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EFFECTS OF PARTICULATE AIR POLLUTION ON ASTHMATIC SUBJECTS

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16. ABSTRACT

While much remains to be understood, individuals with respiratory disease appear to be affected by high levels of air pollution as indicated by subjective reports, clinic and hospital visits, and morbidity. Suspended particulates make up a substantial part of urban air pollution, and specific components of particulates, such as sulfates and nitrates, when combined with moisture, form acids with properties potentially irritating to the lung. The available research literature has not clearly implicated the components of suspended particulates which do exert an immediate effect upon the health status of individuals with respiratory disease.

The present study focuses upon the acute or short-term effects of suspended particulates upon asthmatic individuals. It has incorporated several unique features. First, extensive medical characterization of each subject's asthma was available, and individuals with other respiratory or medical conditions were not included. Secondly, recent advances in methods of particulate measurement, based upon dichotomous sampling of particulates via virtual impactor techniques, were incorporated in the study. Thirdly, the daily health status of the asthmatic subjects was considered to be a concept that is best defined by employing three different types of measurements, selected in order to triangulate on the more immediate health effects of air pollution upon the asthmatic subjects. This report considers the period January through March, 1979 when IPM and most other pollutants were at their highest and most fluctuating levels in Denver.

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FOREWORD

The many benefits of our modern, developing, industrial society are accompanied by certain hazards. Careful assessment of the relative risk of existing and new man-made environmental hazards is necessary for the establishment of sound regulatory policy. These regulations serve to enhance the quality of our environment in order to promote the public health and welfare and the productive capacity of our Nation's population.

The Health Effects Research Laboratory, Research Triangle Park, conducts a coordinated environmental health research program in toxicology, epidemiology, and clinical studies using human volunteer subjects. These studies address problems in air pollution, non-ionizing radiation, environmental carcinogenesis and the toxicology of pesticides as well as other chemical pollutants. The Laboratory participates in the development and revision of air quality criteria documents on pollutants for which national ambient air quality standards exist or are proposed, provides the data for registration of new pesticides or proposed suspension of those already in use, conducts research on hazardous and toxic materials, and is primarily responsible for providing the health basis for non-ionizing radiation standards. Direct support to the regulatory function of the Agency is provided in the form of expert testimony and preparation of afficavits as well as expert advice to the Administrator to assure the adequacy of health care and surveillance of persons having suffered imminent and substantial endangerment of their health.

The study documented in this report was undertaken to identify specifically the effect of inhalable particulate matter on the exacerbation of asthma symptoms. It was designed to incorporate several unique features. First, the dichotomous sampling of particulate matter by recently developed air measurement technology was employed. While this new technology represented an advance in exposure measurement, this study (as have other epidemiologic investigations) suffered the limitation of fixed site exposure measurement. A second unique feature was the three-prong approach to health status measurement. Subject responses were evaluated by two objective measurements (pulmonary function tests and mechanically recorded medication usage) as well as by the usual subjective patient-reported symptoms. Objective measurement of medications used by subjects was for the first time possible by the newly developed nebulizer chronologs designed to record aerosolized bronchodilator usage. Thus, this study offered EPA's Health Effects Research Laboratory new methods for evaluating ambient pollution levels and subject responses, in addition to providing a limited amount of data needed for the preparation of the forthcoming fine particulate criteria document.

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Director
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The Colorado Department of Health Air Pollution Surveillance Section cooperated throughout this project, maintaining the two air pollution monitoring stations located in East and West Denver. We particularly appreciate the cooperation of Steve Arnold, Senior Air Pollution Specialist from that office.

Chemical analyses of the inhaled particulate matter samples were provided by Northrop Services, Inc. in Research Triangle Park, NC, and we thank John Tisch of Northrop for his assistance in regard to these analyses.

Most notably, Dr. Dorothy Calafiore, our project officer at the Environmental Protection Agency, was an invaluable aid to us, ready to help facilitate any aspect of the project under her control.

Finally, we thank the volunteers who participated in this project as subjects. For months, they were required to maintain careful daily records, to perform daily pulmonary function tests, and to return to one of the two Denver stations weekly for additional testing and debriefing. Their consistent cooperation and their willingness to tolerate such inconvenience for no direct personal gain continues to be a source of gratification to us; their patient cooperation was the critical factor in making this work possible.

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1. ABSTRACT

This study evaluated the relationship between inhaled particulate matter (IPM) and the health status of adult asthmatic patients residing in the Denver metropolitan area. All subjects lived within a radius of 2.5 miles of one of our two air pollution monitoring stations (East and West Denver).

Using dichotomous, virtual impactor samplers, IPM was collected daily for two 12-hour periods (7 AM to 7 PM; and 7 PM to 7 AM), providing measurements ($\mu g/m^3$) of IPM total mass, IPM sulfates ($SO_4^=$), and IPM nitrates (NO_3^-) for coarse (2.5 - 15 μm in aerodynamic diameter) and fine (<2.5 μm) fractions. Hourly measures of carbon monoxide (CO), sulfur dioxide (SO_2), and ozone (O_3) also were obtained. Temperature (^oK) and barometric pressure (in. Hg) were available at a single site (West Denver).

Health status of the asthmatic subjects was indexed by twice daily (7 AM and 7 PM) measurements of peak expiratory flow rates (PEFR), subjective report of airways obstruction, and continuous recording of as-needed (PRN) aerosolized bronchodilators by a nebulizer chronolog.

Analyses focused on the time period during which the highest and most variable levels of air pollution occurred and the quality control of the air pollution data were best assured (January through March, 1979). In all analyses, the preceding 12-hour levels of IPM were related to the subsequent health status measurements, while 12-hour gaseous air pollutants and meteorologic variables bracketed the health status measurements.

Initial multiple linear regression analyses were performed by LEAPS AND BOUNDS for individuals and groups. Since the initial LEAPS AND BOUNDS regression analyses did not take into account between-subjects variation, a final phase involved analyses using a random effects model in which the regression coefficients were considered random variables across subjects. Of the air pollution variables, only fine nitrates, an IPM component that was occasionally high in Denver relative to other American cities, were associated with increased symptom reports by the subjects and increased aerosolized bronchodilator usage. Due to the number of comparisons made, this result needs to be viewed as tentative and potentially attributable to chance.

The relative strengths and limitations of the study are discussed.

This report was submitted in fulfillment of Contract No. 68-02-3208 by National Jewish Hospital/National Asthma Center under the sponsorship of the U.S. Environmental Protection Agency. The report describes work completed during the contract period December 7, 1978 to May 15, 1980.

2. INTRODUCTION

While much remains to be understood, individuals with respiratory disease appear to be affected by high levels of air pollution as indicated by subjective report, clinic and hospital visits, and morbidity.[1-10] Suspended particulates make up a substantial part of urban air pollution, and specific components of particulates, such as sulfates and nitrates, when combined with moisture, form acids with properties potentially irritating to the lung.

The available research literature has not clearly implicated the components of suspended particulates which do exert an immediate effect upon the health status of individuals with respiratory disease. A recent extensive review[11] concluded that the minimum "24 hour average levels of total suspended particulates at which increased incidence of illness in bronchitic patients is discernible are levels in excess of ... about 350 $\mu g/m^3$ in the presence of sulfur dioxide of about [.16 ppm]." These levels are based on studies by Lawther[12] and Waller[13] in London and other urban areas of Great Britain. For asthma, the controversial CHESS studies[14,15] have been the most ambitious projects to date that have focused on suspended particulates, but these studies have not provided definitive answers on the effects of various levels of suspended particulates on health. Moreover, the single aspect of health status involved in the CHESS studies concerned the reported incidence of breathing difficulty characteristic of asthma attacks.

The present study focuses upon the acute or short-term effects of suspended particulates upon asthmatic individuals. On a conceptual basis, asthmatic subjects should be among the most highly sensitive of individuals to the more immediate irritant properties of suspended particulates and other irritant air pollutants because of the inherent hyperreactivity of the airways of asthmatics to known irritants.[16-18]

The present study has incorporated several unique features. First, extensive medical characterization of each subject's asthma was available, and individuals with other respiratory or medical conditions (e.g., bronchitis or emphysema) were not included. Medical characterization for most subjects included skin tests with allergens (grasses, trees, weeds, and house dust), and airways hyperreactivity, indexed either by methacholine inhalation challenge[18,19] or demonstrated reversibility of airways obstruction upon inhalation of a bronchodilator medication, or both. Thus, the potentially confounding role of allergic factors upon airways obstruction could be explored by separating the asthmatic subjects according to allergic predisposition, while the level of airways hyperreactivity could also be used to explore any differing response to the air pollution variables.

Secondly, recent advances in methods of particulate measurement, based upon dichotomous sampling of particulates via virtual impactor techniques,[20-24] were incorporated in the study. These procedures enabled two fractions of inhaled particulate matter (IPM) to be measured: A coarse fraction, including IPM with an aerodynamic diameter between 2.5 and 15 μm; and a fine fraction, with an aerodynamic diameter less than 2.5 μm. The fine fraction of IPM may be particularly likely to trigger airways obstruction in asthma because of the deposition of these fine particles throughout the airways, and the potentially irritant qualities of the chemical components with which they are often associated.[26,27] In this regard, supplemental chemical analyses focused upon the sulfate ($SO_4^=$) and nitrate (NO_3^-) components of IPM within the fine and coarse fractions. The health effects of IPM measures were examined against a background of other environmental (carbon monoxide, sulfur dioxide, and ozone) and meteorologic (temperature and barometric pressure) factors.

Thirdly, the daily health status of the asthmatic subjects was considered to be a concept that is best defined by employing three different types of measurements: (A) a physiological measurement, i.e., peak expiratory flow rate (PEFR), (B) a subjective measurement, i.e., report of the severity of airways obstruction symptoms, and (C) a behavioral measurement, i.e., discretionary usage of as-needed (PRN) aerosolized bronchodilators. These three measurements were selected in order to triangulate on the more immediate health effects of air pollution upon the asthmatic subjects.

This report considers only the period of January through March, 1979 when IPM and most other pollutants were at their highest and most fluctuating levels in Denver, although all subjects were followed until June, 1979. After the end of March, 1979, the particulate levels were generally low and showed fewer variations, and information missing from one monitoring station (West Denver) and a suspected equipment malfunction at the other station (East Denver) precluded use of particulate data.

