Effects of Particulate Air Pollution on Asthmatics

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Abstract: Twenty-four asthmatic subjects in Denver were followed from January through March 1979, a three-month period in which Denver air pollution levels are generally high and variable. Dichotomous, virtual impactor samplers provided daily measurements $(\mu g/m^3)$ of inhaled particulate matter (total mass, sulfates, and nitrates) for coarse $(2.5 - 15 \,\mu\text{m}$ in aerodynamic diameter) and fine fractions ($\lt 2.5 \mu m$). Carbon monoxide, sulfur dioxide, ozone, temperature, and barometric pressure were also measured. Twice daily measurements of each subject's peak expiratory

Introduction

Asthma is a chronic respiratory disease characterized by sporadic attacks of dyspnea, wheezing, and coughing, the result of constriction of the bronchi and swelling of the bronchial mucosa. Allergens, emotional stress, and atmospheric conditions of air pollution and weather are factors which may aggravate the disease.

A major constituent of urban air pollution is suspended particulate matter, of which specific components, such as sulfates and nitrates, may combine with moisture to form acids having potentially irritant properties in the lungs. It can be postulated that individuals with respiratory disease, because of their airways hyperreactivity to known irritants, are the most sensitive subjects for study of the more immediate effects of irritant air pollution.' However, while indices of asthmatics' health status suggest that such individuals are affected by high levels of air pollution, $2-4$ the health effects of specific components or levels of suspended particulates have yet to be clearly established.

We report here ^a study to evaluate the short-term effects of inhaled particulate matter (IPM) and other air pollutants

flow rates, use of as-needed aerosolized bronchodilators, and report of airways obstruction symptoms characteristic of asthma were tested for relationships to air pollutants using a random effects model across subjects. During the time period actually observed, there were very few days in which high levels of suspended particulates were recorded. Of the environmental variables studied, only fine nitrates were associated with increased symptom reports and increased aerosolized bronchodilator usage. (Am J Public Health 1983: 73:50-56.)

on health status. Adult asthmatic patients residing in the Denver metropolitan area participated in the study, which was conducted by the National Jewish Hospital and Research Center/National Asthma Center. Two unique features were the assessment and use of multiple health status indices, and the availability of measurements for fine (less than 2.5 μ m in diameter) and coarse (between 2.5 and 15 μ m in diameter) fractions of particulate matter. The health status of each subject was evaluated by three types of measurement: 1) a physiological measurement-peak expiratory flow rate; 2) a subjective measurement-subjective reporting of airways obstruction; and 3) a behavioral measurementprescribed-as-needed (PRN) aerosolized bronchodilator usage. The dichotomous measurements, made possible by recent advances in the technology of particulate sampling, allowed examination of a component (fine fraction) believed to be especially likely to trigger airways obstruction in asthmatics.5.6

Methods and Materials

Subjects

Using medical characterization of disease and diagnostic confirmation of asthma as preliminary screening factors, 41 subjects were selected from an initial panel of 60 candidates and followed during the study period. Screening included confirmation of perennial asthma symptoms, methacholine inhalation challenge, twice daily peak expiratory flow rates measured over a 5- to 7-day period, medical history, physical examination, prick tests to allergens, chest x-ray, electrocardiogram, and use of the Panic-Fear Personality Scale to identify and exclude patients with excessively

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C ¹⁹⁸² American Journal of Public Health

TABLE 1-Means and Standard Errors for the Health Status Measurements*

*Data expressed as mean \pm SEM; data are from January 1-March 31, 1979. Maximum possible $n = 1080$.

high characterological anxiety known to be associated with medication overuse and arbitrary use.78 All subjects lived within a two-and-a-half mile radius of either of two air pollution monitoring stations (East Denver station at National Jewish Hospital, and West Denver station at National Asthma Center).

After eliminating observations recorded for any 12-hour measurement period in which the subject reported an upper respiratory infection or was outside the Denver metropolitan area for more than three hours, 24 of the 41 subjects met a criterion of at least 60 per cent complete data for the study period. These requirements were best met for the period January 9, 1979, through March 28, 1979, which became the focal period of study. Data from these 24 subjects were used for the analyses presented in this paper. The 17 subjects eliminated were not unique with respect to any demographic or medical measurement. These remaining 24 subjects were equally divided between the two monitoring stations; all were non-smokers. Additional demographic and medical information on the subjects is provided in the Appendix Table 1.

