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Associations Between Air Pollution and Peak Expiratory Flow Among Patients with Persistent Asthma

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Abstract

Responses of patients with persistent asthma to ambient air pollution may be different from those of general populations. For example, asthma medications may modify the effects of ambient air pollutants on peak expiratory flow (PEF). Few studies examined the association between air pollution and PEF in patients with persistent asthma on well-defined medication regimens using asthma clinical trial data. Airway obstruction effects of ambient air pollutants, using 14,919 person-days of daily self-measured peak expiratory flow (PEF), were assessed from 154 patients with persistent asthma during the 16 wk of active treatment in the Salmeterol Off Corticosteroids Study trial. The three therapies were an inhaled corticosteroid, an inhaled long-acting β -agonist, and placebo. The participants were nonsmokers aged 12 through 63 yr, recruited from 6 university-based ambulatory care centers from February 1997 to January 1999. Air pollution data were derived from the U.S. Environmental Protection Agency Aerometric Information Retrieval System. An increase of 10 ppb of ambient daily mean concentrations of NO_2 was associated with a decrease in PEF of 1.53 L/min (95% confidence interval [CI] -2.93 to -0.14) in models adjusted for age, gender, race/ethnicity, asthma clinical center, season, week, daily average temperature, and daily average relative humidity. The strongest association between NO_2 and PEF was observed among the patients treated with salmeterol. Negative associations were also found between PEF and SO_2 and between PEF and PM_{10} , respectively. The results show that the two medication regimens protected against the effects of PM_{10} . However, salmeterol increased the sensitivity to NO_2 and triamcinalone enhanced the sensitivity to SO_2 .

Ambient air pollutants, including nitrogen dioxide (NO_2), particulate matter $<10 \mu\text{m}$ (PM_{10}), ozone (O_3), and sulfur dioxide (SO_2), adversely affect asthmatics (Desqueyroux et al., 2002; Delfino et al., 2006; Schildcrout et al., 2006; Rabinovitch et al., 2006). Asthma management emphasizes the role of chronic medication to control airway inflammation, but the interaction of chronic medication with air pollution health effects is unknown (Thurston & Bates, 2003; Gent et al., 2003). Asthma medication may modify the effects of a pollutant. In addition, the impact of exposure to the pollutant may modify the effects of the asthma medication. Thus,

the scope of this problem is likely to continue to grow. Therefore, understanding this pollution–medication interaction is of practical importance in the clinical management of patients with asthma.

Previous studies showed that long-acting beta-adrenergic agonists are effective as bronchodilators as they (1) prevent bronchoconstriction induced by methacholine, histamine, and allergens and (2) induce bronchodilation that lasts at least 12 h in patients with asthma (Lemanske et al., 2001). In addition, anti-inflammatory properties of salmeterol were confirmed in asthmatics by bronchoscopy and bronchoalveolar lavage (Dahl et al., 1991). However, overuse of inhaled long-acting β_2 -agonists, or their use as monotherapy, may contribute to a worsening of asthma control or increase the risk of asthma exacerbations and fatalities (Lazarus et al., 2001). McIvor et al. (1998) showed that patients with persistent asthma well controlled with low doses of triamcinolone can not be switched to a long-acting β_2 -agonist (salmeterol) monotherapy without risk of clinically significant loss of asthma control. McIvor et al. (1998) further proposed that treatment with long-acting β_2 -agonists may mask worsening airway inflammation and delay awareness of worsening asthma.

Under conditions of air pollution, it is plausible that asthma patients treated with β_2 -agonists may experience more inhalation exposure to air pollutants because bronchodilation may result in greater pollutant deposition in the lower airways. Unfortunately, no study has tested this hypothesis. Therefore, this study was designed to examine whether typical asthma regimens modify adverse health effects of exposure to air pollution. The central hypothesis is that air pollutants adversely affect the health of asthmatics despite medication use.

