 Combined

It may be impossible to completely isolate the effects of individual pollutants due to their statistical correlations (see Tables 8 and 9) and also the fact that ambient exposures are always to combinations. Nevertheless it may be of interest to enter the most significant threshold levels for each pollutant together in one multiple logistic regression to see which pollutants are the strongest predictors.

The pollutant/thresholds above which exposure was found to be most significantly associated with chronic respiratory disease symptoms were: TSP above 200 mcg/m^3, TSP(200), oxidants above 10 pphm, OX(10), and SO_2 above 4 pphm, SO_2(4). These were entered along with NO_2 at a threshold of 25 pphm and then again with a threshold of 5 pphm into one multiple logistic regression analysis incorporating the 8 co-variates shown in Table 2. In the initial combined regression equations NO_2 again was not found to contribute in any consistent or significant manner. In addition, as stated above, none of the NO_2 threshold exposures were statistically associated with symptoms in the individual logistic regression analyses. Consequently NO_2 was excluded from further logistic analyses.

In the three pollutant combined analyses TSP(200) exposure effects overshadowed the effects of OX(10) and SO_2(4), and TSP(200) was the only pollutant/threshold where significant association with chronic respiratory disease symptoms was seen, ($p = 0.008$). The likelihood ratio statistic which can be used as a relative measure of the predictive power or "fit" of the model for this combined analysis was 60. This compares to likelihood ratio statistics for SO_2(4) alone of 45, for OX(10) alone of 52 and SO_2(4) and OX(10) together of 53. However, the likelihood ratio statistic was the highest when TSP(200) was entered alone, 63. This indicates that for these data, TSP(200) is the best predictor of chronic respiratory disease symptoms of the air pollutant/thresholds considered.

When we replaced TSP(200) in the above analysis with hours of TSP exposure above 100 mcg/m^3, TSP(100), we found that the

likelihood ratio statistic for TSP(1ØØ) alone was 51 and when combined with OX(1Ø) and SO_2(4) it was 53. This was not a statistically significant improvement in the likelihood ratio as indicated by the Chi-Square test. Thus OX(1Ø) and SO_2(4) do not significantly improve the fit of the model over TSP(1ØØ) alone.

To assess possible synergistic effects, interaction terms were developed by taking the product of hours in excess of a threshold for all possible combinations of two pollutants. All possible combinations were tried one at a time in the logistic regression equation with the three pollutant/thresholds. In no case did the interaction terms improve the likelihood ratio statistic by more than one indicating no significant improvement in the model. Neither did any of the terms have regression coefficients which approached statistical significance.

Because of the potential problems of multicolinearity in the above regressions, a set of multiple regression analyses were performed to determine what percent of the variation in each ambient pollutant threshold variable [TSP(2ØØ), OX(1Ø), SO_2(4), or NO_2(25)] was explained by the other three pollutant threshold variables as indicated by the multiple R^2. It was found that 8Ø% of the variation in TSP(2ØØ) was explained by the other three, 74% of the variation of OX(1Ø) by the other three, and 49% of the variation of SO_2(4) by the other three. This would suggest that TSP(2ØØ) is presently the single best surrogate indicator of overall ambient air pollution level in Southern California.

Discussion

We have illustrated a method to assess long-term cumulative effects of air pollution exposure on symptoms of chronic

obstructive pulmonary disease in a manner which utilizes existing data collected at air quality monitoring stations. Two statistics for estimating cumulative exposure were proposed, cumulative excess dosage and exceedance frequency. We found the two to be highly correlated for all threshold levels for all pollutants with all correlation coefficients in excess of Ø.9 except for three, and these were larger than Ø.75. We prefer the statistic exceedance frequency (hours in excess of the threshold) for studying effects of individual pollutants as it is easier to interpret. However, when seeking to separate the effects of different pollutants in multivariate analyses, there may be an advantage in using the statistic excess dosage as the correlations between pollutants were found to be much lower with the exception of total suspended particulates and oxidants which remained high. We also found that converting the relative odds, which is directly obtainable from the multiple logistic regression coefficients to relative risks, enabled ease of understanding of the results. The methods described provide a valuable new tool for decision makers seeking to set standards on the basis of epidemiological data, allowing the impact on relative risks of hours in excess of thresholds to be modeled so that the decision makers can determine what threshold levels and what exposure limits are "safe".