For each of the 24 subjects, three health measures were recorded twice daily, at approximately 7am and 7pm, providing data respectively for AM and PM phases of the analysis. These measures were: 1) a score obtained from subjective assessment of symptoms,⁹ computed by summing the values recorded for each of the nine items;* 2) peak expiratory flow rates (PEFR) as measured on regularly calibrated Mini-Wright Peak Flow Meters; and 3) continuously recorded usage of as-needed aerosolized bronchodilators by nebulizer chronologs.** Aerosolized bronchodilator

usage was measured since it can increase during periods of high pollution and mask the effect of pollution upon more direct measures of airways calibre.

Prior to data collection, all subjects were trained to use log books, in which they made entries corresponding to the 12-hour measurement periods used for the study. They were also trained in the use of the Mini-Wright Peak Flow Meters and the aerosolized bronchodilators equipped with the nebulizer chronologs. On a daily basis, each subject completed the morning log between 6 am and 8 am $(-7am)$ prior to taking any scheduled medications. The subject used the Mini-Wright three times, with an interval of one to two minutes between each measurement, and recorded the Mini-Wright gauge readings of PEFR in the morning log. Information about mobility and activity over the past 12 hours and subjective ratings of airways obstruction (total scores were computed during data analysis) were also recorded by the subject. Uses of as-needed bronchodilators, automatically registered by the nebulizer chronologs attached to the bronchodilators, were also documented by patient records of usage written in the logs. The morning log, including PEFR measurements, required only about five to ten minutes to complete. An identical procedure was followed for the evening log, completed between 6pm and 8pm $(-7pm)$ each day.

Subjects reported on a weekly basis to the East or West Denver monitoring station for pulmonary function testing and equipment inspection. During these visits, for which the compliance level was approximately 98 per cent,*** the Mini-Wright Peak Flow meter calibrations were checked, log books were examined, and the nebulizer chronologs were interpreted. Interpretation was accomplished by temporarily detaching the chronolog from its bronchodilator and reading its stored information into a microcomputer, producing a printed report of usage and the time and date of each usage. The chronolog was then reset and re-attached to the bronchodilator.

^{*}Shortness of breath, mucous congestion, difficulty breathing, chest congestion, chest tightness, chest filled up, uncomfortable, cough, wheezing. Item severity scored on a five-point scale from ¹ (not at all serious) to 5 (extremely severe).

^{*}The nebulizer chronolog (Advanced Technology Products, Inc., Denver, Colorado) is a small instrument which attaches to any commercially manufactured aerosolized bronchodilator; it is capable of logging up to 256 nebulizer usages with a resolution of four minutes and an accuracy of \pm one minute per month.

^{***}Two per cent of visits missed or occurred later than designated time.

For subjects monitored at the East Denver station, approximately 15 per cent of observations were missing; for subjects at the West Denver station, the proportion of missing observations was approximately 25 per cent. Descriptive statistics for the health status measurements are provided in Table 1.

Environmental

Three categories of environmental data comprising 11 variables were used in the analysis. These were: 1) fine (2.5 μ m in aerodynamic diameter) and coarse (between 2.5 and 15 μ m) fractions of inhaled particulate matter (total mass, sulfates, and nitrates); 2) gaseous air pollutants (sulfur dioxide, carbon monoxide, and ozone); and 3) meteorologic measures (temperature and barometric pressure).

Measurements of IPM $(\mu g/m^3)$ and gaseous pollutants, expressed in parts per million (ppm), were obtained at the East Denver and West Denver stations. Identical dichotomous samplers using virtual impactor techniques were used at each station to measure IPM.5.6 Barometric pressure was available only at the West Denver station, and temperature was monitored at a third station equidistant between the other two. The single-source readings of temperature and barometric pressure were paired with data for all subjects, while the other measurements were matched with subject data based on proximity of subject's residence to collection site. Particulate levels represent aggregate collection over 12-hour intervals, terminating at 7am and 7pm. For gaseous pollutants and meteorologic data, mean readings centering on 7am and 7pm were obtained by averaging values recorded in 12-hour periods bracketing those times. Descriptive statistics and correlations for the environmental and meteorologic variables are shown in Appendix Tables 2-4.

For purposes of analyses, subject and environmental data were matched temporally by pairing subject data at a given observation time (AM or PM) with averaged data centering on that same time and with aggregate data having collection terminated at that time.

Statistical Analysis

The objectives of the statistical analyses were to test the study's null hypotheses pertaining to the effects of air pollution upon each of the three health status measurements, namely that:

• Elevated pollution levels do not significantly *increase* the severity of reported airways obstruction symptoms;

 \bullet Elevated pollution levels do not significantly *decrease* peak expiratory flow rates; and

• Elevated pollution levels do not significantly *increase* the usage of as-needed (PRN) aerosolized bronchodilators.

