Winter air pollution and disease parameters in advanced chronic obstructive pulmonary disease panels residing in Denver, Colorado

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Background: Ambient pollution might worsen chronic obstructive pulmonary disease (COPD).
Objective: We explored the associations of pollution to pulmonary function, rescue medication, and symptoms over 2 winters in 2 panels of subjects with advanced COPD in Denver, Colorado.
Methods: Subjects measured lung function and recorded symptoms and rescue medications. Daily ambient pollution concentrations for particulate matter (PM_{10} and $PM_{2.5}$), carbon monoxide (CO), and nitrogen dioxide (NO_2) were obtained for Denver. Estimated effects of pollution on outcomes were derived for the same day and 1 and 2 days after pollution measurements (lags 0, 1, and 2, respectively).
Results: Sixteen (mean age, 65.8 years; mean FEV_1, 42.3% of predicted value) and 18 (mean age, 67.4 years; mean FEV_1, 39.4% of predicted value) subjects participated in the first and second winters, respectively. There were no differences in demographic or disease characteristics between the 2 panels. In the first winter no detrimental associations were found. In the second winter, however, there were significant detrimental associations of CO in the morning and PM_{10}, CO, and NO_2 in the evening, increasing medication use at lag 0. Total symptom score increased at lag 0 with NO_2. The concentrations of particulates were increased in the second winter compared with in the first winter, and this winter was colder and more humid.
Conclusions: In the second winter, subjects with severe COPD had worse lung function at lags 0 and 1 and increased rescue medication at lag 0 with increases in ambient air pollution. The effects of pollution varied between the 2 winters, perhaps related to levels of pollution and weather patterns. Significant effects were seen despite ambient pollution levels that conformed to US Environmental Protection Agency standards. (J Allergy Clin Immunol 2005;115:337-44.)

Key words: *Air pollution, chronic obstructive pulmonary disease, monitoring, spirometry*

The health effects of outdoor air pollution are manifested across a wide spectrum of effects, and such pollution particularly affects at-risk groups.[1-3] There is increasing concern that current ambient air quality standards might not be stringent enough to protect human subjects from adverse effects.

Patients with respiratory disease, such as chronic obstructive pulmonary disease (COPD), given their abnormal responses to noxious gases and particles, should be considered at risk for the adverse effects of pollution. In addition, patients with advanced disease might experience symptoms after relatively minor insults. There is abundant epidemiologic evidence that acute worsening of environmental air pollution results in increased morbidity and mortality in patients with COPD.[4-7] This evidence is derived from studies on acute severe pollution carried out in London,[8] the Utah valley,[9,10] and Barcelona,[11] together with prospective studies, although these are few in number.[12,13] In the ''Air Pollution and Health—A European Approach'' study, daily variations in total mortality, cardiovascular mortality, respiratory mortality, and emergency department visits for COPD and asthma were studied in relation to daily variations in air pollution levels from 1985 through 1991.[14] A reduction of about 50 $\mu g/m^3$ in particulates and sulfur dioxide was accompanied by a reduction of about 4% and 6%, respectively, in daily deaths from respiratory and cardiovascular causes and emergency department visits for COPD. Oxidant pollutants (nitrogen dioxide [NO_2] and ozone) were related positively with cardiovascular mortality and emergency visits for COPD and asthma. A reduction in ozone levels of 50 $\mu g/m^3$ was associated with a 4% reduction in emergency department visits for COPD and asthma. Harre et al[12] reported that nighttime symptoms in patients with COPD in New Zealand were related to changes in PM_{10} levels, and rescue bronchodilator use was related to changes in NO_2 levels.

Morbidity and mortality from COPD are increased in Colorado.[15,16] This might be due to exaggeration of

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Abbreviations used
APCD: Air Pollution Control Division
CO: Carbon monoxide
COPD: Chronic obstructive pulmonary disease
EPA: Environmental Protection Agency
FEV_1: Forced expiratory volume in 1 second
FVC: Forced vital capacity
NJMRC: National Jewish Medical and Research Center
NO_2: Nitrogen dioxide
PEF: Peak expiratory flow
PM: Particulate matter
$PM_{2.5}$: Particulate matter less than 2.5 μm
PM_{10}: Particulate matter less than 10 μm

hypoxemia at altitude. Particulate air pollution in Denver is predominantly a winter phenomenon, with brief spikes of pollution that last for hours rather than days. In general, apart from ozone levels in 1998 and particulate levels in 1999, the levels of Denver pollution have improved and conform to US Environmental Protection Agency (EPA) standards in recent years. This study was designed to determine whether there were significant effects of ambient pollution on subjects with advanced COPD in metropolitan Denver during the winter. We hypothesized that the relationship between ambient pollution and COPD would be exaggerated at high altitude. Identification of a significant effect of pollution on subjects with COPD, despite conformity to EPA standards, would be important in evaluating current standards.