The technique of multiple logistics regression enables confounding factors which might otherwise overwhelm the effects of air pollution to be removed. Whittemore and Korn [6] used this method to assess the effects of air pollution over time on a

panel of asthmatics. The effects of ten different covariates were removed in the analysis. Multiple discriminate analysis provides another alternative to multiple logistic regression analysis for removing confounding factors. Lebowitz has used this technique to study the effects of smoking and other risk factors on obstructive lung diseases [7]. The multiple discriminate analysis technique was used in our study as a first approximation to the maximum likely estimation method for the multiple logistic regression. One advantage of the multiple logistics regression is that the regression coefficients can be used to estimate relative risks and form dose response curves as was illustrated in this paper.

The conversion of relative odds to relative risks further aids in the interpretation of the data. For outcome variables with a low prevalence, relative odds closely approximates relative risk, but this conversion is necessary when studying an outcome variable which is not rare such as prevalence of symptoms of COPD.

Limitations of Methods

There are a number of sources of errors in estimated population exposures to pollutants. One source of error is the interpolation of monitoring station values to zip code centroids.

The U.S. Environmental Protection Agency has established guidelines for valid interpolation distances [8]. These estimated guidelines have been confirmed by Technology Service Corporation of Los Angeles using data from Los Angeles [9]. In our study each interpolation to a study participant was assigned a quality rating to reflect the distance from the monitoring

station. Key analyses for each pollutant, excluding individuals who did not live within quality interpolation limits, were repeated. Similar results to those cited above were obtained.

Accuracy of recall of residence history could also effect estimated cumulative exposure. This was checked in a stratified random sample of 87 women, chosen to represent extremes in exposure and degree of COPD symptoms. Maps and personal interviewing were used to check on the validity of the residence history reporting on the 1977 mail questionnaire. 10,440 zip code months were reported by these women. 344 of these or 3.3% were due to inaccuracies in filling out the 1977 questionnaire. The errors were divided approximately equally between errors in zip code location and errors in year of a move. The mean discrepancy in year of a move was 1.5 years. Only 5 of the zip code discrepancies were greater than 2 zip code units in magnitude, thus representing the possibility of a different local.

The other factor introducing error into the estimates is the varying lifestyle habits of study participants which affect air pollution exposure, such as time spent indoors vs. outdoors, driving on crowded freeways, working in a different location from their zip code of residence, etc. In this study these lifestyle characteristics were measured and were entered into the multivariate analyses. No statistically significant effects of the lifestyle characteristics were noticed. However, rather than entering these factors as additional covariates, it would be more desirable to modify the exposure variables according to correction factors. Such correction factors need to be

established through further studies utilizing the wearing of portable monitors by a subsample of study participants.

Another problem of the methods proposed here is to isolate the true threshold at which significant effects begin to occur. It was noted previously that high correlations existed between threshold levels for the same pollutant. This was overcome by running a separate multiple logistic regression analysis for each threshold level. The highest level of statistical significance would be obtained for the threshold level having the strongest association with the outcome variable. Thus by running repeated multiple logistic regression analyses and choosing the threshold with the highest level of statistical significance, the determination of what threshold level statistically significant effects begin to occur could be made. One further problem with this however, is the problem of extrapolation. It is important to have a high enough percentage of the population exposed to higher threshold levels. We noted a lack of sufficient exposure in our population to the very highest threshold level of oxidant pollution.

In addition to unscrambling the effects of different thresholds, it would be desirable to isolate the effects of different pollutants. We studied the correlation of cumulative exposure for various pollutants. The correlations between total suspended particulates and total oxidants were too large (>Ø.5) to enable separation of their effects. The correlations between other pollutants were small enough when excess dosage was used so that the effects could be separated in multivariate analyses. Whittemore and Korn [6] observed this problem in their study of

pollutants on a panel of asthma subjects. Their correlations were for daily measures of pollutants rather than 10-year cumulations. They noted that total suspended particulates seemed to be a surrogate measure of the mix of pollutants. Our data would also tend to support this. We regressed total suspended particulates on the other pollutants and then each of the other pollutants on the remaining pollutants and found that the highest multiple R^2 was obtained for total suspended particulates as the dependent variable. Further study needs to be given to analytical and design techniques for assessing the effects of individual pollutants on free living populations. One design method might be to choose subjects with long-term exposure to high levels of a particular pollutant but low levels of other pollutants. This may be difficult due to difficulty of finding locations with high exposure to one pollutant but low exposures to other pollutants.