METHODS

Study Cohort and Protocol

The study subjects were participants in the National Heart, Lung, and Blood Institute (NHLBI)-sponsored Salmeterol Off Corticosteroids Study (SOCS) of the Asthma Clinical Research Network (ACRN). The SOCS study was a 28-wk trial conducted at 6 university-based ambulatory care centers from February 1997 to January 1999 (Lazarus et al., 2001). The six centers are located in six cities: Boston, New York, Denver, Philadelphia, San Francisco, and Madison, WI. The participants were nonsmokers aged 12 through 65 yr. After a 6-wk run-in period, during which the 164 participants received inhaled corticosteroid (triamcinolone, 4 puffs BID) and as-needed rescue albuterol, the participants were randomized into three groups: 54 participants in the group treated with an inhaled corticosteroid (4 puffs twice per day by metered-dose inhaler of triamcinolone acetonide), 54 participants in the group treated with an inhaled long-acting β_2 -adrenergic agonist (2 puffs twice per day by metered-dose inhaler of salmeterol xinafoate), and 56 participants treated with placebo (2 puffs twice per day) for 16 wk. All participants then stopped medication for an additional 6-wk single-blind study period (run-out). Specific to the present study, 14,919 person-days of daily self-measured morning peak expiratory flow (PEF) were used from 154 SOCS participants during the 16 wk of active treatment.

PEF Measurements

All self-measured PEF values were collected from each participant with the use of equipment and procedures that were standardized for the entire ACRN (Irvin et al., 1997). The research staff were trained and certified to ensure proficiency and uniformity in all procedures. Each center strictly followed standardized quality control and assurance procedures (Chinchilli et al., 2001). In each clinical center, written informed consent was obtained, using a document that had been approved by the ACRN as well as by the local institutional review board (IRB). The participants were also taught how to use their AirWatches (ENACT, Palo Alto, CA), an

electronic peak flow meter, and were instructed to measure the daily morning PEF upon arising at home while standing. At each of the scheduled clinical visits, the participant's AirWatch was tested against the Jones flow-volume calibrator and was replaced if it did not meet defined quality control standard. Further, the participant's AirWatch data were uploaded in the clinical centers, where the research staff reviewed the PEF recordings. Each clinical center submitted PEF recordings electronically to the data coordinating center through a distributed data entry system.

Pollution and Climate Variables

Air pollution data were derived from the U.S. Environmental Protection Agency (U.S. EPA) Aerometric Information Retrieval System (AIRS). The measurements from AIRS are subject to uniform criteria for monitoring, siting, instrumentation, and quality assurance (U.S. EPA, 1993). First, all of the monitors closest to the ZIP code centroid of the participants' home addresses were identified (less than 20 miles between a monitor location and the centroid of a ZIP code). Then, monitor-specific 24-h mean concentrations of NO₂, PM₁₀, and SO₂ and 8-h maximum O₃ concentrations were calculated. Further, ZIP-code-specific 24-h mean and 8-h maximum concentrations were calculated by averaging all available monitor-specific concentrations in each ZIP code. Based on the dates of the PEF measures and of pollutant measures, individual-specific daily mean concentrations were determined for the 2 days prior to the PEF measures for each participant. Thus, individual variables were developed to serve as surrogates for the short-term exposure to NO₂, PM₁₀, SO₂, and O₃, respectively. Meteorological data such as daily average temperature and daily average relative humidity were obtained from the National Climate Data Center for the same ZIP code areas.

Statistical Analysis

Descriptive statistics were generated first to check the validity of the variables and identify potential outliers. To determine the shape of the response and exposure relationship for each pollutant by treatment group, the PEF data were plotted against the pollutant data with a smoothed line. The curves all appeared to be linear within the 10th and 90th percentile range of the exposure data. Subsequently, the analyses were conducted using longitudinal data analysis based on fitting the pollutant data, a mean PEF at each week, and an overall mean shift for each of the three treatment groups (Laird & Ware, 1982). In addition, a random-intercepts model was specified to allow individual variation in PEF. The covariance matrix of the repeated PEF was unstructured. In addition, the models controlled for age, gender, race/ethnicity, asthma clinical center, season, daily average temperature, and daily average relative humidity. A pollutant effect was estimated by entering a pollutant separately into the model (single-pollutant model). Daily pollutant concentrations lagged up to 2 d were examined to take into account air pollution exposure on the days preceding the PEF measures. The effects of cumulative exposure to the pollutants were also examined by entering the exposure variable (up to 3 d) into the models. The effect estimates in each medication group were obtained from the main effect and pollutant×medication group interaction models, and represent the absolute change (unit: L/min) in PEF for a 10-unit increase in a pollutant. The analysis was performed using SAS v9.1 (SAS, Inc., Cary, NC).