METHODS

Study design

This was a panel study of subjects with advanced COPD in which the effects of air pollution on symptoms, rescue medication use, and spirometry were investigated. The study took place during the winters of 1999-2000 (henceforth first winter) and 2000-2001 (henceforth second winter) with 2 independent panels of subjects.

Subjects

We recruited subjects residing in the Denver area with COPD, as defined by the American Thoracic Society.[17] Subjects were recruited from outpatient clinics, from registries of previous participants in projects at National Jewish Medical and Research Center (NJMRC), and by advertisement. The study was approved by the NJMRC Institutional Review Board. Subjects underwent the informed consent process, signed an informed consent form, and received compensation for participation.

Inclusion criteria

Subjects were 40 years old and older, with a history of more than 10 pack-years of tobacco use, airflow limitation with FEV_1 of less than 70% of predicted value, and FEV_1/forced vital capacity ratio of less than 60%.[18] Pulmonary function tests were compatible with COPD (ie, increased lung volumes), with a carbon monoxide (CO) diffusing capacity of less than 70% of predicted value, and chest radiography showed no other lung diseases.

TABLE I. Baseline demographic mean data and comparisons

Variable	1999-2000 (n = 16)	2000-2001 (n = 18)	*P* value*
Age (y)	65.8	67.4	.66
Smoking (pack-years)	65.2	65.4	.80
Sex	11 M/5 F	9 M/9 F	.27
Supplemental oxygen use	9/16	13/18	.33
Prebronchodilator FEV_1 (L)	1.15	0.90	.10
Prebronchodilator FEV_1/FVC (%)	41.5	38.1	.39

FVC, Forced vital capacity.
**P* value compares the 2 winters. Spirometry was performed in the laboratory.

Exclusion criteria

Subjects who had smoked within 6 months before enrollment or had significant passive smoke exposure or occupational exposures in the 4 weeks before the study or for the duration of the study were excluded. Subjects using inhaled corticosteroids within 2 weeks or oral steroids within 4 weeks of the study were ineligible. However, subjects (with their physician's assent) who agreed to be withdrawn from inhaled corticosteroid treatment from 2 weeks before the study start until the study end were eligible unless postbronchodilator FEV_1 after 2 weeks had decreased by 20% or greater and greater than 200 mL from postbronchodilator FEV_1 on the screening day.

Subjects were permitted to take inhaled or nebulized short- and long-acting β_2-agonists and short-acting anticholinergic medications. Subjects were not allowed to use long-acting β_2-agonists or inhaled steroids. Antibiotic use was permitted, and all medication use was recorded by subjects on diary cards.

Other exclusions were the presence of other pulmonary disease, inability to cooperate with the study protocol, inability to register spirometry on an AirWatch meter (Mountainview, Calif), and significant exacerbation requiring antibiotics in the 4 weeks before enrollment.

Screening visit

Subjects withheld bronchodilator medications, when possible, from 12 AM on the day before the screening visit. History and physical examination were performed, and demographic data, including regular medication use, were recorded. Training in completion of home diary cards and spirometry (see Home monitoring below) was provided. Subjects completed diary cards at home for several days and then returned to the laboratory to ascertain that this was performed adequately.

Home monitoring

Diary cards were completed twice daily between 5 and 8 AM and 5 and 8 PM and included the following: (1) prebronchodilator peak expiratory flow (PEF) and FEV_1 measured with the AirWatch spirometer; (2) symptoms; and (3) bronchodilator use. Subjects also recorded intercurrent illnesses, health care use, new medication use, and absences from Colorado. Subjects who were unable to adhere to the study protocol because of intercurrent illnesses or absences from Colorado were monitored as frequently as possible, and the absent periods were handled as missing data. An example of the evening diary card completed by the subjects is shown in the Journal's Online Repository at www.mosby.com/jaci.