Since July 1, 1983, the measurement of TSP has been separated into two components, coarse (10 to 2.5 microns) and fine (less than 2.5 microns). This refinement of measure may reduce the correlation with other pollutants sufficiently to allow separate assessment of effects in multivariate analyses.

As in all cross-sectional studies of this type a number of biases due to the study design may be present. Our study population consists of a relatively stable population: a population that has lived for 11 years or longer at their 1977 residential area. Thus self selection factors could be present that might have altered the prevalence of COPD symptoms in

relationship to the level of ambient air pollution. There may be selective out migration of either sick people or healthy people from polluted areas resulting in an artificially produced relationship between chronic respiratory disease symptoms and ambient air pollution exposure. A presently planned re-survey of the population will include those who have moved and could thus partially assess the migration effect.

Measurement bias may be introduced to the degree of inaccuracy that self reported symptoms of chronic respiratory disease actually measure the presence of these symptoms. The findings of the American Lung Association of Southern Florida in an unpublished report 1981 [10] indicate that when chronic symptoms of respiratory disorders are self-reported underreporting is much more common (45-54%) than overreported (13%) as detected by medical examination and spirometry. If the same situation exists in this California population the group reporting chronic respiratory disease symptoms is more correctly defined than the group without reported chronic symptoms and the group not reporting chronic symptoms has poorer respiratory health than reported. This would result in the positions of the two groups on the discriminating variables being closer than in reality, producing a conservative bias. A non conservative bias would result if those living in the higher pollution areas had less underreporting.

The methods described in this paper would be applicable to assessing health effects of exposures other than air pollutants. Wherever exposures can be measured and quantified the techniques could be used. Examples might include assessing the health

effects of radiation exposure [11], long-term usage of medications such as estrogen, X-ray exposure, microwave exposure, etc.

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Table 1

Threshold Levels for Pollutants
1-Hr Concentration Unless Otherwise Specified

Pollutant	Concentration Threshold			
	1st Level	2nd Level	3rd Level	4th Level
OX	10 pphm (Calif. std.)	15 pphm	20 pphm (1st stage alert)	25 pphm
NO_2	5 pphm (primary 1 yr. std.)	15 pphm	20 pphm	25 pphm (Calif. 1-Hr. std.)
SO_2	2 pphm	4 pphm (Calif. 24-Hr. std.)	8 pphm	14 pphm (primary 24-Hr. std.)
TSP*	60 mcg/m^3 (Calif. 1 yr. std.)	100 mcg/m^3 (Calif. 24-Hr. std.)	150 mcg/m^3 (secondary 1 yr. std.)	200 mcg/m^3

*24-Hr Concentration

Table 2

Multiple Logistic Regression for Definite COPD Symptoms
Using Air Pollution Exposure as a Dichotomous Variable
Southern California Residents
25 Years of Age and Older, 1966-1976
n = 6066; cases = 965

Variable	Regression Coefficient	Increment	Approx. Relative Risk°	p-value
Smog Exposure	0.17707	(Low; High)*	1.16	0.02
Occupational Exposure	0.21035	(No; Yes)	1.19	0.17
Years Lived With Smoker	0.00783	10 yrs.	1.07	0.008
Years Worked With Smoker	0.01145	10 yrs.	1.11	<0.001
Past Smoker	0.13447	(No; Yes)	1.12	0.15
Sex	0.08109	(Male; Female)	1.07	0.34
Age	0.00473	30 yrs.	0.12	0.08
Race	0.18259	(Non White; White)	1.17	0.13
Education	0.01579	2 categories+	1.02	0.58

* Outside SCAB; Inside SCAB
+ Approximately four educational years
° Obtained from odds ratio (see Appendix)

Table 3

Correlations Between Cumulative Hours
in Excess of Thresholds (1973-1976)*

TSP

TSP Threshold → mcg/m³ ↓	60	100	150	200
60	.91	.70	.86	
100		.89	.75	
150			.93	
200				