3. METHODS

3.1 SUBJECTS

From an initial panel of 60 volunteers, 41 well-characterized asthmatic subjects were selected and carefully followed for approximately five months, January 1 to June 10, 1979. All lived within 2.5 miles of one of two air pollution monitoring stations, an East Denver station (National Jewish Hospital) and a West Denver station (National Asthma Center). Two subjects were dropped from the study due to lengthy absences from the Denver metropolitan area which were not anticipated at the outset. Of the remainder, 24 subjects, 12 at each station, met a criterion of 60% complete data within the target period of January, 1979 through March, 1979, after eliminating daily measurement periods when upper respiratory infections (URI's) were reported and periods when subjects were out of the Denver metropolitan area for more than three hours during a 12-hour measurement period. All subsequent analyses focused upon these 24 subjects that met these criteria. The 17 subjects eliminated were not unique with respect to any demographic or medical measurement. Table 1 (shown on pages 7 and 8) provides detailed demographic and medical information about the 24 subjects (9 males and 15 females) accepted for analyses. All were taking a theophylline preparation or an oral beta agonist on a regular schedule as a basic bronchodilator, while 8 subjects also supplemented this medication regimen with daily or alternate day oral corticosteroids. In addition, all subjects took an

TABLE 3.1 DESCRIPTIVE DATA FOR 24 ASTHMATIC SUBJECTS INVOLVED IN THE ANALYSES

(A) East Denver Station

Patient	Age (Years)	Sex	Methacholine[a] (Threshold Dose) (mg/ml)	Skin Tests[b]	As-Needed Broncho-dilator[c]	Steroid Medication	Peak Flow[d] (l/min) (AM)	Peak Flow[e] (l/min) (PM)	Reported Irritant Exposure
B.A.	49	F	2.50	-	Bronkometer	Daily	310 ± 50	360 ± 30	
S.B.	25	F	Not Done	+	Alupent	Alternate Day	400 ± 40	410 ± 30	
V.B.	26	M	.31	+	Bronkosol	Alternate Day	350 ± 80	370 ± 90	Coal Smelter
J.C.	49	M	1.25	-	Alupent	None	360 ± 20	420 ± 40	
P.G.	27	M	.15	-	Bronkosol	None	540 ± 70	560 ± 60	
G.H.	53	M	.15	+	Alupent	None	270 ± 40	360 ± 70	
G.M.	59	F	Not Done	-	Bronkometer	Alternate Day	210 ± 50	190 ± 40	
B.S.	46	M	.62	+	Mistometer	None	460 ± 30	520 ± 30	Asbestos and Creosote
L.S.	28	F	.31	+	Medihaler	None	370 ± 30	390 ± 20	
H.S.	48	F	.31	+	Alupent	None	280 ± 20	370 ± 30	
D.T.	26	M	2.50	-	Alupent	Alternate Day	390 ± 100	400 ± 120	
B.W.	26	M	.62	+	Bronkometer	None	370 ± 50	380 ± 60	Cigarette Smoke

TABLE 3.1 - Continued

(E) West Denver Station

Patient	Age (Years)	Sex	Methacholine[a] (Threshold Dose) (mg/ml)	Skin Tests[b]	As-Needed Broncho-dilator[c]	Steroid Medication	Peak Flow[d] (l/min) (AM)	Peak Flow[e] (l/min) (PM)	Reported Irritant Exposure
D.B.	22	F	.15	+	Bronkosol	Alternate Day	340 ± 30	370 ± 40	
M.B.	24	F	.15	+	Bronkosol	None	360 ± 60	360 ± 50	Chemical Cleaners
B.L.	48	F	.62	-	Bronkosol	None	270 ± 30	270 ± 30	
E.M.	47	M	.31	-	Alupent	None	440 ± 40	450 ± 40	
T.M.	21	F	Not Done	+	Alupent	Alternate Day	430 ± 70	470 ± 60	
C.M.	27	F	.07	+	Alupent	None	280 ± 60	290 ± 60	
B.N.	32	F	.15	+	Bronkometer	Alternate Day	390 ± 20	380 ± 30	
P.S.	24	M	Not Done	Not Done	Bronkosol	None	480 ± 30	480 ± 40	
S.S.	25	F	.07	-	Alupent	None	370 ± 60	410 ± 50	Developing Solution
R.S.	60	F	.07	-	Alupent	None	190 ± 60	260 ± 70	
A.V.	28	F	.15	-	Alupent	None	190 ± 50	300 ± 80	
P.W.	45	F	1.25	+	Alupent	None	400 ± 60	400 ± 60	

[a]Possible 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.

[b]Skin 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 antigen.

[c]Brand names of the aerosolized bronchodilators taken on an as-needed (PRN) basis are shown.

[d]Mean values ± SD from January 9 - March 28 for 7 AM.

[e]Mean values ± SD from January 9 - March 28 for 7 PM.

aerosolized bronchodilator on a discretionary, as-needed (PRN) basis to relieve episodes of acute breathing difficulty.

Prior to acceptance for the study, the subjects were screened to confirm the diagnosis of asthma. All had perennial symptoms of asthma as defined by the American Thoracic Society.[18] Methacholine inhalation challenges, conducted according to the recommendations of the National Institute of Allergy and Infectious Disease Panel on Standardization of Bronchial Inhalation Challenge Procedures,[19,20] were given to 20 of the subjects, and all had positive results, consistent with a diagnosis of asthma. Four of the 24 subjects were not given methacholine challenges, at their physician's requests. However, for all subjects, hyperreactive airways disease was also confirmed by marked variations in twice-daily peak expiratory flow rates (PEFR) during a 5- to 7-day prescreening period, by medical history, and by physical examination. Prick tests with mixed weeds, mixed grasses, mixed trees, and house dust were given to 23 of the 24 subjects accepted for the analyses.[21] Four of the 23 subjects reacted positively (indicating the presence of Ige) to mixed trees, 7 to mixed grasses, 7 to mixed weeds, and 6 to house dust. Ten of the subjects reacted negatively to all antigen skin tests.

All subjects were given a chest x-ray during prescreening to rule out the existence of pulmonary conditions other than asthma, and an electrocardiogram to exclude individuals with heart disease or related cardiopulmonary problems. All of the subjects were nonsmokers, however, five reported being exposed to irritants at their work or in their homes.

Finally, prescreening by brief psychological testing eliminated those subjects likely to overuse as-needed (PRN) aerosolized bronchodilators when airways obstruction is not present, or to use these PRN aerosolized bronchodilators in arbitrary ways independent of the levels of airways obstruction. The specific psychological instrument employed was the MMPI Panic-Fear Personality Scale used to identify and exclude patients with excessively high characterological anxiety known to be associated with PRN overuse and arbitrary use.[22,23]

3.2 MEASUREMENTS EMPLOYED

Two classes of measurements were obtained twice each day: (A) environmental and Meteorologic Variables (average temperature and barometric pressure); and (B) Health Status Measurements, including peak expiratory flow rates (PEFR), use of as-needed (PRN) aerosolized bronchodilators, and report of the airways obstruction symptoms characteristic of asthma.

3.2.1 Environmental Variables

The environmental variables considered included: (A) coarse and fine fractions of inhaled particulate matter (mass, nitrates, and sulfates), (B) gaseous air pollutants (sulfur dioxide, carbon monoxide, and ozone), and (C) meteorologic measurements (temperature and barometric pressure).

Inhaled Particulate Matter (IPM). The principal environmental variables were two fractions of inhaled particulate matter (IPM) which were simultaneously monitored at the East (National Jewish Hospital, 3800 East Colfax Avenue) and West (National Asthma Center, 1999 Julian Street) Denver stations. Identical dichotomous samplers using virtual impactor techniques[24-28] were used at each station to measure two IPM fractions, a fine fraction consisting of particulates ≤ 2.5 μm in aerodynamic diameter, and a coarse fraction consisting of particulates between 2.5 and 15 μm in aerodynamic diameter. Via the dichotomous samplers, IPM for both fractions were collected on glass wool slides during two daily 12-hour collection periods, i.e., from 7 AM to 7 PM (7 PM) and from 7 PM to 7 AM (7 AM). The glass wool slides were inspected visually in Denver to insure their integrity (e.g., no tears, etc.) and shipped bi-monthly to Northrop Services, Inc. (Research Triangle Park, NC) for IPM analyses. The glass wool slides were weighed and subjected to ion exchange chromatography analyses to determine the IPM sulfate ($SO_4^=$) and nitrate (NO_3^-) mass concentrations for both the fine and coarse IPM fractions.[29] In summary, the IPM measures that were obtained included mass ($\mu g/m^3$), sulfates ($\mu g/m^3$), and nitrates ($\mu g/m^3$) for the fine and coarse IPM fractions during each 12-hour period.[24-28]

For IPM, quality control considerations required that dichotomous sampler flow rates be checked by an independent agent at the outset of the study period (December, 1978), and by the Colorado Department of Health in December, 1978 and February, 1979. The dichotomous sampler trays were checked weekly while the dichotomous samplers were in operation, and proper sealing and alignment of the trays were verified on a bi-weekly basis at the time that new trays were loaded into the samplers. Visual checks of the glass wool slides were made to assure their integrity prior to shipping to Northrop for analyses.

Gaseous Air Quality. Gaseous air pollutant measurements, including sulfur dioxide (SO_2), carbon monoxide (CO), and ozone (O_3), were obtained hourly by the Colorado Department of Health through their continuous monitoring program.[30] In order to bracket each health status measurement period for the gaseous air quality measurements, each day was divided into two 12-hour periods, 12 AM to 12 PM (bracketing 7 AM) and 12 PM to

12 AM (bracketing 7 PM). Average values, expressed in parts per million (ppm), were obtained for each of these periods.

All measurements of the gaseous air quality variables were made using continuous automated methods, with data collection made by a computer-operated telemetered data acquisition system. Intake manifolds for air sampling were consistent with Environmental Protection Agency design criteria,[31] with the intake ports being uniform in elevation, from 15 to 20 feet above the ground at botn stations.

Sulfur dioxide was measured with Thermo Electron Model 43 pulsed fluorescence analyzers.[32] Carbon monoxide was monitored using Beckman Model 866 nondispersive infrared analyzers. Ozone was measured using ethylene chemiluminescent McMillan 110 equipment. All analytical methods for gaseous air quality measurements were designated equivalent under Federal specifications.[32]

For the gaseous air quality measurements, quality assurance procedures were utilized to assure compatability with National Bureau of Standards reference standards through methods employed by the Colorado Department of Health.[33] All gaseous analyzers were calibrated with a multipoint calibration at the outset of the study period, and received daily purge and span checks on the values to help assure identification of malfunction on a day-to-day basis. During data processing, the gaseous air quality data were visually audited by Colorado Health Department personnel, to identify any unreasonable values.

<u>Meteorologic Measurements</u>. Hourly temperatures (°K) were available from the Colorado Health Department Welby monitoring station, approximately two miles equidistant from the East and West Denver stations. Average values

were obtained for the 7 AM and 7 PM periods. Four daily barometric pressure measurements (in. Hg.) adjusted to sea level equivalencies, were obtained from the West Denver station (7 PM, 1 AM, 7 AM, and 1 PM). Barometric pressures were checked every day against values provided by the National Weather Bureau at Stapleton International Airport. The average barometric pressure was obtained by averaging the value for the period of interest and the two barometric pressure values from six hours before and six hours after that period.

3.3.2 Health Status Measurements

The effects of the inhaled particulate matter, gaseous air pollutants, temperature, and barometric pressure upon the health status of asthmatics were evaluated by obtaining twice daily measurements of three health status variables: (A) Physiological: Pulmonary function measurements; (B) Behavioral: Usage of as-needed (PRN) aerosolized bronchodilators; and (C) Subjective: Ratings of the symptoms of airways obstruction. Each of these health status measurements provides an unique index of the potential effects of IPM upon individuals with hyperreactive airways disease.

Physiological: Pulmonary Function Measurements. Each subject was equipped with, and trained to use, a Mini-Wright Peak Flow Meter (Armstrong Industries, Inc., Northbrook, IL). This small, portable device reliably measures the peak expiratory flow rate (PEFR) -- the maximum flow rate (liters/min) achieved during a forced expiration following a full inspiration. As airways obstruction increases, PEFR values decrease.

On each occasion (7 AM and 7 PM), the subject used the Mini-Wright Peak Flow Meter (Mini-Wright) three times, with a one-minute rest between expirations. The three PEFR values (read from a gauge on the Mini-Wright) were recorded at the bottom of their morning (or evening) log.