Periodic monitoring visits

All subjects attended the laboratory every 14 ± 3 days throughout the 4-month study period to return completed diary cards and receive

TABLE II. Comparison of descriptive pollution and weather parameters between the 2 winters

Variable	Year	Days	Mean	SD	Minimum value	25% quantile	Median	75% quantile	Maximum value	*P* value comparing years
PM_{10} ($\mu g/m^3$)	1999-2000	136	25.1	12.3	4.0	16.0	23.0	30.3	72.0	.005
	2000-2001	135	29.6	13.8	7.0	19.0	26.0	38.0	72.0	
$PM_{2.5}$ ($\mu g/m^3$)	1999-2000	127	9.0	5.2	1.8	5.4	7.7	11.3	36.6	.000
	2000-2001	136	14.3	9.6	3.4	7.6	11.7	17.2	59.6	
CO (ppm)	1999-2000	138	1.2	0.555	0.340	0.810	1.100	1.430	3.790	.147
	2000-2001	136	1.1	0.500	0.360	0.715	0.975	1.340	2.810	
NO_2 (ppm)	1999-2000	138	0.016	0.017	0.000	0.000	0.008	0.030	0.054	.000
	2000-2001	134	0.029	0.011	0.006	0.022	0.028	0.036	0.054	
Relative humidity (%)	1999-2000	136	47.8	15.9	19.5	35.8	45.2	55.9	94.6	.000
	2000-2001	136	55.6	15.7	22.0	43.3	54.1	68.0	91.8	
Barometric Pressure (mm Hg)	1999-2000	138	625.2	4.5	615.2	622.0	625.5	627.9	636.5	.867
	2000-2001	136	625.2	4.0	615.4	622.2	625.5	628.0	633.9	
Temperature (°F)	1999-2000	136	39.4	8.2	22.3	32.3	39.2	46.0	57.8	.000
	2000-2001	136	32.1	8.1	8.9	27.1	33.0	37.5	49.0	

new cards. Data were downloaded from the spirometers, and prebronchodilator and postbronchodilator spirometry was performed.

Air quality monitoring

Data for PM_{10}, $PM_{2.5}$, NO_2, and CO were obtained from Denver's air quality monitoring stations operated by the Air Pollution Control Division (APCD) of the Colorado Department of Public Health and Environment. Additional monitors for PM were operated at NJMRC to address the issue of spatial variation.

Particulate matter data. PM data were obtained from APCD monitoring stations located in downtown Denver, 2.7 miles west of NJMRC. In addition, fine PM was collected at NJMRC on Teflon filters by using a federal reference method $PM_{2.5}$ air sampler (Partisol Plus Model 2025 Sequential Air Sampler; Rupprect & Patashnick Co, Inc, Albany, NY) and PM on quartz fiber filters with a high-volume federal reference method PM_{10} air sampler (Thermo Andersen, Smyrna, Ga). There were good correlations between particulate monitors at different locations in the metropolitan Denver area.

Gaseous pollutant measurements. NO_2 measurements were obtained from the nearest community monitoring station located 7.3 miles north of NJMRC, whereas CO data were obtained from community monitoring stations located downtown and at NJMRC.

Weather. In both winters, the average daily barometric pressure monitored at Denver International Airport was obtained from the National Climatic Data Center, and average daily temperature and relative humidity monitored near downtown Denver were obtained from the APCD.

Statistical methods

The 2 winters of data were analyzed separately to examine different response patterns in the 2 years with the intent of combining the data if the patterns appeared to be similar. There were 4 outcome variables for this study: FEV_1, PEF, rescue medication use, and total symptom score. For both winters, morning and evening data were analyzed separately. For FEV_1 and PEF, the highest value of the first 3 blows in the morning or evening on a given day was used. A 12-hour medication score was derived from the sum of activations of rescue β_2-agonist and anticholinergic agents from metered-dose inhalers, with a nebulized therapy regarded as the equivalent of 2 activations. Over a 12-hour period, shortness of breath, cough, chest tightness, wheeze, and expectoration were each rated on a 7-point scale to create a total symptom score ranging from 0 to 35. Sputum color, although surveyed, was dropped from the score because many patients were not able to report sputum color. Estimated effects of the pollution parameters on the outcomes were assessed for lags 0 to 2, where lags 0, 1, and 2 refer to an effect on the same day, next day, or 2 days in relationship to the measured concentration of a particular pollution parameter, respectively. Twenty-four-hour mean values for each air pollutant were used in the analysis. For $PM_{2.5}$ and PM_{10}, the outcomes were derived from the mean values from a central monitor in downtown Denver and a local monitor located at NJMRC.

Analyses were performed with the SAS 8.2 statistical analysis package (SAS Institute, Inc, Cary NC). Mixed-effects models that allowed for the correlation of measurements within an individual were used for the continuous outcome variables FEV_1 and PEF. Several models were examined, and model selection was based on the change in -2 log likelihood and the smallest Akaike's Information Criterion within the ensemble of models.[19] The first-order, autoregressive, moving-average, variance-covariance structure was used to account for serial correlations within each subject. All models included as fixed effects the meteorological factors on the same day (temperature, relative humidity, and barometric pressure) as linear terms. For the pollutant fixed effect, a linear term was sufficient. For the random effect, allowing each subject to have his or her own intercept was sufficient.