Despite the directional nature of these hypotheses, twotailed tests were used in all analyses since many comparisons were made.

Since the analysis involved lagged variables, covariates such as meteorologic variables and a number of pollution variables, it was decided, in advance, to carry out the analysis in stages. This would allow the significance of the pollution variables to be tested after removing serial correlation and the effect of significant covariates, and would also reduce the total number of statistical tests. The philosophy of testing variables singly within groups was adopted, and the variables which were significantly correlated with the response were then tested as a group. The stagewise procedure first considered lagged variables to remove serial correlation, then covariables, then pollution variables. At each stage of the analysis, a random effects model was assumed for the regression coefficients. Under this model, a coefficient is assumed to have a given value for each subject and to be a random variable across subjects. The hypotheses to be tested are that the mean values of the coefficients across subjects are zero.

Because of strong diurnal variations in asthma symptoms and pollutants, the three dependent variables observed for each subject were analyzed separately for AM measurements and PM measurements. Since day to day correlation (serial correlation) exists in these response variables, a lagged value of the response variable was included in the regression as a covariate to remove the major cause of serial correlation and to give errors which are nearly uncorrelated. Both 12-hour and 24-hour lagged values were examined as predictors, and a 12-hour lag was chosen as being more strongly correlated with the response.

The method of analysis was to fit the model:

$$
Y_t = \beta_o + \beta_1 Y_{t-\ell} + \epsilon_t \tag{1}
$$

to each subject's data, where Y_t denotes a response value at time "t", and " ℓ " denotes the time lag. When either Y_t or $Y_{t-\ell}$ is missing, this time is dropped from the regression. The regression coefficient β_1 is then estimated by simple linear regression and is tested under the assumptions of the random effects model. A non-parametric procedure is appropriate if the assumption of a Gaussian distribution is in doubt, and is 95 per cent efficient if the assumption is satisfied.¹⁰ Therefore, the hypothesis was tested using the non-parametric Wilcoxon signed rank test. Although coefficients for both the 12-hour and 24-hour lagged values were highly significant ($p < .0005$), regressions using the 12-hour lagged value produced smaller mean square errors; therefore, the 12-hour lag was chosen as the stronger relationship and was included as a covariate in all subsequent analyses. Plots of residuals were also examined and were found to be free of trends, but not necessarily normally distributed.

The covariates considered were: 1) weekend/not weekend; 2) temperature; 3) barometric pressure; and 4) seasonality.

The first three were tested using the model:

$$
Y_t = \beta_0 + \beta_1 Y_{t-\ell} + \beta_2 X_t + \varepsilon_t \tag{2}
$$

The weekend/not weekend variable was coded one for weekend and zero for weekdays. When Y_t , Y_{t-t} , or X_t is missing, this time was dropped. The β 's were estimated by multiple linear regression for each subject, and the coefficient β_2 tested across subjects as above using the Wilcoxon signed rank test. This tests the partial effect of X_t with the time lag effect removed.

Seasonality was tested using the model:

$$
Y_{t} = \beta_{0} + \beta_{1}Y_{t-\ell} + \beta_{2} \cos (2\pi t/365) + \beta_{3} \sin (2\pi t/365) + \epsilon_{t}
$$
\n(3)

Health Status Measurement	Time Period	Temperature	Barometric Pressure	Weekend Effect	Seasonality	
Peak Flow	7am	$.5602 -$.5840+	$.6152+$.5460	
	7om	$.8414-$	$.8047+$	$.7443-$.1894	
Symptomatology	7am	$.5522+$	$.6680 +$	$.5919+$.7886	
	7om	$.6075+$	$.6382 -$	$.8210+$.7643	
Nebulizer Usage	7am	.7475-	.5641-	$.5300+$.8987	
	7pm	.8339-	$.6861 +$	$.0001 +$.4155	

TABLE 2-Two-Tailed P-Values from Tests of Significance on Covariates Performed Across Subjects*

*A Wilcoxon Signed Rank Test was used for each test of significance for temperature, barometric pressure, and weekend effect. Hotelling's T^2 was used to test simultaneously the two coefficients of seasonality. Where appropriate, + and - demonstrate the sign of the regression coefficients having the larger rank sum in the Wilcoxon Signed Rank Test.

where the index ^t denotes the day. This is the fundamental frequency of one cycle per year fitted over part of a year. The true shape of a seasonality function will not be exactly a sine wave, but over a quarter year this should give a good approximation to the seasonality effect. Because the data consist of only a part of a year, and because of missing data, the sine and cosine functions are not orthogonal and must be fit by multiple linear regression methods. If there is no seasonal effect, the random effects model states that the mean values of both β_2 and β_3 across subjects are zero. The estimates from subject j, $b_2^{(j)}$ and $b_3^{(j)}$ are correlated, so the appropriate test assuming a bivariate Gaussian distribution is Hotelling's T^2 .¹¹

The results of the random effects tests for the four covariates are shown in Table 2. The only significant result is ^a weekend PM effect for nebulizer use indicating that there is an increase in nebulizer usage during the day (i.e., the 12 hour period ending at 7pm) on weekends. This covariate was included in subsequent analyses involving PM nebulizer usage.