Quality control procedures were also established for the Mini-Wrights.[34] During the study, the peak flow readings on the Mini-Wrights were checked weekly against the readings on a standard adult Wright Peak Flow Meter (Std-Wright), using a reproducible flow source. This flow source consisted of a gallon plastic bottle fitted with a compressed air source, a large respiratory valve which could be operated manually to release pressure and hence flow through the Std- or Mini-Wright. By interchanging two valves fitted with fixed (but different) resistors and by delivering a range of pressures up to 12 pounds/square inch to the flow meters, peak flows between 75 and 800 l/min could be generated. Mini-Wright readings versus Std-Wright readings fell along the same linear regression line regardless of whether the flows were generated by the pressurized bottle or a Brooks rotameter using a constant flow source. The relationship between actual flow and Std-Wright readings allowed the values from both types of peak flow meters to be corrected by a constant to reflect actual flow. The adequacy of the Mini-Wrights was supported by the remarkable reproducibility and consistent readings for each Mini-Wright over the period of the study, although, as noted, small variations in uncorrected readings did occur among Mini-Wrights for the same flow.

To supplement the twice-daily PEFR values obtained by the Mini-Wrights, once each week the subjects returned to their assigned station and more extensive spirometric pulmonary function measurements were obtained using a Medistor spirometer (Cybermedic, Inc., Boulder, CO). These weekly pulmonary function measurements were supervised by a trained pulmonary function technician, and provided measurements of PEFR, forced vital capacity (FVC), first-second forced expiratory volume (FEV_1), and mid-maximum expiratory flow rate (MMEF).

Behavioral: Usage of As-Needed (PRN) Aerosolized Bronchodilators. All subjects were equipped with a nebulizer chronolog (Advanced Technology Products, Inc., Denver, CO) to measure usage of as-needed (PRN) aerosolized bronchodilators. Usage measurements were also confirmed by having the subject record the time and amount for each occasion of nebulizer use on the daily logs.

The nebulizer chronolog is a small instrument (about one-half a cigarette package in size) that attaches to any commercially manufactured aerosolized bronchodilator (e.g., Bronkosol, Bronkometer, Alupent). The nebulizer chronolog consists of a battery-operated, crystal-controlled timepiece capable of logging up to 256 nebulizer usages with a resolution of four minutes and an accuracy of ± one minute per month. A nebulizer chronolog interpreter (a micro-computer) provided a printed report of the nebulizer usage times stored within the nebulizer chronolog, upon demand. Each week, when the subject returned to the East or West Denver station, the nebulizer chronolog was removed from the aerosolized bronchodilator cartridge, interpreted, and reset. To assure as reliable a measurement as possible of nebulizer usage, subjects in the study were required to agree to use only that aerosolized bronchodilator equipped with the nebulizer chronolog, and to deposit any existing, supplementary aerosolized bronchodilators at one of the two stations prior to data collection.

Subjective: Ratings of the Symptoms of Airways Obstruction. The morning (7 AM) and evening (7 PM) logs required the subject to rate nine discrete symptoms of breathing difficulty, each on a 5-point scale of severity (1 = not at all severe; 5 = extremely severe). The symptoms included in this Airways Obstruction Scale have been found to be component symptoms of airways obstruction in asthma,[35] and together provide a symptom score with a potential range of 37 points (9 to 45). The composition of the symptom scale is shown in Appendix A.

3.3 PROCEDURE

Prior to data collection, all subjects were trained to use the daily log books, both morning (7 AM) and evening (7 PM), the Mini-Wright Peak Flow Meters, and the aerosolzied bronchodilators equipped with the nebulizer chronologs. This pretraining period complied with the protocol of the study precisely, and consisted of five (minimum) to seven (maximum) days for all subjects.

The two stations (East Denver station: National Jewish Hospital, 3800 East Colfax Avenue; West Denver station: National Asthma Center, 1999 Julian Street) are located in Denver on an east-west line, approximately five miles apart. Both stations were identical in equipment and function for both air pollution and health status monitoring. During data collection, the procedures were separated into (A) Daily and (B) Weekly requirements.

Daily. On a daily basis, each subject completed the morning log between 6 AM and 8 AM (7 AM) prior to taking any daily, scheduled medications. Upon completion of the morning log, the subject used the Mini-Wright three times, with an interval of one to two minutes between each measurement. The PEFR values, read from a gauge on the Mini-Wright, were entered on the morning log. Upon completion of the log, information about mobility and activity (past 12 hours), subjective ratings of airways obstruction, and PEFR were available. 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 6 PM and 8 PM (7 PM) each day. The health status measurements obtained were available to be related to IPM values for the preceding 12-hour period.

Finally, usage of as-needed (PRN) aerosolized bronchodilators was registered by the nebulizer chronologs, supplemented by patient records of usage written on the logs.

Weekly. Once each week, each subject reported to the East or West Denver station, returning with the aerosolized bronchodilator equipped with the nebulizer chronolog, and the daily log book. The nebulizer chronolog was interpreted, and all occasions of usage of the nebulizer were recorded and entered into a running record. The daily log book was examined to assure that it was being completed diligently, and any problems in record-keeping were resolved at this time. Finally, the nebulizer chronolog was reset, and the log book replenished for the next week.

The subject then underwent the weekly pulmonary function testing, supervised by a trained pulmonary technician, using a Medistor spirometer.

3.4 DATA MANAGEMENT

Two classes of data, (A) Environmental and Meteorologic Variables, and (B) Health Status Measurements were coded onto computer forms, and a computer-based file established and maintained on the University of Colorado (Boulder) CDC 6400 computer system.

The environmental variables were reported as two separate classes. IPM variables were recorded as 12-hour totals conforming to AM (7 PM to 7 AM) and PM (7 AM to 7 PM) periods. These included mass, sulfates, and nitrates divided into fine and coarse fractions, and were reported in $\mu g/m^3$. The second class of environmental variables was the gaseous pollutants which were collected hourly over the 12-hour periods: 12 midnight to 12 noon (bracketing the 7 AM period) and 12 noon to 12 midnight (bracketing the 7 PM period). These included carbon monoxide, sulfur dioxide, and ozone, and were reported in ppm. Temperature data were converted to averages calculated for 12-hour morning (7 PM to 7 AM [7 AM]) and evening (7 AM to 7 PM [7 PM]) periods. Barometric pressure was converted to average values at 7 AM or 7 PM, based on the barometric pressure at the time of interest and the six hours before and after that time.

For the health status measurements, each subject's record was scanned prior to analyses to eliminate those days during the study when (A) the subject reported being outside the metropolitan Denver area for more than three hours during any 12-hour period, and/or (B) reported an upper respiratory infection at the time the log was completed. Due to failure to service the dichotomous samplers, an eight-day period of IPM collection was lost during February (February 13 to February 21).

3.5 STATISTICAL ANALYSES

3.5.1 Statistical Hypotheses

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:

(1) Elevated pollution levels do not significantly increase the severity of reported airways obstruction symptoms;

(2) Elevated pollution levels do not significantly decrease peak expiratory flow rates; and that

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

Separate analyses were made for the 7 AM and 7 PM health status measurements relating the health status measurements to the IPM collection and other environmental and meteorologic variables for the appropriate 12-hour period. Two series of analyses were performed to test the hypotheses, using (A) LEAPS AND BOUNDS multiple linear regression, and (B) a random effects model. Despite the directional nature of these hypotheses, in all analyses two-tailed tests were used since many comparisons were to be made.

The potential existed for health status measurements to be correlated serially more strongly between either consecutive 12-hour measurements or 24-hour measurements. As a preliminary step to both series of analyses, these serial correlations were checked for both the 12- and 24-hour lags for each of the health status measurements. While for both lags, all serial correlations were statistically significant for each of the health status measurements, the serial correlation between consecutive 12-hour measurement periods was the strongest (see Appendix B for p-values for both lag periods) and was selected as the covariate in both analyses so as to remove this lag effect.

3.5.2 LEAPS AND BOUNDS Multiple Linear Regression Analyses

The first series of analyses involved correlations and the application of multiple linear regression by LEAPS AND BOUNDS for individuals and group averages. Averaged health status measurements were obtained by averaging data from the 12 subjects at each station. For each subject, a mean response was calculated and then subtracted from his/her observations to remove a possible subject effect. This was done for each response variable, separately for AM and PM time periods. Then, at each time point (7 AM and 7 PM for each day of the study period), data were averaged across all subjects having data for that time point.

For this initial series, since the data were not Gaussian, transformations to normality were used to minimize the effect of outliers and to produce more robust tests of the hypotheses. Thus, the first step in the analyses was to apply a nonparametric normalizing transformation sometimes referred to as "normal scores."[36] All variables used in the analyses, both health status measurements and environmental and meteorologic variables, were transformed separately by ranking the data from the smallest to the largest value. Accordingly, if R is the rank of a variable from N observations, this variable is assigned the transformed value of:

$$Y = \Phi \left(\frac{R}{N + 1}\right)$$

where Φ denotes the cumulative distribution function of a standard normal distribution (mean = 0; standard deviation = 1).

The purpose of this normalizing transformation was to prevent spurious correlations caused by a few extremely outlying data points. Additionally, standard methods can be used to calculate p-values from the transformed data where these methods are inappropriate for highly-skewed data.

Three types of statistical analyses were then conducted.

(A) Correlational Analyses. Using transformed data, correlations were calculated between each individual environmental and meteorologic variable and each health status measurement, using all available data for each pair of variables. From these analyses, for each environmental and meteorologic variable, 12 correlations resulted, defined by three health status measurements (PEFR, subjective report of airways obstruction, and as-needed aerosolized bronchodilator usage), two time periods (7 AM and 7 PM), and two stations (East and West Denver). Given no relationship between an environmental variable and the set of 12 health status measurements, the p-values would be expected to be distributed uniformly between zero and one. Given any relationship, these p-values would tend to cluster toward zero. A test of the hypothesis that the p-values are uniformly distributed (no relationship) is available by using Fisher's[37] method of combining probabilities for several mutually independent tests:

$$-2 \sum_{i=1}^{K} \ln p_i \sim \chi^2_{2K}$$

where K is the total number of tests, and p_i is any p-value. The statistic is distributed as chi square with 2K degrees of freedom.

Based on these preliminary correlational analyses and Fisher's test for combining the probabilities of several mutually independent tests, the variables to be used in the next phase of the analyses were selected. These subsequent analyses involved multiple linear regressions for individuals and groups of 12 subjects assigned to each of the stations (East and West Denver).

(B) Multiple Linear Regression Analyses for Individuals. Using the best environmental and meteorologic variables identified by the preceding correlational analyses, multiple linear regression analyses were conducted for each health status measurement on a subject-by-subject basis. These analyses used the LEAPS AND BOUNDS algorithm of Furnival and Wilson.[38] The program was adapted to include Akaike's Information Criterion (AIC)[39] as a method to select the best set of predictors for each health status measurement. As noted, since daily data are serially correlated, the value of each health status measurement from the preceding 12-hour measurement period was used as a predictor variable.[40] This lagged variable acts as a covariate, removing a significant portion of the serial correlation and reducing the error variance. When included in the LEAPS AND BOUNDS algorithm as a possible predictor, it may or may not be selected as being among the best predictors by the AIC criteria. If not selected, the serial correlation is weak. If selected, the effect of the serial correlation is largely removed.

If there are P possible predictor variables in the LEAPS and BOUNDS regression, there are 2^P possible subsets. In such extreme multiple comparison cases, there is no way known to determine the true significance levels. The p-values output by the program can only be used as guides and not interpreted as true values. For this reason, only variables which were significant at the $p < .01$ level were considered.

(C) Aggregate Multiple Linear Regression Analyses for Groups. Multiple linear regressions by LEAPS AND BOUNDS were then done for the 12 subjects from each station considered as a group, using the best and most pertinent set of environmental variables based on the analyses described above. For each health status measurement, the best set of predictors was identified by the AIC criteria.