OX

OX Threshold → pphm ↓	10	15	20	25
10	.97	.89	.77	
15		.97	.87	
20			.96	
25				

SO_2

SO_2 Threshold → pphm ↓	2	4	8	14
2	.68	.20	-.15	
4		.78	.36	
8			.64	
14				

NO_2

NO_2 Threshold → pphm ↓	5	15	20	25
5	.92	.88	.82	
15		.98	.93	
20			.98	
25				

*The unit of measure is the individual study participant. n = 6350

Table 4

Correlations of Cumulative Hours Between Thresholds for Total Oxidants (1973-1976)*

Threshold Levels → pphm ↓	10.1-15.0	15.1-20.0	20.1-25.0	>25
10.1-15.0	|	.86	.67	.42
15.1-20.0		|	.87	.62
20.1-25.0			|	.82
>25				|

*The unit of measure is the individual study participant.
n = 6350

Table 5

Estimates of COPD Relative Risk from Multiple Logistic Regression for Different Incremental Increases of Exposure Above Various Threshold Levels of Total Oxidants

Threshold Level	p-Value	Percent Population Exposed	Increment Size	Relative Risk Estimate
10 pphm	<0.004	50	250 hrs/yr	1.07
		43	500 hrs/yr	1.13
		18	750 hrs/yr	1.20
15 pphm	<0.005	49	75 hrs/yr	1.04
		45	125 hrs/yr	1.07
		23	250 hrs/yr	1.15
20 pphm	<0.02	45	24 hrs/yr	1.03
		40	48 hrs/yr	1.07
		16	96 hrs/yr	1.13
25 pphm	0.11	45	6 hrs/yr	1.02
		33	12 hrs/yr	1.03
		16	24 hrs/yr	1.07

Exposure time period was 1966-1976; however, 1973-1976 air monitoring data was used for the analysis represented in this table. See text for rationale. Number of study participants = 6482.

Table 6

Estimates of COPD Relative Risk from Multiple Logistic Regression for Different Incremental Increases of Exposure Above Various Threshold Levels of Total Suspended Particulates

Threshold Level	p-Value	Percent Population Exposed	Increment Size	Relative Risk Estimate
60 mcg/m^3	0.12	91	1000 hrs/yr	1.02
		78	3500 hrs/yr	1.07
		27	7500 hrs/yr	1.16
100 mcg/m^3	0.006	77	1000 hrs/yr	1.04
		67	2500 hrs/yr	1.11
		24	5000 hrs/yr	1.23
150 mcg/m^3	<0.0001	69	500 hrs/yr	1.05
		60	1000 hrs/yr	1.11
		24	2500 hrs/yr	1.30
200 mcg/m^3	<0.00001	55	250 hrs/yr	1.07
		28	500 hrs/yr	1.14
		25	750 hrs/yr	1.22
		23	1000 hrs/yr	1.28

Exposure time period was 1966-1976; however, 1973-1976 air monitoring data was used for the analysis represented in this table. See text for rationale. Number of study participants = 6472.

Table 7

Estimates of COPD Relative Risk from Multiple Logistic Regression for Different Incremental Increases of Exposure Above Various Threshold Levels of Sulfur Dioxide

Threshold Level	p-Value	Percent Population Exposed	Increment Size	Relative Risk Estimate
2 pphm	0.24	80	500 hrs/yr	1.03
		62	1000 hrs/yr	1.04
		16	2000 hrs/yr	1.09
4 pphm	0.03	77	100 hrs/yr	1.03
		31	250 hrs/yr	1.09
		13	500 hrs/yr	1.18
8 pphm	0.18	43	15 hrs/yr	1.02
		37	30 hrs/yr	1.03
		23	60 hrs/yr	1.07
14 pphm	0.58	45	1 hrs/yr	1.00
		26	5 hrs/yr	1.01
		17	10 hrs/yr	1.03

Exposure time period was 1966-1976; however, 1973-1976 air monitoring data was used for the analysis represented in this table. See text for rationale. Number of study participants = 6350.