RESULTS

Description of Study Population

There were 164 participants in the SOCS study. Consent was withdrawn for 10 of them. PEF measures were collected from the remaining 154 SOCS participants. Of the 154 participants, a total of 14,919 PEF measures were available for this study during the 16 wk of active treatment period. Approximately 5% of the PEF measures were missing due to adverse events (Lazarus et al., 2001). Further exclusions were made because of missing pollution data (i.e.,

approximately 9% missing for O₃). Thus, the remaining sample size is 14,919 person-days of observations in this study. Subject characteristics and their relationship with PEF are shown in Table 1. A majority of the participants were female and within an age range of 20 to 40 yr old. Thirty percent of participants were minority.

Air Pollution Levels

The mean concentrations of NO₂, PM₁₀, SO₂, and O₃ were all below the current U.S. National Ambient Air Quality Standard (Table 2) (U.S. EPA, 1990). Specifically, no days had PM₁₀ and SO₂ concentrations higher than the 24-h average standards of 150 µg/m³ and 140 ppb, respectively. Mean concentrations of NO₂ did not exceed the annual arithmetic mean standard of 53 ppb. However, the maximum daily mean concentration of NO₂ was higher than this standard. The maximum 8-h O₃ concentration was higher than the current 8-h standard of 80 ppb, but lower than the 1-h standard of 120 ppb.

Regression Analyses

Table 3 shows the associations between air pollution levels and changes in PEF. The strongest association between NO₂ and PEF was observed on the lag 0 day. An increase of 10 ppb of NO₂ daily concentrations was associated with a decrease in PEF of 1.53 L/min on the same day. Across the three medication regimen groups, the strongest association was observed in the salmeterol group (−2.52 L/min). These results show that the long-acting β₂-agonist not only did not effectively counteract adverse effects of NO₂ but actually intensified the adverse effects in this study. Our explanation is that the asthma patients treated with β₂-agonists may experience more inhalation exposure to air pollutants because bronchodilation results in greater pollutant deposition in the lower airways. NO₂ is a marker of motor vehicle emissions (Rosenlund et al., 2008). The observed NO₂ effects may be due to traffic-related air pollution in the study cities, where local traffic was much heavier than that in a suburban area (Gauderman et al., 2007).

The PM₁₀ was negatively associated with PEF, but the effects were weak, compared to those of NO₂. The effects were consistently larger for placebo than for medicated groups for all lags. These results suggest that the medications were effective in protecting the subjects from the effects of PM₁₀ on PEF. Similar findings were found by Pope et al. (1991) that weaker association between PM₁₀ and effects were observed in subjects who more likely took asthma medication.

The consistent and negative associations were observed between SO₂ and PEF only in the triamcinolone group. The results indicate that triamcinalone enhanced the sensitivity to SO₂ in this study. In the salmeterol group, a positive association was observed between PEF and SO₂. Similar results were reported in Europe, where SO₂ was positively associated with PEF in asthmatic children using respiratory medication (Roemer et al., 1999).

No statistically significant association was observed between changes in 8-h maximum O₃ and changes in PEF. However, interpretation needs to be performed cautiously. In this study the mean of 8-h maximum concentrations was 37.7 ppb, below the U.S. EPA air quality standards for the O₃ 8-h average of 80 ppb. Although the maximum value of the 8-h concentration exceeded 80 ppb, it was not likely that this O₃ maximum concentration occurred inside the house in the morning when the participants got up having the PEF measured. Therefore, the low O₃ levels might have provided a narrow pollution range to this study, thus limiting our ability to fully explore the relation between exposure to O₃ and PEF.