3.5.3 Application of a Random Effects Model

A potential weakness of the initial series of regression analyses by

LEAPS AND BOUNDS is that it disregards between-subjects variability. The second series of analyses therefore involved a random effects model which takes into account between-subjects variability, and also explored potential additional sources of bias, including weekends, temperature, barometric pressure, and seasonality, which could affect tests of the statistical hypotheses.

In this second series of analyses, the regression coefficients were considered to be random variables across subjects, and the null hypothesis was that the mean effect of air pollution variables was zero. A normalizing transformation of the data was not used, but the residuals were checked and found to be reasonably Gaussian.

The first step of the analysis was to fit the following model:

$$Y_t = \beta_o + \beta_1 Y_{t-\iota} + \epsilon_t \qquad (1)$$

where ι denotes the 12-hour time lag of each subject's response variable. When either Y_t or $Y_{t-\iota}$ is missing, this time was dropped from the regression. The regression coefficient β_1 is then estimated by a simple linear regression. In the random effects model, β_1 is assumed to be a random variable across subjects. The hypothesis to be tested is that the mean effect across subjects is zero. If the assumption of a Gaussian distribution of β_1 across subjects is in doubt, as in the present case, the appropriate test is the nonparametric Wilcoxon signed rank test. This test is performed by ranking the absolute values of the regression coefficients for subjects, and summing the ranks of the negative coefficients and of the positive coefficients.

For these analyses, the 12-hour lag was retained as a covariate, and additional covariates were considered:

(1) Weekend-not weekend

(2) Temperature

(3) Barometric pressure

(4) Seasonality

As a preliminary step, the first three of these potential covariates were tested using the model:

$$Y_t = \beta_0 + \beta_1 Y_{t-1} + \beta_2 X_t + \epsilon_t \qquad (2)$$

The weekend-not weekend variable was coded one for weekend and zero for weekdays. When Y_t, Y_{t-1}, or X_t were 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 potential effect of X_t with time lag effect removed.

Seasonality was tested using the model:

$$Y_t = \beta_0 + \beta_1 Y_{t-1} + \beta_2 \cos(2\pi t/365) + \beta_3 \sin(2\pi t/365) + \epsilon_t \qquad (3)$$

where the index t denotes the day. This is the fundamental frequency of one cycle per year fitted over part of a year. The time shape of a seasonality function will not be exactly a sine wave, but over a quarter of a year, this should give a good approximation of the seasonality effect. Because the data consist of only a part of a year, and because some data are missing, 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 b_2 and b_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.[41] For n subjects, let:

$$S = \frac{1}{n-1} \begin{bmatrix} \sum_{j=1}^{n} (b_2^{(j)} - \bar{b}_2)^2 & \sum_{j=1}^{n} (b_2^{(j)} - \bar{b}_2)(b_3^{(j)} - \bar{b}_3) \\ \text{sym} & \sum_{j=1}^{n} (b_3^{(j)} - \bar{b}_3)^2 \end{bmatrix} \qquad (4)$$

be the estimated 2 by 2 covariance matrix of the cosine and sine coefficients estimated across subjects, and sym denotes that the matrix is symmetric. Hotelling's T^2 is:

$$T^2 = n \begin{bmatrix} \bar{b}_2 \bar{b}_3 \end{bmatrix} S^{-1} \begin{bmatrix} \bar{b}_2 \\ \bar{b}_3 \end{bmatrix} \qquad (5)$$

which is a scalar. This can be tested using F tables, as:

$$\frac{n-2}{2(n-1)} T^2 \sim F_{2,n-2} \qquad (6)$$

The results of the random effects tests for the four covariates are shown in Table 2 of Appendix B. The only significant result is a weekend PM effect for nebulizer use, indicating that there is an increase in nebulizer usage during the day on weekends. This covariate was included in subsequent analyses involving PM nebulizer usage.

The final analyses used model 3 to test each of the nine pollutants one at a time, except that for PM nebulizer use the extra covariate for the weekend effect was included, where X_t represents the value of the pollutant. The Wilcoxon signed rank test was used to test the significance of the regression coefficients.

4. RESULTS

4.1 ENVIRONMENTAL AND METEOROLOGIC VARIABLES

Monthly means (and standard errors) for the environmental and meteorologic variables are presented in Tables 4.1 and 4.2 (shown on pages 28 and 29) for the East and West Denver stations. For each variable, two means are shown, one for the collection period ending at 7 AM (7 AM) and one for the other collection period ending at 7 PM (7 PM). Daily fluctuations in the environmental and meteorologic variables across the full three-month period are summarized in the frequency distributions presented in Appendix D. For both stations, average values for fine and coarse IPM were high and variable during the months of January and February compared with March levels. In general, the East Denver station, located at the busiest intersection in Denver, had notably higher 7 AM fine IPM mass levels than the West Denver station, a difference that was particularly noticeable in January and February. For the IPM components, fine and coarse IPM sulfates, and fine IPM nitrates were also generally higher for the 7 AM collection period, and higher at the East than the West Denver station. For these variables, a continuous decrease in monthly mean levels was discernible from January through March. Average coarse IPM nitrate levels were generally low throughout the study period, and at both stations.

For the gaseous air quality measurements, mean carbon monoxide and sulfur dioxide levels reflected certain tendencies similar to those of the IPM variables, showing higher levels at the East Denver station. These

TABLE 4.1 MONTHLY MEANS AND STANDARD ERRORS FOR INHALED PARTICULATE MATTER (IPM)

Station	Month	N	Time Period	Fine Mass ($\mu g/m^3$)	Coarse Mass ($\mu g/m^3$)	Fine Sulfates ($\mu g/m^3$)	Coarse Sulfates ($\mu g/m^3$)	Fine Nitrates ($\mu g/m^3$)	Coarse Nitrates ($\mu g/m^3$)
East	January	23	7 AM	36.5 ± 5.6	29.5 ± 4.8	3.80 ± 0.70	0.45 ± 0.07	2.22 ± 0.80	0.07 ± 0.03
			7 PM	31.4 ± 4.2	42.1 ± 6.9	4.00 ± 0.54	0.45 ± 0.08	1.89 ± 0.62	0.02 ± 0.01
	February	20	7 AM	35.4 ± 6.5	42.9 ± 5.3	3.03 ± 0.71	0.27 ± 0.04	3.33 ± 1.33	0.02 ± 0.01
			7 PM	21.7 ± 2.8	29.2 ± 6.4	2.53 ± 0.42	0.31 ± 0.08	0.83 ± 0.41	0.05 ± 0.03
	March	28	7 AM	14.1 ± 1.3	23.2 ± 2.4	1.95 ± 0.29	0.45 ± 0.08	0.41 ± 0.20	0.05 ± 0.02
			7 PM	16.9 ± 1.1	28.2 ± 2.6	2.52 ± 0.38	0.49 ± 0.10	0.28 ± 0.11	0.06 ± 0.03
West	January	23	7 AM	26.2 ± 3.3	24.0 ± 3.2	2.72 ± 0.35	0.48 ± 0.07	1.88 ± 0.57	0.05 ± 0.01
			7 PM	23.9 ± 3.2	29.5 ± 4.1	2.89 ± 0.32	0.60 ± 0.09	1.50 ± 0.35	0.16 ± 0.08
	February	20	7 AM	26.0 ± 4.3	30.4 ± 4.4	2.41 ± 0.44	0.59 ± 0.11	2.21 ± 0.73	0.30 ± 0.15
			7 PM	16.9 ± 2.3	34.1 ± 4.3	1.92 ± 0.42	0.64 ± 0.10	1.02 ± 0.45	0.33 ± 0.14
	March	28	7 AM	11.9 ± 1.2	19.5 ± 2.9	1.65 ± 0.20	0.32 ± 0.06	0.38 ± 0.18	0.03 ± 0.01
			7 PM	11.5 ± 1.0	18.4 ± 1.9	1.75 ± 0.31	0.30 ± 0.08	0.26 ± 0.10	0.01 ± 0.00

TABLE 4.2 MONTHLY MEANS AND STANDARD ERRORS FOR GASEOUS AIR QUALITY AND METEOROLOGIC VARIABLES

				Gaseous Air Quality Variables			Meteorologic Variables	
Station	Month	N	Time Period	Carbon Monoxide (CO; ppm)	Sulfur Dioxide (SO_2; ppm)	Ozone (O_3; ppm)	Temperature (^oK)	Barometric Pressure[a] (in. Hg)
East	January	23	7 AM	6.8 ± 0.8	.0125 ± .0020	.0054 ± .0008	264 ± 1	29.84 ± .03
			7 PM	7.9 ± 0.8	.0125 ± .0019	.0066 ± .0009	266 ± 1	29.83 ± .02
	February	20	7 AM	5.5 ± 0.8	.0095 ± .0016	.0079 ± .0020	267 ± 1	29.91 ± .04
			7 PM	7.1 ± 0.6	.0093 ± .0008	.0089 ± .0014	274 ± 1	29.92 ± .04
	March	28	7 AM	4.4 ± 0.3	.0065 ± .0007	.0194 ± .0017[b]	274 ± 1	29.93 ± .03
			7 PM	5.8 ± 0.3	.0063 ± .0004	.0278 ± .0021[b]	278 ± 1	29.93 ± .03
West	January	23	7 AM	4.0 ± 0.6	.0082 ± .0014	.0096 ± .0014	264 ± 1	29.84 ± .03
			7 PM	3.4 ± 0.5	.0081 ± .0011	.0134 ± .0013	266 ± 1	29.83 ± .02
	February	20	7 AM	3.1 ± 0.6	.0071 ± .0012	.0144 ± .0019[c]	267 ± 1	29.91 ± .04
			7 PM	2.5 ± 0.3	.0071 ± .0001	.0175 ± .0018[c]	274 ± 1	29.92 ± .04
	March	28	7 AM	1.8 ± 0.3[d]	.0041 ± .0008	.0194 ± .0017[b]	274 ± 1	29.93 ± .03
			7 PM	1.3 ± 0.2[d]	.0029 ± .0004	.0278 ± .0021[b]	278 ± 1	29.93 ± .03

[a] Sea-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.

[b] Due 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.

[c] N = 12

[d] N = 25

levels generally were decreasing from January through March. By contrast, mean levels of ozone, while consistently low, show a definite increase across months.

Morning (7 AM) temperatures rose from an average of 264^{o}K (-9^{o}C) to 274^{o}K (+1^{o}C), while average evening (7 PM) temperatures increased from 266^{o}K (-7^{o}C) to 278^{o}K (+5^{o}C) during the same period.

Monthly average 7 AM and 7 PM barometric pressures (sea level equivalent) were consistently at approximately 29.9 in. Hg across the three months.

Table 4.3 (shown on pages 31 and 32) presents the correlation matrix for the environmental and meteorologic variables for both stations during the 71 days available for the three-month period studied. For both stations, fine and coarse IPM mass shared approximately 25% common variance. Fine IPM mass was also moderately related to the gaseous air quality variables (inversely to ozone), and to fine IPM sulfate and nitrate levels at both stations. By contrast, while coarse IPM mass showed the same relationships to the gaseous air quality measurements, its relationships to fine and coarse IPM sulfates and nitrates were consistently low. Fine IPM mass values were always correlated with temperature (r's ranging from +.40 to +.50). In contrast, coarse IPM mass levels were nearly independent of temperature.

4.2 HEALTH STATUS MEASUREMENTS

Table 4.4 (shown on page 33) presents the raw 7 AM and 7 PM means and standard errors for each health status measurement for both stations. To evaluate the relationships among the three health status measurements, individual correlations were obtained for each subject. The average correlations among the health status measurements at each station are shown in Table 4.5. (shown on page 34).