For the analysis of rescue medication use and total symptom score, the generalized estimating equations approach in SAS PROC GENMOD was used, with Poisson distributions assumed. The first-order, autoregressive, variance-covariance structure was used, and temperature, relative humidity, and barometric pressure were included as covariates. A fixed-effects linear term was used for each pollutant variable.

For FEV_1 and peak flow, our final results were expressed as the standardized slopes with error bars, which represent ± 2 times the standardized SE of the slopes (expressed by the following equation):

$$\hat{\beta} \times \textit{Standard deviation of the pollutant} \pm \left(\textit{Standard error of } \hat{\beta}\right) \times \textit{Standard deviation of the pollutant},$$

where $\hat{\beta}$ is the parameter estimate from the mixed-effects model.

For rescue medication use and symptom scores, the results were expressed as the rate change per SD change in pollutant. They were calculated by exponentiating the $\hat{\beta}$ value derived from the ESTIMATE statement in SAS PROC GENMOD.

Demographic characteristics for the subjects, prebronchodilator FEV_1, FEV_1/forced vital capacity (measured in the laboratory)

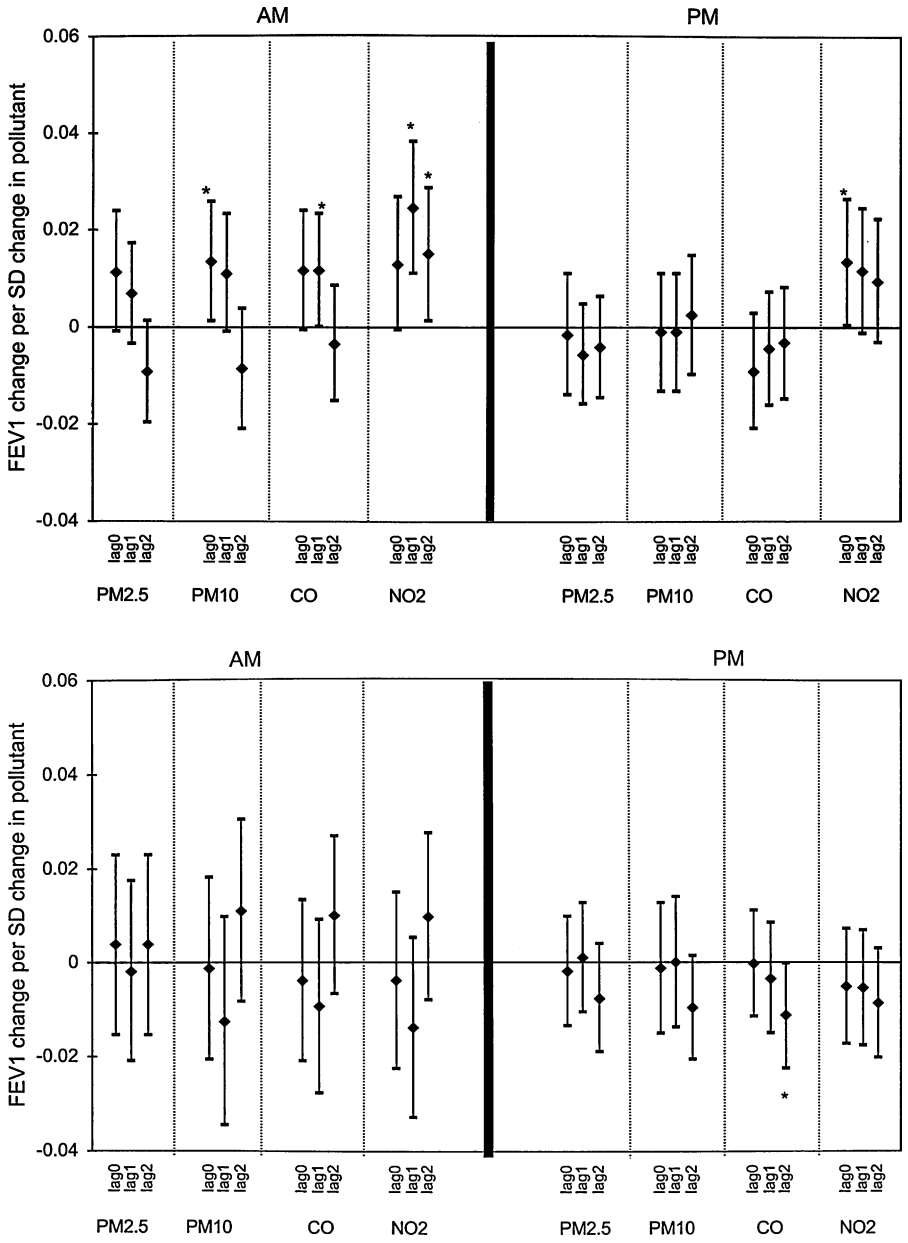

FIG 1. Estimates for FEV_1 change expressed per SD change of the individual pollutants $PM_{2.5}$, PM_{10}, CO, and NO_2 for the first **(A)** and second **(B)** winter at lags 0, 1, and 2. In the first winter associations were in the opposite direction from expected. The *asterisk* indicates a significant association ($P < .05$).