Table 8

Correlation Coefficients Between Pollutants for Cumulative Hours in Excess of Different Thresholds
(Entire Population Cumulative Exposure 1973-1976)

		TSP mcg/m^3			
	Threshold →	60	100	150	200
	↓				
	10	.59	.74	.82	.79
OX	15	.52	.69	.81	.80
pphm	20	.46	.63	.76	.76
	25	.40	.55	.67	.67

		SO_2 pphm			
	Threshold →	2	4	8	14
	↓				
	10	.47	.10	-.28	-.39
OX	15	.41	.08	-.29	-.37
pphm	20	.37	.08	-.26	-.34
	25	.34	.11	-.20	-.28

		NO_2 pphm			
	Threshold →	5	15	20	25
	↓				
	10	.38	.10	.06	.03
OX	15	.30	.02	-.02	-.05
pphm	20	.24	-.03	-.06	-.07
	25	.21	-.03	-.05	-.06

		TSP mcg/m^3			
	Threshold →	60	100	150	200
	↓				
	5	.74	.69	.35	.11
NO_2	15	.53	.45	.07	-.17
pphm	20	.46	.42	.05	-.18
	25	.46	.40	.04	-.17

		SO_2 pphm			
	Threshold →	2	4	8	14
	↓				
	5	.84	.41	.07	-.14
NO_2	15	.73	.33	.08	-.11
pphm	20	.70	.33	.09	-.09
	25	.68	.32	.09	-.08

		TSP mcg/m^3			
	Threshold →	60	100	150	200
	↓				
	2	.75	.82	.61	.42
SO_2	4	.48	.56	.48	.32
pphm	8	.08	.05	.03	.01
	14	-.18	-.29	-.26	-.22

Table 9

Correlation Coefficients Between Pollutants for Excess Dosage Above Different Thresholds
(Entire Population Cumulative Exposure 1973-1976)

		TSP mcg/m^3			
	Threshold →	60	100	150	200
OX pphm	↓ 10	.77	.82	.83	.82
	15	.72	.78	.80	.79
	20	.65	.70	.72	.72
	25	.54	.67	.60	.60

		SO_2 pphm			
	Threshold →	2	4	8	14
OX pphm	↓ 10	.10	-.20	-.34	-.39
	15	.09	-.18	-.32	-.36
	20	.11	-.14	-.28	-.31
	25	.14	-.07	-.21	-.25

		NO_2 pphm			
	Threshold →	5	15	20	25
OX pphm	↓ 10	.19	.00	-.02	-.03
	15	.14	-.04	-.05	-.06
	20	.12	-.04	-.05	-.05
	25	.12	.00	-.01	-.01