In the two-pollutant models, results generally show confounding of a copollutant (Table 4). This confounding was likely the result of multicollinearity; for example, NO₂ was correlated

with PM₁₀ ($r = .47$) and SO₂ (.58). However, O₃ did not confound the association between NO₂ and PEF.

DISCUSSION

Our study demonstrated that air pollution is associated with morning PEF in patients with moderate asthma on well-defined asthma medication regimens. The significant, negative associations were observed in all the three asthma medication regimens. These results support our hypothesis that air pollutants adversely affect the health of asthmatics despite medication use.

To our knowledge, asthma clinical trial data have not been used with respect to air pollution, and this study is the first attempt to explore the interaction between air pollutants and PEF in patients with persistent asthma with well-defined asthma medication regimens from multiple asthma clinical centers. There are several strengths in this study. First, although there are 154 subjects in this study, the sample size provides 14,919 person-days of observations, which makes our study one of the largest pollution/asthma panel studies. Second, it was possible to make full use of (1) more specific and more precise medication information, (2) extensive and high-quality health outcome measures, and (3) precise documentation of asthma status. Lastly, successful identification of more homogeneous asthmatic subpopulations from the SOCS asthma clinical trial may also facilitate addressing issues such as asthma pathogenesis.

Several studies were conducted to evaluate if asthma medications were related to differences in response to air pollution. The findings from these studies are contradictory. For example, significant positive associations were found between air pollution and PEF in asthmatic children on respiratory medication (Roemer et al., 1999). Hiltermann et al. (1998), however, reported that stratification by steroid use did not affect the magnitude of the observed associations between the prevalence of shortness of breath with NO₂, PM₁₀, O₃, and black smoke. Contrary to this observation, Peters et al. (1997) reported that medication use was not a confounder but attenuated the associations between particulate air pollution and PEF in asthmatics. Furthermore, Delfino et al. (2002) found enhancement of exposure-response relationships in asthmatics not taking anti-inflammatory medications. The disagreements already discussed are probably due to the major difficulties involved in the studies, which stem largely from the participants who are living in uncontrolled environments. A traditional epidemiological study is difficult to collect precise information about various asthma medications. Lack of precise asthma medication information may bring serious misclassification, thus biasing health effect estimation. It is also difficult to collect accurate asthma status. The difference in asthma severity status may significantly contribute to the disagreement of estimated air pollution health effects.

Close analyses suggest nonhomogeneity of health effects of different pollutants by different medication regimens. In other words, there is no clear evidence that the pollution effects on PEF are modified by these medications because pollutant-specific effects for each medication group are not consistently greater or lesser than those of the placebo group, across pollutants. This nonhomogeneity may indicate that an individual pollutant interacts with asthma medication regimens through a different major pathway/mechanism. However, Koutrakis et al. (2005) suggested that ambient gaseous pollutants were not well correlated with personal measures of the same gas but were reasonably correlated with personal PM_{2.5} measures in Baltimore, MD, and Boston. Thus, the studied ambient gaseous pollutants might just be surrogates for particulates or particulates from different sources in this study. Unfortunately, this study is limited to addressing the study question, and further studies with improved exposure assessment are needed.