TABLE 4.3 CORRELATIONS AMONG THE ENVIRONMENTAL VARIABLES[a,b]

	East Station										
	Carbon Monoxide	Sulfur Dioxide	Ozone[c]	Temper- ature	Barometric Pressure	Fine Mass	Coarse Mass	Fine Sulfates	Coarse Sulfates	Fine Nitrates	Coarse Nitrates
Carbon Monoxide	----	.64	-.58[c]	.02	-.28	.66	.50	.46	.30	.46	.26
Sulfur Dioxide		----	-.48	-.22	-.26	.65	.33	.57	.24	.47	.28
Ozone			----	.06	.04	-.38	-.23	-.36	-.29	-.15	-.35
Temperature				----	.14	-.52	.07	-.59	.19	-.50	.15
Barometric Pressure					----	-.30	-.04	-.33	-.18	-.30	-.16
Fine Mass						----	.52	.74	.11	.81	.21
Coarse Mass							----	.10	.10	.26	.17
Fine Sulfates								----	.33	.73	.19
Coarse Sulfates									----	.10	.47
Fine Nitrates										----	.24
Coarse Nitrates											----

TABLE 4.3 - Continued

	West Station										
	Carbon Monoxide	Sulfur Dioxide	Ozone[c]	Temper-ature	Barometric Pressure	Fine Mass	Coarse Mass	Fine Sulfates	Coarse Sulfates	Fine Nitrates	Coarse Nitrates
Carbon Monoxide	----	.54	-.55	-.23	-.31	.56	.66	.41	.48	.49	.27
Sulfur Dioxide		----	-.48	-.29	-.11	.50	.35	.50	.45	.51	.41
Ozone			----	.49	-.06	-.36	-.47	-.44	-.38	-.38	-.20
Temperature				----	.14	-.52	.26	-.60	-.18	-.53	-.31
Barometric Pressure					----	-.06	.07	-.29	-.32	-.25	-.06
Fine Mass						----	.48	.61	.54	.75	.43
Coarse Mass							----	-.05	.15	.10	.12
Fine Sulfates								----	.56	.77	.30
Coarse Sulfates									----	.63	.56
Fine Nitrates										----	.54
Coarse Nitrates											----

[a]For $N = 60$, $r = .30$ at $p < .01$.

[b]For $N = 35$, $r = .39$ at $p < .01$.

[c]$N = 34$; all other N's = 64 to 70.

TABLE 4.4 MEANS AND STANDARD ERRORS FOR THE HEALTH STATUS MEASUREMENTS[a]

Station	Period	Health Status Measurement: PEFR (l/min)	Symptom Rating (Scale: 9 to 45)	Nebulizer Usage (Occasions/12-hour period)
East Denver	7 AM	361 ± 3	12.4 ± 0.1	0.8 ± 0.1
	7 PM	397 ± 4	11.7 ± 0.1	1.0 ± 0.1
West Denver	7 AM	346 ± 4	13.0 ± 0.2	1.6 ± 0.1
	7 PM	371 ± 3	11.9 ± 0.1	1.2 ± 0.1

[a]Data expressed as mean ± SEM; data from January 9 - March 28.

TABLE 4.5 MEANS AND STANDARD ERRORS OF THE CORRELATION COEFFICIENTS AMONG HEALTH STATUS MEASUREMENTS

Station	Period	Health Status Measurement	Symptom Rating	Nebulizer Usage
East Denver	7 AM	PEFR	$-.47 \pm .07$[a]	$-.26 \pm .05$[b]
		Symptom Rating	---	$+.33 \pm .04$[a]
		Nebulizer Usage		---
	7 PM	PEFR	$-.44 \pm .08$[a]	$-.14 \pm .06$
		Symptom Rating	---	$+.22 \pm .06$[c]
		Nebulizer Usage		---
West Denver	7 AM	PEFR	$-.58 \pm .04$[a]	$-.11 \pm .06$
		Symptom Rating	---	$+.21 \pm .04$
		Nebulizer Usage		---
	7 PM	PEFR	$-.51 \pm .06$[a]	$-.16 \pm .08$
		Symptom Rating	---	$+.27 \pm .06$[b]
		Nebulizer Usage		---

[a] $p < .001$, for r with df = 80.

[b] $p < .02$, for r with df = 80.

[c] $p < .05$, for r with df = 80.

While certain moderate relationships exist among the health status measurements, there is actually notable variation in the magnitude of the relationships. For example, PEFR was clearly negatively related to subjective ratings of airways obstruction for both time periods (7 AM and 7 PM) at both stations (average r's between -.44 and -.58). On an individual basis, 12 of the 24 subjects had correlations of at least -.60, while two had correlations of almost +.20. The average relationships between nebulizer usage and the objective measurements of airways obstruction (PEFR) were always negative and quite low (-.26 to -.11), although the relationships for individual subjects ranged from -.57 to +.29. Finally, nebulizer usage was somewhat more reliably related to subjective ratings of airways obstruction than to PEFR, indicating a tendency for subjects to use their nebulizers more frequently when they reported more airways obstruction.

4.3 HEALTH STATUS MEASUREMENTS IN RELATION TO ENVIRONMENTAL AND METEOROLOGIC VARIABLES

4.3.1 Univariate Correlational Analyses

Table 4.6 (shown on page 36) presents the correlations calculated between each environmental variable by station and the average health status measurements of the 12 subjects. These were done for both time periods (7 AM and 7 PM) at each station based on all of the available data during the January through March period. The probabilities associated with each correlation were calculated (p-values), enabling Fisher's test, shown at the bottom of the table for each environmental and meteorologic measure, to be calculated to test the hypothesis that the p-values were uniformly distributed.

TABLE 4.6 CORRELATIONS BETWEEN ENVIRONMENTAL VARIABLES AND HEALTH STATUS MEASUREMENTS

Health Status Measurement	Time Period	Carbon Monoxide	Sulfur Dioxide	Ozone	Temperature	Barometric Pressure	Fine Mass	Coarse Mass	Fine Sulfates	Coarse Sulfates	Fine Nitrates	Coarse Nitrates
						(A) East Station						
Peak Flow	7 AM	.240	.110	-.297	-.091	-.311	.150	.005	.191	-.050	.217	-.104
	7 PM	.025	.007	-.291	.053	-.017	-.060	-.085	-.050	-.045	-.150	-.152
Symptomatology	7 AM	-.133	.037	.048	-.112	.092	-.048	-.111	-.067	.180	-.054	.082
	7 PM	.016	.096	.271	-.361	-.192	.178	.077	.196	-.022	.464	.092
Nebulizer Usage	7 AM	-.092	-.052	.081	-.116	-.039	-.029	-.081	.092	-.164	-.062	.160
	7 PM	-.186	-.056	.236	-.244	.003	-.071	-.077	-.110	-.269	.023	-.073
						(B) West Station						
Peak Flow	7 AM	-.215	-.221	.190	.231	.230	-.254	-.087	-.193	.119	-.356	-.208
	7 PM	-.003	.154	-.102	-.187	.069	.035	.076	-.011	.247	.006	-.003
Symptomatology	7 AM	.109	.104	.042	-.081	.002	.031	-.064	.066	-.065	.214	.017
	7 PM	.148	-.147	.011	.126	.040	.011	.010	-.014	-.135	-.165	.064
Nebulizer Usage	7 AM	.061	-.053	-.046	-.165	-.063	.047	-.062	.070	.012	.198	.165
	7 PM	.116	-.115	.053	-.187	.092	-.060	-.222	.053	-.290	.146	-.095
$Z = -2\sum_{i=1}^{n} \ln p_i$[a] =		31.15	24.46	31.59	52.91[b]	29.55	22.18	19.93	21.75	36.74[c]	57.80[b]	23.68

[a] $-2\sum_{i=1}^{n} \ln p_i$ is distributed as χ^2 with 2n df, where n = number of correlation coefficients for which p-values were calculated.

[b] $\chi^2 24 = 43.0$ at $p = .01$.

[c] $\chi^2 24 = 36.4$ at $p = .05$.

Inspection of the correlations and their signs in Table 4.6 shows that there was inconsistency in the pattern of correlations among the health status measurements across both stations. By inspection, this inconsistency obtained for each of the environmental and meteorologic variables, although Fisher's tests indicated that a significant relationship obtained among the associated p-values for the correlations for coarse IPM sulfates and fine IPM nitrates. It would be expected that PEFR would be negatively related to both of these IPM components, while subjective reports of airways obstruction and increased nebulizer usage consistently would be positively related, given a clear effect of these IPM components upon the health status of the asthmatic subjects. For the subjects at the West Denver station, this pattern was closely approximated, but the pattern was not demonstrated at the East Denver station.

On the basis of these preliminary analyses, both fractions of IPM sulfates and nitrates were retained for the subsequent multiple linear regression analyses, while gaseous air quality, meteorologic, and fine and coarse IPM mass variables were all excluded.

4.3.2 LEAPS AND BOUNDS Multiple Linear Regression Analyses by Individual Subjects

The extensive series of multiple linear regression analyses using both fractions, coarse and fine, for IPM sulfates and nitrates for the 24 individual subjects are summarized in Table 4.7 on page 38. The analyses summarized involved both time periods (7 AM and 7 PM) and each health status measurement. The counts shown in the table indicate the number of times a specific IPM variable appeared among the best predictors of the multiple linear regression model. The predictor variables also included

TABLE 4.7 SUMMARY TABLE FOR LEAPS AND BOUNDS MULTIPLE LINEAR REGRESSION ANALYSES

FOR THE 24 INDIVIDUAL SUBJECTS

Variable			7 AM									7 PM								
			PEFR			Symptom Rating			Nebulizer Usage			PEFR			Symptom Rating			Nebulizer Usage		
Number	Name	N/Group	+	-	No	+	-	No	+	-	No	+	-	No	+	-	No	+	-	No
1	Previous Health Status Measurement	24	7	0	17	10	0	14	8	0	16	11	0	13	11	0	13	8	0	16
2	Fine Sulfates	24	2	0	22	1	1	22	1	0	23	2	1	21	2	1	21	1	2	21
3	Coarse Sulfates	24	2	2	20	1	0	23	0	1	21	3	0	21	3	2	19	0	1	23
4	Fine Nitrates	24	0	2	22	2	0	22	1	2	21	2	2	20	4	1	19	2	1	21
5	Coarse Nitrates	24	1	1	22	0	0	24	1	0	23	0	0	24	1	0	23	2	0	22

+ = Variable appeared in significant regression with positive coefficient.

- = Variable appeared in significant regression with negative coefficient.

No = Variable did not appear.

the previous health status measurements, in an attempt to exclude (and account for) an effect attributable to changes in the health status of the subjects that was not due to air pollution during the past 12 hours.

With the possible exception of the previous health status measurement, the individual multiple linear regression analyses included no predictor variables that improved upon no regression or the best univariate regression. This was true for each health status measurement. Most notably, IPM measurements of fine and coarse sulfates and nitrates rarely predicted the health status of individual subjects, and generally were inconsistent in direction (sign of the regression coefficient) among individuals when they appeared at all.

4.3.3 Aggregate LEAPS AND BOUNDS Multiple Linear Regression for Groups

In the aggregate multiple linear regression analyses, the 12 subjects assigned to each station were considered as a group. For each health status measurement (PEFR, subjective report of airways obstruction, and nebulizer usage), there are four aggregate regressions defined by two stations (East and West Denver) and two time periods (7 AM and 7 PM). In all cases, the model conformed to the analyses for individuals, using the previous health status measurement, and fine and coarse IPM sulfates and nitrates as the predictor variables.