pollutant levels, and meteorological factors between the 2 winters were also compared by using Wilcoxon rank sums tests for the continuous variables and χ^2 tests for the categoric variables. Significance was set at the .05 level for all statistical tests.

RESULTS

Demographic and baseline subject data are presented in Table I and did not differ significantly between the 2 panels of subjects recruited for the 2 winters. COPD severity according to the Global Initiative for Chronic Obstructive Lung Disease classification (http://www.goldcopd.com) was moderate (24.2%), severe (48.5%), and very severe (27.3%) for subjects in both years combined. Compliance in diary card completion was high, with 6.2% and 6.6% of morning and evening missing cards and 3.9% and 3.8% of morning and evening missing cards in the first and second winters, respectively. For the first winter, AirWatch data were discarded for 1 subject (much higher home FEV_1 values than laboratory spirometry), and in the second winter data were discarded for 4 subjects because visual inspection indicated unreliability of data.

Estimated effects of the pollution parameters on outcomes were assessed for lags 0 to 2, where lag 0 indicates that the effect was observed on morning and evening diary cards on the same day, and lags 1 and 2 refer to an effect on

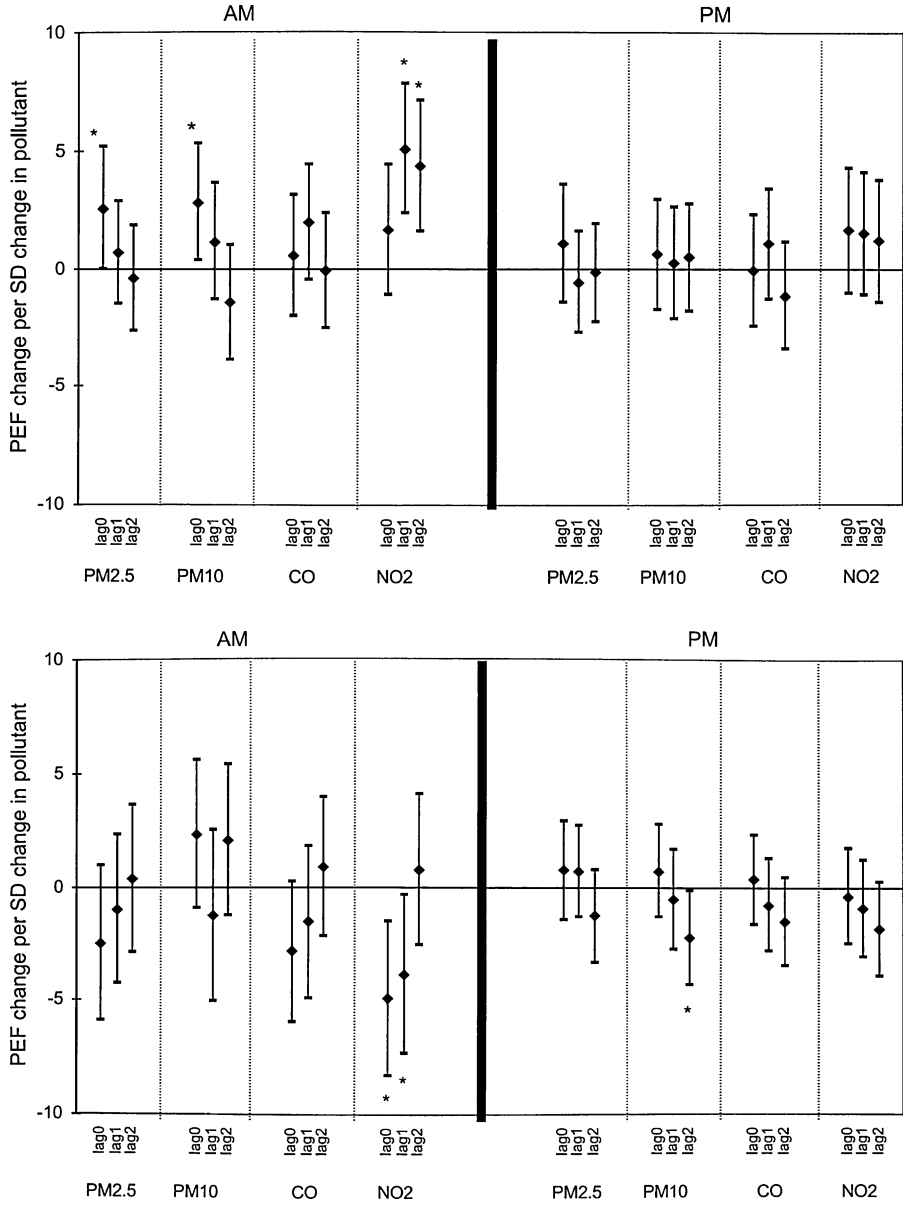

FIG 2. Estimates for PEF change expressed per SD change of the individual pollutants $PM_{2.5}$, PM_{10}, CO, and NO_2 for the first **(A)** and second **(B)** winter at lags 0, 1, and 2. In the first winter associations were in the opposite direction from expected. In the second winter the associations were in the hypothesized direction. The *asterisk* indicates a significant association ($P < .05$).

the next day or 2 days after the change in concentration of a particular pollution parameter, respectively. Table II shows the distribution of pollution and weather measurements for both winters.

First winter (1999-2000)

Monitoring was performed from November 11, 1999, until March 31, 2000. Sixteen subjects were recruited and completed the study that winter.

Lung function. The direction of all significant associations was opposite from that expected (Fig 1, *A*). FEV_1 increased in the morning with PM_{10} at lag 0, with CO at lag 1, and with NO_2 at lags 1 and 2; PEF increased in the morning with $PM_{2.5}$ at lag 0, with PM_{10} at lag 0 (Fig 2, *A*), and with NO_2 at lags 1 and 2.

Medication use. There were no significant associations for morning data, but medication use decreased significantly in the evening at lag 1 with NO_2.

Symptoms. For evening data, there was a significant decrease in the symptom score at lag 2 for CO.

Second winter

Monitoring was performed from November 1, 2000, until March 16, 2001. Nineteen subjects were recruited, and 18 completed the study. One subject died of a myocardial infarction during the study for reasons unrelated to this study.