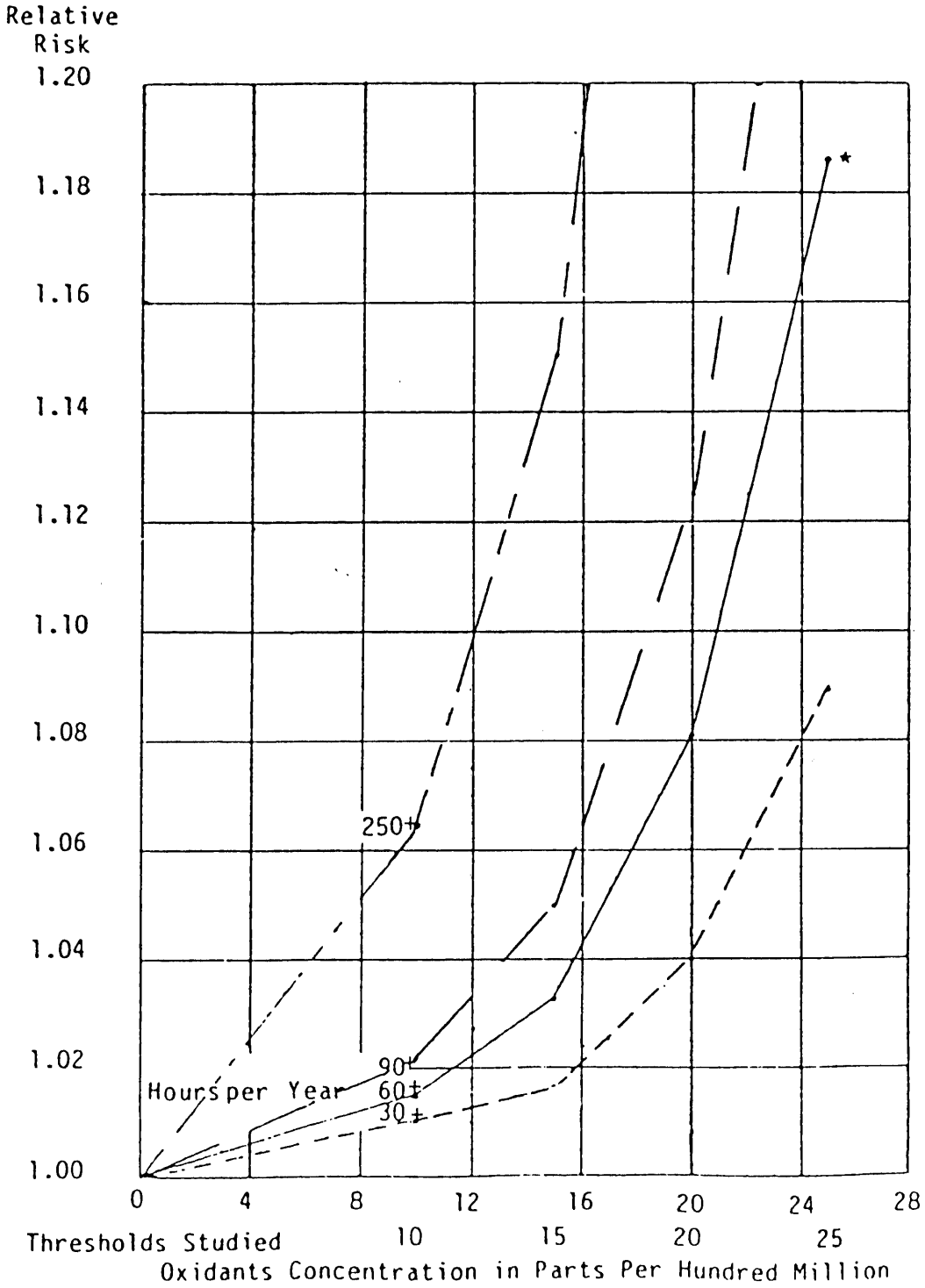
		TSP mcg/m^3			
	Threshold →	60	100	150	200
NO_2 pphm	↓ 5	.42	.25	.03	.04
	15	.26	.10	-.12	-.19
	20	.24	.09	-.12	-.19
	25	.22	.08	-.11	-.17

		SO_2 pphm			
	Threshold →	2	4	8	14
NO_2 pphm	↓ 5	.45	.12	-.12	-.24
	15	.42	.14	-.09	-.21
	20	.40	.13	-.08	-.19
	25	.37	.12	-.08	-.18

		TSP mcg/m^3			
	Threshold →	60	100	150	200
SO_2 pphm	↓ 2	.53	.48	.37	.35
	4	.15	.13	.09	.10
	8	-.15	-.15	-.13	-.10
	14	-.36	-.35	-.29	-.27

FIGURE 1

Relative Risk for 30, 60, 90, and 250 Hours Per Year of Exposure Above Each of Four Thresholds of Total Oxidants (OX)