The final analyses used model (2) to test each of the nine pollutants one at ^a time, except that for PM nebulizer use the extra covariate for weekend effect was included. Here X_t represents the value of the pollutant. The p-values for the two-tailed Wilcoxon signed rank tests are shown in Table 3. The notational signs indicate the sign of the regression coefficients having the larger rank sum, which is also the sign of the mean regression coefficient. If pollution has an

adverse effect, the sign should be positive for symptomatology, negative for peak flow, and positive for nebulizer use. The smallest p-value is .0229 in the direction indicating an adverse effect of fine nitrates on symptomatology. The second smallest p-value is .0249, indicating that fine nitrates were also associated with increased aerosolized bronchodilator usage. Although there are three p-values showing significance at less than the .05 level in the hypothesized direction, this needs to be viewed cautiously due to the number of tests run. At best, the study has not convincingly demonstrated a statistically significant relationship between the air pollution factors monitored and exacerbation of asthma.

Discussion

Using a methodology similar to that outlined by Whittemore and Korn,^{12,13} the analysis is designed to avoid weaknesses of some previous studies. Results of this study support earlier conclusions regarding high dependence between asthma status in successive observation periods. Therefore, in all stages of the analysis, a lagged variable is included to adjust for the effects of this serial correlation. Regression analyses are performed separately for each individual rather than with data averaged across subjects, thereby avoiding potential bias created if missing data are not well distributed among subjects. A strength of this study is the

TABLE 3-Two-Talled P-Values from Wilcoxon Signed Rank Tests Performed Across Subjects*

Health Status	Time	Carbon	Sulfur	Ozone	Overall	Overall	Fine	Coarse	Fine	Coarse
Measurement	Period	Monoxide	Dioxide		Fine Mass	Coarse Mass	Sulfates	Sulfates	Nitrates	Nitrates
Peak Flow	7am	-0866.	$.8262 -$.7038+	$-6306 -$	$.6680 +$.7311-	-0866.	.1434 –	$.7634+$
	7om	+3066.	$.0366+$.1355-	$.7108 +$	$.5522-$.5682+	$.7817+$	$.5562+$	$.7176+$
Symptomatology	7am	=000.1	$.5282+$.6303-	$.8075 -$	$.7571 -$	$.8157+$	$.8019 +$	$.0229 +$.7539-
	7om	$.6152+$.8047-	.6303+	$.000 =$	$.7003+$	$.8262+$.8364-	$.1011 +$	$.7108 +$
Nebulizer Usage	7am	.5300+	.5300+	.5809+	$.6546-$	$.7193 -$	$.0650+$.6507+	$.0415+$	$.7336+$
	7pm	.6344 –	.6267—	.6625+	$.5879+$.5282-	$.0604 +$	$.6152-$	$.0249 +$.5997+

*+ and - indicate the sign of the regression coefficients having the larger rank sum.

use of multiple measures of health status, with weekly clinical validation of physiological measures and automatic, timed recording of as-needed aerosolized bronchodilator usage. These additional measures control for possible bias in subjective reporting.

One limitation of the study was its failure to include the entirety of the period considered to be Denver's high air pollution season, which extends from early November to mid-March. During the time period observed, there were very few days in which high levels of suspended particulates, the pollutant of major interest in this study, were recorded. Also, the decision to exclude data when subjects were out of the area for more than three hours of a 12-hour observation period caused elimination of some data collected during peak periods (6am-8am and 6pm-8pm) when the subject was away only during the middle of the day or late in the evening.

While the associations observed between air pollution and asthmatic health status were few and need to be viewed cautiously, the possibility is not excluded of finding reliable associations in a susceptible group exposed to consistently high levels of pollution over a sufficient length of time.