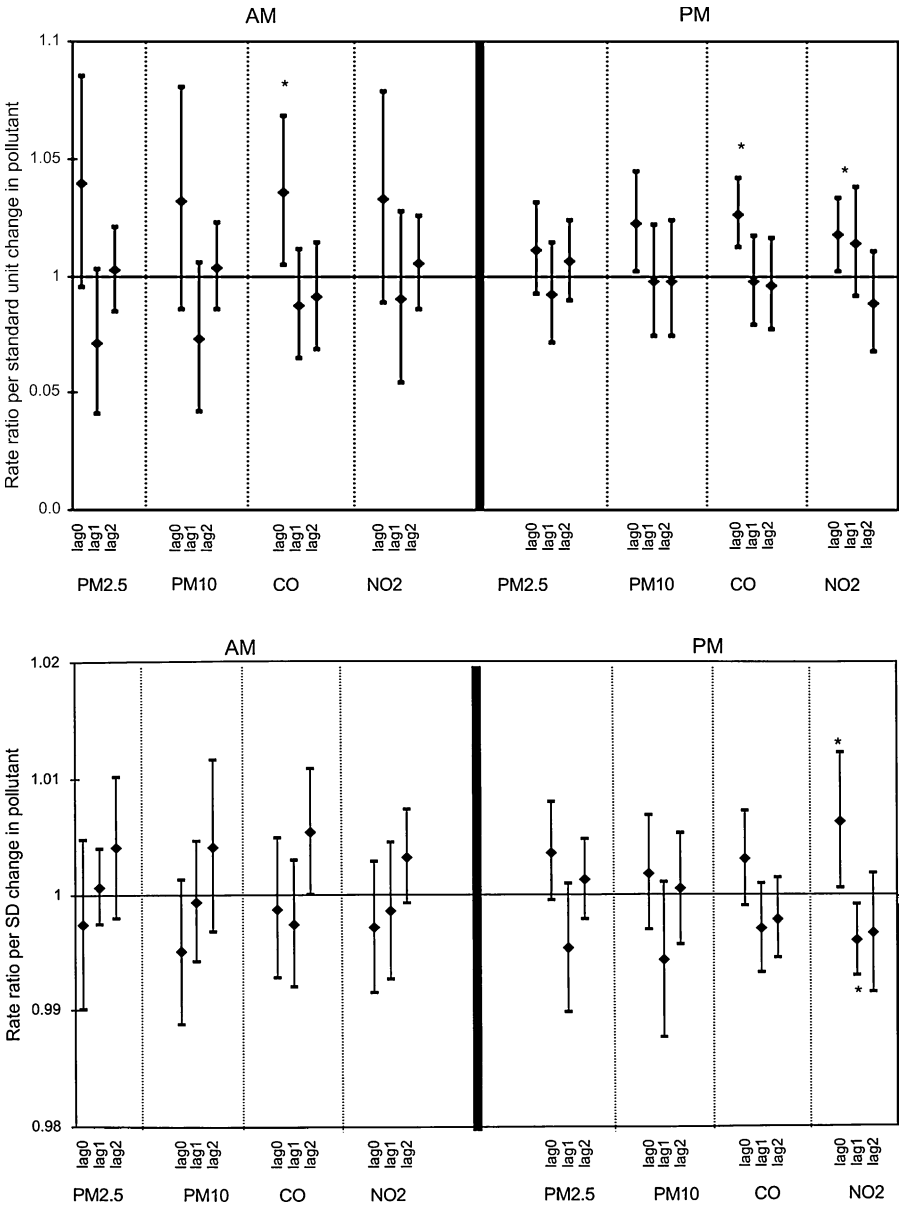

FIG 3. Estimates for medication use **(A)** and symptoms reporting **(B)** expressed as rate ratios per SD of individual pollutants for the second winter at lags 0, 1, and 2. The *asterisk* indicates a significant association ($P < .05$).

Lung function. As for the first winter, there were significant associations of pollutants with FEV_1 or PEF, but these were in the expected direction (Figs 1, *B*, and 2, *B*). FEV_1 decreased significantly with CO at lag 2 in the evening. Morning PEF decreased significantly with NO_2 at lag 0 and lag 1, whereas evening PEF decreased at lag 2 with PM_{10}.

Medication use. For morning medication use, there was a significant increase at lag 0 for CO and increases in evening medication use for PM_{10}, CO, and NO_2 (Fig 3, *A*) at lag 0.

Symptoms. For evening symptom score, there was a significant increase for NO_2 at lag 0 but a decrease at lag 1 (Fig 3, *B*).

Influence of baseline lung function on outcomes

When adding in baseline characteristics to the model, there was a significant negative association between FEV_1 and PEF and the increase in medication use associated with CO and PM_{10} seen in the second winter.

Comparison between the first and second winter

In view of the contrasting findings between the 2 winters, we performed a comparison of the panels' demographics and clinical characteristics and of the pollution and weather between the 2 winters. No significant differences were detected for demographic and

TABLE III. Average lung function over the winter measured approximately biweekly in the laboratory

Variable	Year	N	Mean	SD	*P* value for comparing the 2 years
Prebronchodilator FEV_1 (L)	1999-2000	116	1.15	0.094	.09