There are several limitations involved in this study. First, data are not available on a number of factors that are known or suspected to affect respiratory health, such as indoor air pollution sources. Nevertheless, these factors are not likely to vary with daily pollution exposures, and thus the estimated pollution effects are unlikely to be confounded significantly by these factors (Dockery & Brunekreef, 1996; Pope, 1998). Second, exposure misclassification is clearly applicable to this study because stationary air monitoring data were used as a surrogate of personal exposure. While there was only a surrogate of personal exposure, it was as close as possible to participants by using the monitoring station closest to their home ZIP codes. Given the 2-yr duration of the study, it was impossible to equip the whole panel with personal samplers, especially since multiple pollutants were studied. Third, the exposure unit is day, and the PEF was measured upon awakening in the morning, which would lead to exposure classification. Delfino et al. (2002) showed that hourly pollution data captured adverse effects of exposure to ambient air pollutants better than 24-h averages. Unfortunately, hourly pollution data are not available for this study and further effort is needed in the future. Lastly, aeroallergens and viral respiratory infections are potential confounders. However, previous studies reported no confounding of outdoor fungi and pollen (Delfino et al., 1996; Anderson et al., 1998; Lewis et al., 2000). In addition, it is possible, at least partially, to remove such confounding by temporal filtering of the regression model analyses, since the levels of aeroallergens generally follow seasonal and sub-seasonal weather patterns (Lewis et al., 1991). As to the viral respiratory infections, published literature reported that controlling for respiratory infections did not substantially alter the associations between pollutants and health outcomes (Neukirch et al., 1998). Findings from Peters et al. (1997) further confirmed the “no confounding” findings just described. Even so, supplement analyses were conducted by restricting data analyses to the nonepidemic winter seasons, and no significant change of the estimated effects was found (results not shown).

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TABLE 1
Participant Characteristics and Their Relation With Peak Expiratory Flow (PEF) During the 16 wk of Active Treatment

Characteristic	Number (%) of subjects	Number (%) of samples	PEF (L/min)		
			Total, mean (SD)	Triamcinolone, mean (SD)	Placebo, mean (SD)
All subjects	154 (100)	14919 (100)	452.4 (118.2)	468.8 (125.3)	423.8 (92.3)
Gender					
Male	52 (34)	5020 (34)	548.2 (104.8)	579.2 (94.0)	486.4 (80.0)
Female	102 (66)	9899 (66)	403.7 (91.9)	419.1 (104.1)	394.1 (82.3)
Age					
≤20	19 (12)	1427 (10)	464.7 (124.9)	426.6 (102.3)	402.9 (73.4)
20 to ≤40	99 (64)	9699 (65)	455.8 (115.9)	458.9 (125.5)	439.0 (94.9)
>40	36 (24)	3793 (25)	439.0 (120.2)	501.2 (124.5)	379.5 (70.8)
Minority					
Yes	46 (30)	4364 (29)	485.2 (138.6)	493.5 (146.2)	454.5 (90.3)
No	108 (70)	10555 (71)	438.8 (105.7)	456.0 (110.9)	411.2 (90.1)
Study center					
Boston, MA	32 (21)	3338 (22)	471.4 (104.5)	507.3 (115.5)	448.4 (86.7)
Denver, CO	34 (22)	3431 (23)	425.6 (119.8)	431.4 (106.7)	408.2 (110.5)
Madison, WI	30 (19)	2403 (16)	463.8 (102.1)	470.1 (102.8)	426.9 (79.2)
Philadelphia, PA	25 (17)	2472 (17)	444.2 (110.5)	468.4 (123.6)	412.5 (90.5)
San Francisco, CA	30 (19)	2942 (20)	440.6 (125.0)	451.0 (148.6)	414.3 (85.6)
New York, NY	3 (2)	333 (2)	619.0 (152.1)	625.0 (84.7)	445.4 (37.2)

TABLE 2
Pollution and Meteorological Variables, 0-d Lag for the Daily Concentrations of Pollutants During the 16 wk of Active Treatment