Only two of the IPM components appeared as best predictors in these analyses. Coarse IPM sulfates were positively associated with PEFR ($p < .01$) for the 7 AM period and negatively associated with nebulizer usage ($p < .001$) for the 7 PM period at the West Denver station. Both of these relationships are paradoxical, suggesting a beneficial effect of coarse IPM sulfates on the health status of the subjects on these two occasions.

The paradoxical nature of these relationships and the failure of coarse IPM sulfates to appear within the regressions at the East Denver station or at the other time period suggest that the relationships are due to chance.

Fine IPM nitrates appeared as a best predictor three times, negatively for 7 AM PEFR's ($p < .0001$) and positively for 7 PM nebulizer usage ($p < .01$) at the West station, and positively for the 7 PM subjective report of airways obstruction ($p < .0001$) at the East station. Note that these relationships between fine IPM nitrates and the health status measurements, while always in a direction indicative of a clear health effect upon the subjects, did not consistently occur across both time periods and for each of the two stations.

4.3.4 Application of the Random Effects Model

For this model (pages 22-26), weekend was selected as an additional covariate. The p-values for the two-tailed Wilcoxon signed rank test are shown in Table 4.8, shown on page 41, testing the regression coefficients for each air pollution variable. The signs indicate larger rank sums of the positive and negative regression coefficients. For pollution to have 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 usage of aerosolized bronchodilators. While both these results were in the expected direction, the results must be considered cautiously. Results support the preceding LEAPS AND BOUNDS multiple linear regression analyses, suggesting that fine IPM nitrates may have influenced nebulizer usage and symptom reports, while no other air pollutant adversely affected health status.

TABLE 4.8 TWO-TAILED P-VALUES FROM WILCOXON SIGNED RANKS TESTS PERFORMED ACROSS SUBJECTS[a]

Station	Health Status Measurement	Time Period	Carbon Monoxide	Sulfur Dioxide	Ozone	Overall Fine Mass	Overall Coarse Mass	Fine Sulfates	Coarse Sulfates	Fine Nitrates	Coarse Nitrates
East Denver	Peak Flow	7 AM	.3394+	.2661+	.3013-	.1763+	.2036+	.6221+	.2036-	.4238+	.4238+
		7 PM	1.0000=	.9097+	.3394-	.8501-	.3804-	.6221+	.9097-	.2661-	.6778+
	Symptomatology	7 AM	.3013-	.3804-	.5693-	.3013-	.3804-	.2334+	.0269+	.1514+	.9697+
		7 PM	.6772+	.3394+	.6221+	.2334+	.8501+	.0522+	.9697-	.0122+	.4238+
	Nebulizer Usage	7 AM	.7002-	.4131-	.2783+	.4131-	.5195-	.3652+	.7002-	.5771+	.7646+
		7 PM	.6221-	.9697+	.6377+	.7910+	.9097+	.1294+	.8501+	.1763+	.2334+
West Denver	Peak Flow	7 AM	.1099-	.0049-	.0269+	.1294-	.8501-	.1294-	.5186+	.0269-	.7910+
		7 PM	.4238+	.0122+	.1763-	.2661+	.5693+	.8501+	.1514+	.3394+	.3804+
	Symptomatology	7 AM	.6221+	.7910+	.8501-	.4238-	.6772-	.9697+	.5186-	.1099+	.1099-
		7 PM	.8501+	.0425-	1.0000=	.3394-	.5186+	.3804-	.0771-	1.0000=	.8501+
	Nebulizer Usage	7 AM	.6221+	.3013+	.5186-	.9097+	.6772-	.1514+	.2036+	.0425-	.3394+
		7 PM	.9697-	.4697-	.9697+	.8501+	.7334-	.4238+	.4238-	.1763+	.4238-
Combined	Peak Flow	7 AM	.6680-	.8262-	.7038+	.6306-	.6680+	.7311-	.6680-	.1434-	.7634+
		7 PM	.6606+	.0366+	.1355-	.7108+	.5522-	.5682+	.7817+	.5562+	.7176+
	Symptomatology	7 AM	1.0000=	.5282+	.6306-	.8075-	.7571-	.8157+	.8019+	.0229+	.7539-
		7 PM	.6152+	.8047-	.6306+	1.0000=	.7003+	.8262+	.8364-	.1011+	.7108+
	Nebulizer Usage	7 AM	.5300+	.5300+	.5809+	.6546-	.7193-	.0650+	.6507+	.0415+	.7336+
		7 PM	.6344-	.6267-	.6625+	.5879+	.5282-	.0604+	.6152-	.0249+	.5997+

[a] As described in the text (pages 24 and 25), the 12-hour lag for health status measurements and weekend were selected as covariates from among lag, weekend, barometric pressure, temperature, and seasonality for these analyses. The symbols "+," "-," and "=" indicate whether the positive or negative rank sum is larger in the Wilcoxon procedure.

5. DISCUSSION

Of all the atmospheric pollutants studied, only the fine IPM nitrate fraction gave any indication of a relationship to the health status of the asthmatic subjects. As seen in Table 4.8, in the final series of analyses, increased fine IPM nitrates tended to be associated with increased subjective reports of airways obstruction and increased aerosolized bronchodilator usage when all subjects were combined. Because of the number of comparisons made, these results, while in the expected direction indicative of an effect, may well be attributed to chance. We did, however, select a conservative approach to help guard against chance results by using two-tailed statistical tests for clearly directional _a priori_ hypotheses. Neither any other fraction of IPM, any gaseous air quality variable, nor any meteorologic measurement produced any consistent effect on the health status of asthmatic subjects. The determination of any threshold at which a change in health status occurs is thus precluded by the nature of these results.

Any discussion would be incomplete without a presentation of the inherent strengths and limitations of this particular investigation. One obvious strength is the _a priori_ manner in which the study was designed, and the prospective nature in which it was conducted. Another is the rigorous medical characterization of our asthmatic subjects with respect to (A) allergic factors, (B) airways hyperreactivity, (C) medical history, and (D) the absence of any other form of cardiopulmonary abnormality. Concerning each subject's response to allergenic factors, two points need emphasis. First, each subject's allergic status was determined by skin tests with mixed grasses, mixed trees, mixed weeds, and house dust. Second, the seasonal allergens were monitored daily and were found to be almost non-existent during the entire three-month period the study encompassed. This assured that allergic factors, rather than air pollution per se, did not affect the health status measurements.

A third and important strength of the present study was that the asthmatic subjects' health status was evaluated by three types of measurements: A physiological measurement -- peak expiratory flow rate; a subjective measurement -- subjective report of airways obstruction; and a behavioral measurement -- as-needed (PRN) aerosolzied bronchodilator usage. How each of these measurements should be affected by environmental pollution was predicted on an a priori basis, thus diminishing the likelihood of drawing false inferences from the statistical analyses. Additionally, since the airways caliber as indexed by PEFR can be influenced by aerosolized bronchodilator usage, continuous monitoring of aerosolized bronchodilators was an integral part of this study. Such a behavioral measurement not only reflects the health status of asthmatic subjects; but, beyond that, discretionary usage of these medications can influence prodoundly any direct measurement of airways caliber. It should be noted that the nebulizer chronologs used in this study were of an original design, and their reliability required back-up by the subjects' own written records of nebulizer usage. A more technically advanced version of the nebulizer chronologs is now available which corrects for principal sources of unreliability (e.g., rare accidental triggering, occasional interference due to static electricity) observed in this study. Finally, also of importance in this study's design was the inherent replicability introduced by establishing two separate monitoring stations in the same metropolitan area. This accorded added reliability in terms of pollution data accuracy, while providing a means for an independent validation of any observed pattern of results.

Several limitations should be listed in regard to the practical execution of this study. First, as shown in Appendix D, there were only six or seven "dirty" 12-hour periods (above 70 $\mu g/m^3$ for fine IPM sulfates and nitrates). Clearly, more such "dirty" days were needed to ascertain the actual effect of air pollution on health status. Furthermore, it should be stated that, although the NO_3^- levels reported here are relatively high compared with those in other U.S. metropolitan areas,[42] $SO_4^=$ levels are noticeably lower than data reported for other areas.[29] This is particularly interesting in view of the fact that nitrates were the single environmental variable possibly associated with reports of increased airway obstruction and increased nebulizer usage. With regard to gaseous air pollutants, carbon monoxide is the only one included in our analysis that is fairly high vis-a-vis U.S. air quality standards. Ozone and sulfur dioxide are very low in comparison to other metropolitan areas.[10,11,44-46] Optimally, the study should have included the entire high air pollution season, which in Denver extends approximately from early November to mid-March.

Another possible drawback was the manner in which medical status data were treated. Our <u>a priori</u> decisions required that data collected while a subject was reporting an upper respiratory infection (URI) be eliminated, since airways caliber in asthmatic patients is known to be affected by these infections, certainly a potential confound for this study. However, it is possible that URI's in asthmatics might be associated with periods of higher air pollution levels, although a post-hoc analysis failed to reveal any such relationship. Also, a further possibility to be considered in future studies is that URI's may sensitize asthmatic subjects to irritant inhaled matter.[47] These considerations suggest that detailed records should be kept of reported URI's and that these data should be included in the overall analysis or should be explored independently.

A final drawback should be considered. The decision was made a priori to exclude data collected when subjects had ventured outside the metropolitan Denver pollution bubble for more than three hours of any 12-hour period. This decision, unfortunately, resulted in the elimination of some data that were recorded during periods of peak pollution levels (6 AM to 8 AM and 6 PM to 8 PM) merely because the subject was away from the area during the middle of the day or overnight. However, the approach represented a serious attempt to insure that subjects' resided and remained within a defined radius of the station where air pollution was monitored. These efforts to insure proximity to the fixed monitoring station may, in fact, represent the best compromise until the technology becomes available to track exposure to a broad range of pollutants by use of personal monitors.

The unique impact of each of these considerations upon the results has been impossible to determine, although in various combinations, they may conceivably have had a profound effect on the final outcome reflected by this report. Consequently, appropriate weight should be given to each of these considerations in any future studies.

6. RECOMMENDATIONS

Establishing realistic standards for daily particulate air pollution levels depends partly upon careful evaluation of the relationship between health status and the pattern of air pollution that occurs. In this study, asthmatic individuals were studied. The inherent hyperreactivity of their airways puts these individuals among the people potentially most sensitive to irritant IPM components. However, the necessary prospective studies are difficult to design and to construct. The difficulties can arise from confounding variables (e.g., airborne allergens), from the impracticability of controlling the independent variables (air pollution levels), and from problems inherent in the measurement of the dependent variables (health status). Several recommendations are appropriate.

First, in any study of this kind, careful prescreening and training are required of the volunteer subjects. Prescreening is needed to characterize the subjects medically, and particularly to identify those that appear most likely to persevere. In this study, logs were required to be completed twice daily, pulmonary function tests were also required each day, and the subjects were required to return to their station weekly for additional testing and debriefing. Selection of responsible and committed subjects is essential to good collection of data, even at the risk of violating certain assumptions about "good" sampling procedures. In the present study, we began with a panel of 60 volunteers, and by adhering to thorough selection procedures accepted 41 subjects. Of those finally accepted, 39 stayed with us throughout a period of almost six months. Certain obstacles must be overcome to assure that reliable subjects are accepted in such a study. At a minimum, these include:

(1) Complete explanation of what will be required on a daily basis, for how long, and for what time period;

(2) Prescreening requirements that need to be fulfilled (e.g., medical examination, X-ray, etc.);

(3) A pretest run, identical in every way with what will be required on a daily basis for the duration of the study;

(4) Discouragement of participation if there is any indication of potential noncompliance with the protocol. Such indicators include failure to keep appointments during prescreening, hesitation about making a commitment to remain in the metropolitan area throughout the period of study, failure to complete the logs reliably during prescreening, reluctance to complete most of the required medical tests, and so on.