	2000-2001	126	0.92	0.089	
Prebronchodilator FEV_1/FVC (%)	1999-2000	116	42.95	2.08	.010
	2000-2001	115	35.97	1.97	

FVC, Forced vital capacity.

clinical characteristics at baseline between the 2 subject panels (Table I). Lung function, although not significantly different at baseline (Table I), was worse in the second winter panel compared with that in the first winter panel (Table III) when averaged over the study. There was a significant positive time trend independent of the pollutant effect for morning and evening PEF in the first winter ($P = .0102$ and $P = .0207$, respectively) but no significant time trend for FEV_1, symptom score, or medication use in either winter. Concentrations of PM_{10}, $PM_{2.5}$, and NO_2 were significantly higher in the second winter compared with those in the first winter (Table II). The second winter was significantly colder and more humid than the first winter (Table II).

DISCUSSION

This is the first panel study on the effects of ambient air pollution on patients with severe COPD. Additionally, this study was performed at high altitude, which itself has been associated with increased mortality in patients with COPD.[15,16] There were significant differences in the outcomes between the 2 winters that were studied. In the first winter significant effects on lung function were identified, but these were in the opposite direction from expected, whereas no effects on symptoms or medication use were identified. In the second winter there were significant effects of pollutants on PEF in the morning, PEF and FEV_1 in the evening, rescue bronchodilator use in the morning and evening, and total symptom score in the evening, with most effects on the same day as the pollution increase.