Parameter	Number	Mean	SD	Min	Max	Percentile		
						25th	50th	75th
Total samples								
NO ₂ (ppb)	12,493	20.8	8.3	1.4	60.7	15.3	20.6	25.5
PM ₁₀ (µg/m ³)	7919	24.7	12.5	4.4	110.0	16.0	21.7	30.2
SO ₂ (ppb)	14,377	4.8	3.9	0.0	31.5	2.0	3.7	6.2
O ₃ (ppb)	14,919	37.7	17.5	1.3	105.9	25.3	35.9	49.2
Temperature (°F)	14,919	58.0	14.4	11.4	87.0	49.3	60.5	68.6
Relative humidity (%)	14,919	69.8	16.5	16.2	100.0	58.1	72.3	83.1
Triamcinolone								
NO ₂ (ppb)	4266	20.6	8.8	1.4	57.8	14.6	20.5	25.6
PM ₁₀ (µg/m ³)	2572	25.3	13.2	4.8	110.0	16.3	22.0	31.0
SO ₂ (ppb)	4860	4.7	3.9	0.0	31.5	1.9	3.5	6.2
O ₃ (ppb)	5236	37.5	17.4	1.9	105.9	25.4	35.8	48.6
Temperature (°F)	5236	57.2	14.7	11.4	87.0	48.4	60.0	68.0
Relative humidity (%)	5236	69.8	16.7	16.2	100.0	58.1	72.4	83.3
Salmeterol								
NO ₂ (ppb)	4002	21.3	8.0	2.5	60.7	15.9	20.8	25.8
PM ₁₀ (µg/m ³)	2662	24.3	12.0	4.4	110.0	16.0	21.6	30.0
SO ₂ (ppb)	4433	4.9	3.9	1.0	31.5	2.0	3.9	6.3
O ₃ (ppb)	4481	37.8	17.6	1.3	103.4	25.5	35.9	49.5
Temperature (°F)	4481	58.5	14.4	11.4	87.0	50.0	61.0	69.0
Relative humidity (%)	4481	69.7	16.5	16.2	100.0	58.3	72.3	82.9
Placebo								
NO ₂ (ppb)	4225	20.7	8.1	1.4	57.7	15.3	20.4	25.2
PM ₁₀ (µg/m ³)	2685	24.5	12.3	5.0	110.0	16.1	21.7	30.0
SO ₂ (ppb)	5084	4.8	3.9	1.0	31.5	2.0	3.8	6.2
O ₃ (ppb)	5202	37.7	17.5	1.3	105.9	25.0	36.1	49.3

Parameter	Number	Mean	SD	Min	Max	Percentile		
						25th	50th	75th
Temperature (°F)	5202	58.3	14.2	11.4	87.0	49.7	60.6	68.9
Relative humidity (%)	5202	69.8	16.4	16.2	100.0	58.3	72.3	83.0

TABLE 3

Change in PEF (L/min) and 95% Confidence Intervals Associated With Each 10-Unit Increase in Mean Pollutant Concentration, Single-Pollutant Models

Pollutant	Lag [†]	Change in PEF (L/min) for a 10-unit change in pollutant measures ^d			
		Total	Triamcinolone	Salmeterol	Placebo
NO ₂	0	-1.53 (-2.93, -0.14)*	-1.44 (-3.77, 0.89)	-2.52 (-4.93, -0.11) ^b	-0.62 (-3.06, 1.82)
	1	-0.37 (-1.80, 1.05)	-0.91 (-3.27, 1.44)	-0.94 (-3.35, 1.46)	0.79 (-1.65, 3.24)
	2	-0.13 (-1.53, 1.27)	0.40 (-1.93, 2.73)	-0.24 (-2.65, 2.16)	-0.60 (-3.04, 1.84)
PM ₁₀	0-2	-1.31 (-3.23, 0.61)	-1.29 (-4.43, 1.85)	-2.32 (-5.58, 0.93)	-0.28 (-3.61, 3.05)
	0	-0.52 (-1.57, 0.53)	-0.25 (-1.98, 1.49)	-0.32 (-2.15, 1.52)	-1.00 (-2.79, 0.79)
	1	-0.47 (-1.52, 0.58)	-0.49 (-2.21, 1.23)	-0.21 (-2.02, 1.61)	-0.70 (-2.47, 1.07)
SO ₂	2	-0.83 (-1.85, 0.20)	-0.41 (-2.11, 0.28)	0.26 (-1.55, 2.07)	-2.28 (-4.03, -0.54)*
	0-2	-1.04 (-2.09, 0.02)	-0.43 (-2.19, 1.34)	-0.95 (-2.82, 0.92)	-1.70 (-3.43, 0.03)
	0	-0.12 (-2.96, 2.71)	-8.29 (-13.15, -3.43) ^b	4.39 (-0.49, 9.27)	3.29 (-1.40, 7.99)
O ₃	1	-2.15 (-4.97, 0.68)	-7.93 (-12.72, -3.14) ^b	3.71 (-1.18, 8.60)	-2.01 (-6.70, 2.69)
	2	-0.65 (-3.45, 2.14)	-4.86 (-9.66, -0.06) ^b	1.48 (-3.36, 6.33)	1.36 (-3.35, 6.07)
	0-2	-1.93 (-5.56, 1.70)	-12.40 (-18.42, -6.38) ^b	6.40 (0.14, 12.67) ^b	0.85 (-5.20, 6.90)
O ₃	0	-0.03 (-0.76, 0.71)	-0.32 (-1.42, 0.78)	-0.71 (-1.90, 0.48)	0.89 (-0.23, 2.01)
	1	0.33 (-0.39, 1.04)	0.51 (-0.58, 1.60)	-0.09 (-1.27, 1.08)	0.51 (-0.60, 1.61)
	2	0.24 (-0.44, 0.92)	0.39 (-0.68, 1.46)	-0.87 (-2.03, 0.29)	1.06 (-0.02, 2.15)
	0-2	0.33 (-0.64, 1.30)	0.35 (-1.05, 1.74)	-0.82 (-2.33, 0.69)	1.34 (-0.09, 2.76)