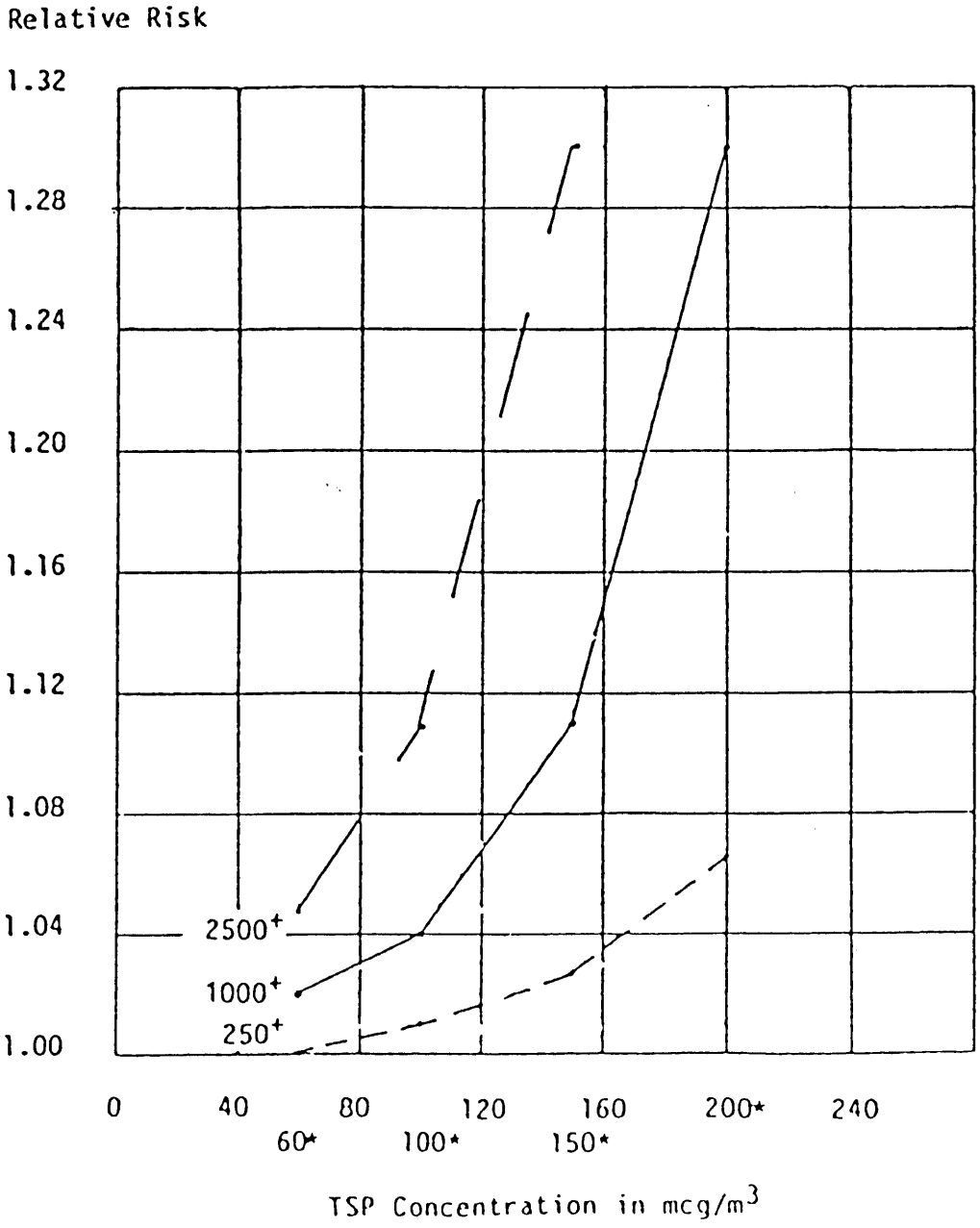


*This point is an extrapolation

+Hours per year

FIGURE 2

Relative Risk for 250, 1000, and 2500
Hours Per Year of Exposure Above Each of
Four Thresholds of Total Suspended Particulates (TSP)



+Hours per year
*Thresholds Studied

APPENDIX

Denote the probability of an event given a k-unit increase in exposure for factor x_1 by P_k and let P_0 be the probability of an event given no exposure to factor x_1. Then according to the multiple logistics regression model:

$$\underline{1}.\ P_k = \frac{e^{\alpha + k\beta_1 + \beta_2 x_2 + \cdots}}{1 + e^{\alpha + k\beta_1 + \beta_2 x_2 + \cdots}}$$

$$\underline{2}.\ P_o = \frac{e^{\alpha + \beta_2 x_2 + \cdots}}{1 + e^{\alpha + \beta_2 x_2 + \cdots}}$$

Equation 2 implies that:

$$e^{\alpha + \beta_2 x_2 + \cdots} = \frac{P_0}{1 - P_0}$$

The estimated relative risk for a k-unit increase in x_1, R_k is:

$$R_k = \frac{P_k}{P_0}$$

$$= \frac{e^{k\beta_1}\ (\frac{P_0}{1 - P_0})}{P_0\ (1 + e^{k\beta_1}\ (\frac{P_0}{1 - P_0}))}$$

$$= \frac{e^{k\beta_1}}{1 - P_0 + P_0 e^{k\beta_1}}$$