REFERENCES

- 1. Farr RS, Spector SL: What is asthma? In: Petty TL (ed): The Asthmatic Patient in Trouble, Greenwich, CT, Upjohn, 1975.
- 2. Shy CM, Goldsmith JR, Hackney JD, et al: Health effects of air pollution. ^J Thorac Soc News 1978; 4:22.
- 3. Mitchell RS, Judson FN, Moulding TS, et al: The health effects of urban air pollution. JAMA 1979; 242:1163.
- 4. Holland WW, Bennett AE, Cameron IR, et al: Health effects of particulate pollution: reappraising the evidence. Exposure to particulate pollution: studies in children. Am ^J Epidemiol 1979; 110:604.
- 5. Dzubay TG, Stevens RK: Application of the dichotomous sampler to the characterization of ambient aerosols. In: Dzubay TG (ed): X-ray Fluorescence Analysis of Environmental Samples. Ann Arbor, MI: Ann Arbor Science, 1977.
- 6. Loo BW, Jakeivic JM, Goulding FS: Dichotomous virtual impactors for large scale monitoring of airborne particulate

matter. In: Liv BYH (ed): Fine Particles. New York: Academic Press, 1976.

- 7. Jones NF, Kinsman RA, Dirks JF, Dahlem NW: Psychological contributions to chronicity in asthma. Med Care 1979; 17:1103.
- 8. Kinsman RA, Dirks JF, Dahlem NW: Noncompliance to prescribed as-needed (PRN) medication use in asthma: usage patterns and patient characteristics. J Psychosom Res 1980; 24:97.
- 9. Kinsman RA, Dahlem NW, Spector SL, et al: Observations on subjective symptomatology, coping behavior, and medical decisions in asthma. Psychosom Med 1977; 29:102.
- 10. Hoeffding W: Some recent developments in nonparametric statistics. Rev Int Statistical Institute 1968; 36:2.
- 11. Anderson TW: Introduction to Multivariate Statistical Analysis. New York: Wiley, 1958.
- 12. Whittemore AS, Korn EL: Asthma and air pollution in the Los Angeles area. Am ^J Public Health 1980; 70:687.
- 13. Korn EL, Whittemore AS: Methods for analyzing panel studies of acute health effects of air pollution. Biometrics 1979; 35:795.
- 14. Chai H, Farr RJ, Froelich LA, et al: Standardization of bronchial inhalation challenges procedures. J Allergy Clin Immunol 1975; 56:323.

ACKNOWLEDGMENTS

This study was supported by the Environmental Protection Agency, Contract No. 68-02-3208. A full report of the study is available from the U.S. Environmental Protection Agency, Office of Research and Development, Health Effects Research Laboratory, Research Triangle Park, NC 27711; this report provides details about medical screening of subjects, distribution of the environmental and health status variables during the study period, and detailed descriptions of all measures and techniques employed.

Special thanks are due to Dorothy Calafiore, the project officer at EPA, and to the others at EPA whose advice and suggestions made this report feasible. Dr. Gary Zerbe, University of Colorado Health Sciences Center, provided invaluable assistance in his discussions of the statistical analysis. The Colorado Department of Health cooperated throughout the duration of the project, maintaining the air pollution monitoring stations and providing much of the data with which we worked. Chemical analysis of suspended particulates was provided by Northrup Services in Research Triangle Park, NC. The authors especially wish to thank the volunteers with asthma, whose continued cooperation and tolerance of inconvenience made the study possible.

APPENDIX TABLE 1--Descriptive Data for 24 Asthmatic Subjects Involved in the Analyses

aPossible threshold levels (mg/ml) in the standardized methacholine inhalation challenge procedure are: .07, .15, .31, .62, 1.25, 2.50, 5.00, 10.00, and 25.00; See reference 14.

PSkin test reactions were positive (+) to one or more of the following antigens: Mixed weeds, mixed grasses, mixed trees, and/or house dust. Negative (−)
indicates that there were no positive skin test reactions for any a

cBrand names of the aerosolized bronchodilators taken on a prescribed-as-needed (PRN) basis are shown.

dMean values ± SD from January 9-March 28 for 7am. eMean values ± SD from January 9-March 28 for 7pm.

APPENDIX TABLE 2-Monthly Means and Standard Errors for Inhaled Particulate Matter (IPM)

APPENDIX TABLE 3-Monthly Means and Standard Errors for Gaseous Air Quality and Meteorologic Variables

aSea-level equivalent barometric pressure provided by the US Weather Service at Stapleton International Airport. To obtain approximate Denver area barometric pressures, multiply the mean values by 630/760.

bDue to equipment failure, ozone was monitored at only the West station during March; ozone data from the West Denver station were used for both stations during this month.

cN = ¹² dN = 25

APPENDIX TABLE 4-Correlations Among the Environmental Variables^{a,b}

aFor N = 60, r = .30 at $p < .01$.

bFor N = 35, r = .39 at $p < .01$.

cN = 34; all other N's = 64 to 70.