It is possible that the difference in findings between the 2 winters is due to higher pollution concentrations accompanied by somewhat lower temperatures and higher humidity in the second winter (Table II). Overall, the magnitude of the changes was small, and the clinical significance is uncertain. Our study indicates that there were acute associations of winter air pollution with disease outcomes in patients with COPD, despite the compliance of metropolitan Denver with EPA standards for most pollutants. The ability to detect changes in outcomes despite mild pollution concentrations might reflect the severity of COPD in both panels (Table I) or possibly the high altitude of Denver, which could increase the effects of air pollution by mechanisms such as increased minute ventilation, or exaggeration of effects on gas exchange caused by worsening hypoxia.

There any many theoretical factors that can increase susceptibility to air pollution in COPD. These include reduced pulmonary reserve; airways characterized by a chronic inflammatory environment (eg, neutrophils that can respond with a oxidative response to particulates), increased comorbidity (eg, cardiovascular disease perhaps caused by systemic inflammation),[20,21] increased airway particle dosing,[22] and genetic factors (eg, deletion of the glutathione-S-transferase M1 gene)[23] that might have selected out subjects with COPD from the general population of smokers.

The COPD severity in the majority of subjects in our study corresponded to stages III and IV according to current National Heart, Lung, and Blood Institute–World Health Organization guidelines for COPD.[24] A significant majority was also receiving 24-hour oxygen therapy (Table I). Air pollution had no consistent effect on home-monitored pulmonary function. The relative insensitivity of lung function might reflect the severity of our COPD panels and the less variable nature of the airflow obstruction in COPD compared with asthma. Additionally, despite adherence to the manufacturer's operating and calibration procedures and favorable reports,[25] the AirWatch spirometer had drawbacks in our severe COPD panels. Some subjects with very low FEV_1 values failed to register consistently, one subject consistently registered much higher than the in-laboratory spirometry, and another showed a progressive increase in FEV_1 not seen in the periodic laboratory spirometry. These issues led to loss of data and reduced statistical power.

Rescue medication use and symptoms reporting were more responsive than physiology in our setting. Our findings agree with those of Harre et al[12] in patients with COPD, who reported that symptoms and medication use, but not PEF, were significantly affected by NO_2 and PM_{10}. In the same light Brauer et al[13] found only trends for decreases in FEV_1 and PEF related to ambient pollutants. Our model also adjusted for weather parameters (temperature, barometric pressure, and relative humidity). Many other studies have also included weather parameters in their modeling. However, there is the possibility that the weather parameters themselves are independent factors that could increase COPD morbidity. Cold air has been reported to cause decreases in pulmonary function, increases in symptoms, and reductions in exercise tolerance in patients with COPD.[26] Limitations of our study include the relatively low level of air pollution in Denver, which leaves the possibility that the same study on the same panels in a more polluted environment might have yielded more significant effects. Sample size is also a factor. We were unable to recruit 40 subjects in a single winter as planned, which would have increased the power

to detect significant effects. However, the division of the study into separate cohorts over 2 winters allowed us to examine the significance of the differences between the 2 winters. Despite recruiting 34 subjects instead of the 40 intended, significant outcomes were detected. The symptom diary cards were developed specifically for this study, and therefore the sensitivity of the symptom score is therefore uncertain. The baseline mean total symptom score (20 of a possible 35) was also relatively high, leaving less room for worsening.

There is increasing concern that current ambient air quality standards might not be stringent enough to protect human subjects from adverse reactions. Sources of air pollution include direct emissions from transportation, industry, natural sources, and secondary conversion of substances in the atmosphere. Air pollution is a complex mix of particles and chemicals the composition and proportions of which vary daily. In addition, climatic conditions, such as temperature, humidity, sunlight, and wind, influence the generation, as well as the concentration and transport range, of airborne pollutants. This makes the task of separating the effects of individual pollutants difficult, especially when multiple pollutants might vary together. CO might itself be a good surrogate marker for other more pathogenic agents.

The EPA has established average daily exposure limits for several criteria pollutants, including $PM_{2.5}$, PM_{10}, CO, ozone, NO_2, and sulfur dioxide. However, exposure at less than such limits could cause adverse effects, particularly in individuals with respiratory disease, especially COPD. Personal exposures to air pollution will vary between individuals related to lifestyle patterns. Additionally, the effects of air pollution are likely to be additive to the effects of other pollutants in the workplace or home and to cigarette smoke. Our study suggests that effects occur at pollution levels within current EPA standards.

In summary, this panel study indicates that winter pollution in Denver increased symptoms and medication use in subjects with severe COPD. The effects were mild and of uncertain clinical significance but occurred at levels of ambient pollution less than current EPA standards. In light of recent evidence that inhaled steroids might affect morbidity in patients with COPD,[27] future studies on possible protective effects of anti-inflammatory interventions, such as inhaled steroids, would provide information on factors that might modify the effects of air pollution.

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