^aControlling for age, gender, race/ethnicity, asthma clinical center, season, week, daily average temperature, and daily average relative humidity. Lag 0=lager of 0 d, lag 1 = lag of 1 d, lag 2 = lag of 2 d, and lag 0-2 = lag of 3 d (lag 0, 1, and 2).

^bSignificant at $p < .05$.

TABLE 4

Change in PEF (L/min) and 95% Confidence Intervals Associated With Each 10-Unit Increase in Mean Pollutant Concentration, Two \-Pollutant Models, Lag 0 d

Change in PEF (L/min) for a 10-unit change in pollutant measures ^a				
Pollutant	Copollutant	Total	Triamcinolone	Salmeterol
NO ₂	PM ₁₀	-1.82 (-3.87, 0.23)	-2.13 (-5.38, 1.12)	-2.31 (-5.51, 0.89)
	O ₃	-1.54 (-2.96, -0.12) ^b	-1.25 (-3.59, 1.09)	-2.85 (-5.36, -0.35) ^b
	SO ₂	-0.26 (-1.97, 1.45)	-0.68 (-3.35, 1.98)	-0.96 (-3.68, 1.76)
PM ₁₀	O ₃	-0.58 (-1.67, 0.52)	-0.17 (-1.93, 1.60)	-0.50 (-2.43, 1.43)
	NO ₂	-0.01 (-1.25, 1.24)	0.22 (-1.68, 2.12)	0.55 (-1.45, 2.56)
	SO ₂	0.23 (-1.05, 1.50)	-0.35 (-2.42, 1.72)	0.37 (-1.72, 2.46)
SO ₂	PM ₁₀	-1.34 (-5.78, 3.11)	-7.30 (-14.59, 0.00) ^b	3.78 (-3.33, 10.88)
	O ₃	-0.38 (-3.39, 2.63)	-6.46 (-11.50, -1.42) ^b	3.17 (-2.20, 8.55)
	NO ₂	-1.34 (-5.04, 2.35)	-7.55 (-13.32, -1.78) ^b	2.21 (-3.60, 8.01)
O ₃	PM ₁₀	0.56 (-0.54, 1.66)	-0.75 (-2.39, 0.89)	0.10 (-1.57, 1.78)
	NO ₂	0.34 (-0.50, 1.19)	-0.03 (-1.30, 1.24)	-0.53 (-1.87, 0.81)
	SO ₂	-0.21 (-0.98, 0.55)	-0.38 (-1.55, 0.79)	-0.78 (-2.03, 0.46)

^aControlling for age, gender, race/ethnicity, asthma clinical center, season, week, daily average temperature, and daily average relative humidity.

^bSignificant at $p < .05$.