Careful prescreening, subject selection, and training are essential prerequisites of lengthy studies of this kind.

Secondly, any single measurement of health status has its pitfalls. By themselves, daily pulmonary function measurements can be influenced by as-needed (PRN) medications that asthmatic patients often use to relieve airways obstruction. Singly, subjective reports of airways obstruction symptoms are always suspect. Taken alone, behavioral measurements, such as discretionary PRN medication usage or doctor's office visits, may either fail to reflect actual changes in airways caliber or they may occur so rarely as to be nearly meaningless. Taken together, however, these measurements help to triangulate upon health status and enable the prediction of relationships (both negative and positive) with air pollution levels to be specified on an a priori basis. Future studies might consider employing a similar method to triangulate on the concept of daily health status of asthmatic patients.

Thirdly, there is virtually no control over the independent variables (i.e., IPM or other air pollution levels), yet in order to ascertain any impact upon the health status measurements, a sufficient supply of days with high and variable levels of IPM is needed. In practical terms, in a city like Denver, which has a seasonal air pollution period, this means that the entire period of high air pollution should be included in any future study. It may even be desirable to prolong the measurement period by including a second full air pollution season. A single, well-conducted large scale study could well be less costly than a series of smaller, less definitive studies.

Fourthly, for certain asthmatic individuals (i.e., those with allergically triggered asthma), airborne allergens can profoundly influence health status, leading to decreased airways caliber, increased usage of as-needed (PRN) medication, and subjective reports of increased airways obstruction. Such allergic factors, if not considered, potentially can confound the interpretation of any results. In any future study with asthmatic patients, medical characterization, as done in the present study, should include allergy skin tests to identify those individuals likely to be affected by airborne allergens, while pollen counts can identify those periods during which specific airborne allergens occur locally. Additionally, standardized methacholine inhalation challenges help to characterize asthmatic patients, and provide an index of the degree of airways hyperreactivity that may yet prove useful in identifying asthmatic individuals who are particularly responsive to the irritant properties of IPM.

Finally, given the fact that suspended particulates are of interest, dichotomous samplers and supplemental chemical analyses appear to have advanced particulate measurement techniques, enabling measurement of IPM fractions with differing deposition within the airways and having potentially different concentrations of specific IPM components. Our current results, while at best only suggestive in regard to health effects, also indicate that the concentration of specific IPM components differed substantially in Denver between coarse (2.5 to 15 μm aerodynamic diameter) and fine (< 2.5 μm) fractions. The fine fractions of IPM sulfates and nitrates appear quite interesting, notably because of a possible health effect, but also because of their deposition in the airways and the varying relative concentrations at which they occur in each fraction. The dichotomous samplers therefore provide an important technique for future studies.

7. REFERENCES

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APPENDIX A

AIRWAYS OBSTRUCTION SYMPTOM RATING SCALE

AIRWAYS OBSTRUCTION SYMPTOM RATING SCALE

Rate the present severity of each of these symptoms of breathing difficulty (1 = Not at all severe; 5 = Extremely severe). Circle the appropriate phrase.

	1	2	3	4	5
A.	Not at all short of breath	A little short of breath	Quite short of breath	Considerably short of breath	Extremely short of breath
B.	No mucous congestion at all	A little mucous congestion	Quite a bit of mucous congestion	Considerable mucous congestion	Extreme mucous congestion
C.	Not at all hard to breathe	A little hard to breathe	Quite hard to breathe	Considerably hard to breathe	Extremely hard to breathe
D.	No chest congestion at all	A little chest congestion	Quite a bit of chest congestion	Considerable chest congestion	Extreme chest congestion
E.	No chest tightness at all	A little chest tightness	Quite a bit of chest tightness	Considerable chest tightness	Extreme chest tightness
F.	Chest not filled up at all	Chest a little filled up	Chest quite filled up	Chest considerably filled up	Chest extremely filled up
G.	Not at all uncomfortable	A little uncomfortable	Quite uncomfortable	Considerably uncomfortable	Extremely uncomfortable
H.	Not coughing at all	Coughing a little	Coughing quite a bit	Considerable coughing	Extreme coughing
I.	Not wheezing at all	Wheezing a little	Wheezing quite a bit	Considerable wheezing	Extreme wheezing

APPENDIX B

COVARIATE ANALYSES SUMMARY TABLES

TABLE B-1 TWO-TAILED P-VALUES FROM WILCOXON SIGNED RANKS TESTS PERFORMED ACROSS SUBJECTS FOR 12 AND 24 HOUR LAGGED HEALTH STATUS MEASUREMENTS

Station	Health Status Measurement	Time Period	12-Hour Lag	24-Hour Lag
East Denver	Peak Flow	7 AM	.0005+[a]	.0015+
		7 PM	.0034+	.0068+
	Symptomatology	7 AM	.0210+	.0068±
		7 PM	.0020+	.0161+
	Nebulizer Usage	7 AM	.0068+	.0510+
		7 PM	.0093+	.0537+
West Denver	Peak Flow	7 AM	.0005+	.0034+
		7 PM	.0005+	.0015+
	Symptomatology	7 AM	.0020+	.0049+
		7 PM	.0015+	.0161+
	Nebulizer Usage	7 AM	.0010+	.0015+
		7 PM	.0015+	.0015+
Combined	Peak Flow	7 AM	.0000+	.0000+
		7 PM	.0000+	.0000+
	Symptomatology	7 AM	.0001+	.0001+
		7 PM	.0000+	.0004+
	Nebulizer Usage	7 AM	.0000+	.0000+
		7 PM	.0000+	.0001+

[a]A "+" or "-" indicates direction in the Wilcoxon procedure as demonstrated by relative magnitude of the positive and negative rank sums.

TABLE B-2 TWO-TAILED P-VALUES FROM TESTS OF SIGNIFICANCE ON COVARIATES PERFORMED ACROSS SUBJECTS[a]

Station	Health Status Measurement	Time Period	Temperature	Barometric Pressure	Weekend Effect	Seasonality
East Denver	Peak Flow	7AM	.1099-	.3013-	.9097+	.1650
		7PM	.8501-	.3804+	.7910+	.3517
	Symptomatology	7AM	.4697+	.1099+	.0923+	.6286
		7PM	.3013-	.2661-	.8501+	.5001
	Nebulizer Usage	7AM	.8311-	1.0000=	.2783-	.8053
		7PM	.4697-	.7910+	.0010+	.4426
West Denver	Peak Flow	7AM	.1099+	.1294+	.6772+	.3322
		7PM	.2036-	.5186+	.1099-	.5798
	Symptomatology	7AM	.7334-	.7334-	.3804-	.9908
		7PM	.1099+	.8501+	.1294+	.8958
	Nebulizer Usage	7AM	.4238-	.9097-	.3013+	.5248
		7PM	.3013-	.6221+	.0771+	.7516
Combined	Peak Flow	7AM	.5602-	.5840+	.6152+	.5460
		7PM	.8414-	.8047+	.7443-	.1894
	Symptomatology	7AM	.5522+	.6680+	.5919+	.7886
		7PM	.6075+	.6382-	.8210+	.7643
	Nebulizer Usage	7AM	.7475-	.5641-	.5300+	.8987
		7PM	.8339-	.6861+	.0001+	.4155

[a]A Wilcoxon signed ranks 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 which comprise seasonality. The symbols, "+," "-," and "=" indicate whether the positive or negative rank sums is larger in the Wilcoxon procedure.

APPENDIX C

FREQUENCY DISTRIBUTIONS FOR HEALTH STATUS MEASUREMENTS

TABLE C-1 FREQUENCY DISTRIBUTION FOR PEAK EXPIRATORY FLOW RATES (1/MIN)[a]

(1/Min)	East Denver Station		West Denver Station	
	7AM	7PM	7AM	7PM
<175	29	35	61	17
175-200	33	32	39	18
200-225	16	9	38	22
225-250	69	32	51	42
250-275	60	20	41	41
275-300	92	26	63	65
300-325	61	30	32	53
325-350	120	91	57	87
350-375	90	88	73	68
375-400	115	174	98	120
400-425	45	94	52	54
425-450	52	65	80	59
450-475	35	26	49	61
475-500	34	48	61	68
500-525	13	40	11	19
525-550	19	41	7	14
550-575	21	24	2	3
575-600	26	45	0	1
600-High	0	9	0	1
Missing	155	151	225	267
Mean	356	394	343	368
SD	99	106	106	91
SEM	3	3	4	3

[a]Data for the period of January 1 - March 31.

TABLE C-2 FREQUENCY DISTRIBUTION FOR SYMPTOM RATING[a]

(SCALE: 9 to 45)

Scale Values	East Denver Station		West Denver Station	
	7AM	7PM	7AM	7PM
9	266	366	282	351
10	110	122	80	85
11	71	78	46	52
12	79	61	43	51
13	72	54	52	39
14	104	66	50	40
15	52	32	36	31
16	25	25	18	23
17	47	59	32	37
18	32	14	100	56
19	25	8	15	12
20	9	3	10	3
21	4	4	10	4
22	4	2	8	4
23	5	4	6	5
24	1	4	2	2
25	5	2	5	2
26	0	0	3	0
27	3	4	16	5
28	0	0	0	1
29	0	0	0	0
30	0	0	0	1
31	1	0	1	0
⋮				
34	1	0	0	0
36	1	4	0	0
⋮				
45	0	1	0	0
Mean	12.5	11.7	13.0	11.9
SD	3.7	3.5	4.5	3.8
SEM	0.1	0.1	0.2	0.1

[a]Data for the period January 1 - March 31.

TABLE C-3 FREQUENCY DISTRIBUTION OF NEBULIZER USAGE[a]

(OCCASIONS/12-HOUR PERIOD)

No. of Occasions	East Denver Station		West Denver Station	
	7AM	7PM	7AM	7PM
0	617	658	352	409
1	100	68	109	130
2	125	86	154	139
3	18	24	71	60
4	44	50	60	30
5	5	19	27	18
6	16	13	11	6
7	3	0	5	3
8	3	5	5	3
9	1	5	3	1
10	1	5	1	1
11	0	0	0	0
12	1	5	0	0
13	0	1	1	0
14	0	0	0	0
15	0	1	0	0
16	0	0	0	0
17+	1	1	1	0
Missing	145	143	280	280
Mean	0.8	1.0	1.6	1.1
SD	1.6	2.0	2.5	1.5
SEM	0.1	0.1	0.1	0.1

[a]Data for the period January 1 - March 31.

APPENDIX D

FREQUENCY DISTRIBUTIONS OF ENVIRONMENTAL AND METEOROLOGIC VARIABLES

TABLE D-1 FREQUENCY DISTRIBUTION OF CARBON MONOXIDE (PPM)[a]

PPM	East Denver Station		West Denver Station	
	7AM	7PM	7AM	7PM
< 0.5	0	0	3	6
0.6 - 1.5	8	1	29	31
1.6 - 2.5	9	1	20	19
2.6 - 3.5	15	11	8	10
3.6 - 4.5	20	15	6	9
4.6 - 5.5	12	17	7	5
5.6 - 6.5	9	10	5	2
6.6 - 7.5	4	14	1	1
7.6 - 8.5	2	4	2	0
8.6 - 9.5	1	6	2	0
9.6 - 10.5	0	5	1	1
10.6 - 11.5	1	1	0	0
11.6 - 12.5	5	3	0	0
>12.5	3	2	0	0
Mean	5.3	6.6	2.8	2.4
SD	3.2	2.8	2.3	1.8
SEM	0.3	0.3	0.2	0.2
N	89	90	84	84

[a]12-hour averages; data for the period January 1 - March 31.

TABLE D-2 FREQUENCY DISTRIBUTION OF SULFUR DIOXIDE (PPM)[a]

PPM	East Denver Station		West Denver Station	
	7AM	7PM	7AM	7PM
<.0015	5	1	8	9
.0016 - .0045	19	12	33	36
.0046 - .0075	27	33	24	17
.0076 - .0105	7	19	10	13
.0106 - .0135	11	8	6	7
.0136 - .0165	8	7	2	2
.0166 - .0195	5	0	0	2
.0196 - .0225	1	2	0	1
.0226 - .0255	2	1	3	0
.0256 - .0285	1	2	0	0
>.0286	1	2	1	0
Mean	.0087	.0089	.0060	.0059
SD	.0070	.0062	.0053	.0044
SEM	.0007	.0007	.0006	.0005
N	87	87	87	87

[a]12-hour averages; data for the period January 1 - March 31.

TABLE D-3 FREQUENCY DISTRIBUTION OF OZONE (PPM)[a]

PPM	East Denver Station		West Denver Station	
	7AM	7PM	7AM	7PM
<.0040	18	10	6	3
.0041 - .0080	16	17	13	6
.0081 - .0120	8	16	24	14
.0121 - .0160	6	6	16	13
.0161 - .0200	2	1	8	12
.0201 - .0240	0	0	10	16
.0241 - .0280	1	1	3	7
.0281 - .0320	0	0	3	3
.0321 - .0360	0	0	3	6
.0361 - .0400	0	0	1	4
.0401 - .0440	0	0	1	2
>.0441	0	0	0	2
Mean	.0068	.0080	.0144	.0198
SD	.0051	.0048	.0085	.0106
SEM	.0007	.0007	.0009	.0011
N	51	51	88	88

[a]12-hour averages; data for the period January 1 - March 31.

TABLE D-4 FREQUENCY DISTRIBUTION OF TEMPERATURE (°K)[a]

°K	East Denver Station		West Denver Station	
	7AM	7PM	7AM	7PM
<253.2	1	0	1	0
253.3 - 255.7	4	1	4	1
255.8 - 258.2	8	3	8	3
258.3 - 260.7	7	7	7	7
260.8 - 263.2	3	4	3	4
263.3 - 265.7	3	9	3	9
265.8 - 268.2	9	4	9	4
268.3 - 270.7	16	5	16	5
270.8 - 273.2	10	13	10	13
273.3 - 275.7	14	12	14	12
275.8 - 278.2	9	10	9	10
278.3 - 280.7	4	7	4	7
280.8 - 283.2	1	7	1	7
283.3 - 285.7	0	5	0	5
285.8 - 288.2	0	3	0	3
Mean	269	273	269	273
SD	7	8	7	8
SEM	1	1	1	1
N	89	90	89	90

[a]12-hour averages; data for thee period January 1 - March 31.

TABLE D-5 FREQUENCY DISTRIBUTION OF BAROMETRIC PRESSURE (in. Hg)[a]

in. Hg	East Denver Station		West Denver Station	
	7AM	7PM	7AM	7PM
<29.57	2	1	2	1
29.58 - 29.62	2	1	2	1
29.63 - 29.67	2	4	2	4
29.68 - 29.72	3	7	3	7
29.73 - 29.77	12	7	12	7
29.78 - 29.82	7	13	7	13
29.83 - 29.87	8	7	8	7
29.88 - 29.92	9	9	9	9
29.93 - 29.97	9	5	9	5
29.98 - 30.02	8	9	8	9
30.03 - 30.07	6	7	6	7
30.08 - 30.12	8	4	8	4
30.13 - 30.17	6	5	6	5
30.18 - 30.22	4	8	4	8
30.23 - 30.27	1	2	1	2
30.28 - 30.32	1	0	1	0
Mean	29.92	29.92	29.92	29.92
SD	.17	.17	.17	.17
SEM	.02	.02	.02	.02
N	88	89	88	89

[a]Averages for two discrete times within each 12-hour period; data for the period January 1 - March 31.

TABLE D-6 FREQUENCY DISTRIBUTION OF FINE MASS ($\mu g/m^3$)[a]

$\mu g/m^3$	East Denver Station		West Denver Station	
	7AM	7PM	7AM	7PM
< 5.0	4	0	4	4
5.1 - 10.0	7	7	17	19
10.1 - 15.0	18	17	18	21
15.1 - 20.0	13	18	11	20
20.1 - 25.0	13	18	7	6
25.1 - 30.0	8	4	9	4
30.1 - 35.0	2	7	4	2
35.1 - 40.0	3	1	1	0
40.1 - 45.0	0	2	4	2
45.1 - 50.0	2	2	2	1
50.1 - 55.0	1	2	0	2
55.1 - 60.0	3	2	3	1
60.1 - 65.0	2	1	0	0
65.1 - 70.0	2	0	1	0
70.1 - 75.0	0	0	2	0
75.1 - 80.0	2	0	0	0
80.1 - 85.0	0	0	0	0
85.1 - 90.0	1	0	0	0
>90.1	2	1	0	0
Mean	27.4	23.2	21.1	17.0
SD	25.0	15.3	16.5	11.8
SEM	2.7	1.7	1.8	1.3
N	83	82	83	82

[a]Totals for a 12-hour collection period; data for the period January 1 - March 31.

TABLE D-7 FREQUENCY DISTRIBUTION OF COARSE MASS ($\mu g/m^3$)[a]

$\mu g/m^3$	East Denver Station 7AM	East Denver Station 7PM	West Denver Station 7AM	West Denver Station 7PM
< 7.0	9	4	14	7
7.1 - 14.0	10	5	14	12
14.1 - 21.0	9	13	14	17
21.1 - 28.0	12	9	12	20
28.1 - 35.0	22	13	5	11
35.1 - 42.0	10	10	10	5
42.1 - 49.0	4	5	7	3
49.1 - 56.0	3	8	3	1
56.1 - 63.0	5	9	2	2
63.1 - 70.0	1	1	1	2
70.1 - 77.0	2	1	1	0
77.1 - 84.0	1	0	0	1
84.1 - 91.0	1	0	0	0
91.1 - 98.0	0	2	0	1
98.1 - 105.0	1	0	0	0
>105.1	0	2	0	0
Mean	30.6	37.9	24.2	25.7
SD	21.6	27.0	17.5	17.6
SEM	2.4	3.0	1.9	1.9
N	83	82	83	82

[a]Totals for a 12-hour collection period; data for the period January 1 - March 31.

TABLE D-8 FREQUENCY DISTRIBUTION OF FINE SULFATES ($\mu g/m^3$)[a]

$\mu g/m^3$	East Denver Station		West Denver Station	
	7AM	7PM	7AM	7PM
< .400	3	2	3	1
.401 - .800	6	5	5	9
.801 - 1.200	11	5	14	14
1.201 - 1.600	8	11	14	10
1.601 - 2.000	6	3	13	7
2.001 - 2.400	7	9	13	7
2.401 - 2.800	7	6	2	8
2.801 - 3.200	4	5	2	3
3.201 - 3.600	4	3	2	4
3.601 - 4.000	2	2	1	1
4.001 - 4.400	1	3	2	3
4.401 - 4.800	0	2	2	0
4.801 - 5.200	1	2	1	3
5.201 - 5.600	1	1	2	1
5.601 - 6.000	0	3	0	1
6.001 - 6.400	1	0	2	0
6.401 - 6.800	1	1	0	2
6.801 - 7.200	1	0	1	1
7.201 - 7.600	0	1	1	0
7.601 - 8.000	1	0	0	0
8.001 - 8.400	1	0	0	0
8.401 - 8.800	1	0	0	0
8.801 - 9.200	0	1	0	0
>9.201	3	2	1	0
Mean	2.86	2.89	2.22	2.18
SD	2.80	2.15	1.74	1.49
SEM	0.34	0.26	0.19	0.17
N	70	67	81	75

[a]Totals for a 12-hour collection period; data for the period January 1 - March 31.

TABLE D-9 FREQUENCY DISTRIBUTION OF COARSE SULFATES ($\mu g/m^3$)[a]

$\mu g/m^3$	East Denver Station		West Denver Station	
	7AM	7PM	7AM	7PM
< 0 - .100	9	11	14	7
.101 - .200	9	10	8	11
.201 - .300	9	11	9	6
.301 - .400	16	5	9	8
.401 - .500	9	9	15	11
.501 - .600	7	3	7	11
.601 - .700	3	2	3	2
.701 - .800	2	4	5	7
.801 - .900	2	4	2	5
.901 - 1.000	1	3	2	3
1.001 - 1.100	1	1	2	2
1.101 - 1.200	0	2	1	0
>1.201	2	2	4	3
Mean	0.40	0.43	0.46	0.49
SD	0.33	0.38	0.39	0.33
SEM	0.04	0.05	0.04	0.04
N	70	67	81	76

[a]Totals for a 12-hour collection period; data for the period January 1 - March 31.

TABLE D-10 FREQUENCY DISTRIBUTION OF FINE NITRATES ($\mu g/m^3$)[a]

$\mu g/m^3$	East Denver Station		West Denver Station	
	7AM	7PM	7AM	7PM
< 0 - .400	43	39	45	36
.401 - .800	9	12	11	20
.801 - 1.200	3	3	6	3
1.201 - 1.600	2	1	4	2
1.601 - 2.000	0	1	1	1
2.001 - 2.400	1	2	1	4
2.401 - 2.800	0	1	1	2
2.801 - 3.200	0	2	1	2
3.201 - 3.600	1	1	0	1
3.601 - 4.000	0	1	0	1
4.001 - 4.400	3	0	1	1
4.401 - 4.800	0	2	1	0
4.801 - 5.200	0	0	3	0
5.201 - 5.600	0	0	1	0
5.601 - 6.000	1	0	0	0
6.001 - 6.400	0	0	0	1
6.401 - 6.800	0	0	1	1
6.801 - 7.200	2	0	1	0
>7.201	5	2	3	0
Mean	1.79	0.95	1.34	0.93
SD	3.93	1.94	2.41	1.32
SEM	0.47	0.24	0.27	0.15
N	70	67	81	75

[a]Totals for a 12-hour collection period; data for the period January 1 - March 31.

TABLE D-11 FREQUENCY DISTRIBUTION OF COARSE NITRATES ($\mu g/m^3$)[a]

$\mu g/m^3$	East Denver Station		West Denver Station	
	7AM	7PM	7AM	7PM
0 - .060	59	57	55	46
.061 - .120	2	4	7	3
.121 - .180	1	1	6	2
.181 - .240	0	0	4	5
.241 - .300	2	1	1	1
.301 - .360	2	1	2	5
.361 - .400	3	0	1	3
.421 - .480	0	2	0	3
.481 - .540	0	1	0	2
.541 - .600	0	0	2	0
.601 - .660	1	0	0	0
.661 - .720	0	0	1	2
.721 - .780	0	0	1	4
> .781	0	0	1	0
Mean	0.05	0.04	0.12	0.16
SD	0.12	0.11	0.36	0.25
SEM	0.02	0.01	0.04	0.03
N	70	67	81	76

[a] Totals for a 12-hour collection period; data for the period January 1 - March 31.