Joint Effects of Ambient Air Pollutants on Pediatric Asthma Emergency Department Visits in Atlanta, 1998–2004

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Background: Because ambient air pollution exposure occurs as mixtures, consideration of joint effects of multiple pollutants may advance our understanding of the health effects of air pollution.
Methods: We assessed the joint effect of air pollutants on pediatric asthma emergency department visits in Atlanta during 1998–2004. We selected combinations of pollutants that were representative of oxidant gases and secondary, traffic, power plant, and criteria pollutants, constructed using combinations of criteria pollutants and fine particulate matter ($PM_{2.5}$) components. Joint effects were assessed using multipollutant Poisson generalized linear models controlling for time trends, meteorology, and daily nonasthma upper respiratory emergency department visit counts. Rate ratios (RRs) were calculated for the combined effect of an interquartile range increment in each pollutant's concentration.
Results: Increases in all of the selected pollutant combinations were associated with increases in warm-season pediatric asthma emergency department visits (eg, joint-effect RR = 1.13 [95% confidence interval = 1.06–1.21] for criteria pollutants, including ozone, carbon monoxide, nitrogen dioxide, sulfur dioxide, and $PM_{2.5}$). Cold-season joint effects from models without nonlinear effects were generally weaker than warm-season effects. Joint-effect estimates from multipollutant models were often smaller than estimates based on single-pollutant models, due to control for confounding. Compared with models without interactions, joint-effect estimates from models including first-order pollutant interactions were largely similar. There was evidence of nonlinear cold-season effects.
Conclusions: Our analyses illustrate how consideration of joint effects can add to our understanding of health effects of multipollutant exposures and also illustrate some of the complexities involved in calculating and interpreting joint effects of multiple pollutants.

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Although many studies of the health effects of air pollution focus on individual pollutants, actual air pollution exposures are usually multipollutant mixtures. Recognition of the importance of air pollution mixtures has led to increased interest in assessment of their health effects.[1–3] Various approaches to assessing the health effects of air pollution mixtures have been employed.[1,4] For example, some studies have assessed health effects using markers of exposure to specific mixtures, such as measures of traffic volume or proximity to roadways.[5] Other studies have assessed health effects of mixtures characterized through source apportionment metrics,[6] air pollution indices, or sums of pollutant concentrations.[7–12] In this study, we illustrate and discuss an approach to assessing the health effects of air pollution mixtures that extends traditional single-pollutant epidemiologic models of measured pollutant concentrations by using models that include several pollutants to estimate the combined effect of multiple pollutants (ie, joint effects).

Considering the joint effects of pollutants, rather than their individual effects, can advance our understanding of air pollutant mixture health effects. For example, considering the joint effects of groups of pollutants from particular sources may increase our understanding of important sources contributing to health effects. In addition, consideration of joint effects can address issues of confounding between pollutants and may avoid some of the difficulties involved in attempts to isolate individual effects of several correlated pollutants.[13,14]

To date, joint effects have infrequently been considered in studies on air pollution health effects,[15–21] with few studies assessing the precision of the joint-effect estimates.[17–21] Moreover, discussion of the potential complexities involved with this approach has been limited.

In this study, we assess the joint effect of pollutants in several combinations of criteria gases, particulate matter less than 2.5 µm in diameter ($PM_{2.5}$), and $PM_{2.5}$ components, using data from a time-series study of air pollution and pediatric emergency department visits for asthma in the Atlanta metropolitan area for which model performance has been previously described.[22] We selected specific combinations representing pollutants with shared properties (oxidant gases and secondary pollutants) or sources (traffic and coal-fired power plant pollutants), or common air pollutants with US National Ambient Air Quality Standards (NAAQS). We also discuss issues that must be considered when applying this analytic approach.

METHODS

We used the data and modeling strategy applied by Strickland et al,[22] building upon previous results by considering joint effects of pollutant combinations. Methods for the original study are described in detail elsewhere.[22] Briefly, for the period 1 August 1998 through 31 December 2004, researchers obtained from several ambient monitoring networks in Atlanta information on daily concentrations of the following: ambient 1-hour maximum carbon monoxide (CO), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2); 8-hour maximum ozone (O_3); and 24-hour average $PM_{2.5}$ and the $PM_{2.5}$ components elemental carbon (EC), sulfate (SO_4^{2-}), nitrate (NO_3^-), and ammonium (NH_4^+).[23,24] Daily pollutant measurements across monitors were combined using population weighting.[25] Individual-level data on emergency department visits during this time period were obtained from metropolitan Atlanta hospitals. Using *International Classification of Diseases, 9th Revision* (ICD-9), pediatric asthma emergency department visits were defined as visits with a code for asthma (493.0–493.9) or wheeze (786.09 before 1 October 1998; 786.07 after 1 October 1998) that did not have a code for an external injury or poisoning (E800–E999) among children 5–17 years of age. Emergency department visits for acute upper respiratory infections (codes 460.0–466.0) among children in the same age group who did not also have a code for asthma or wheeze were also identified.

We examined the joint effects of combinations of commonly measured pollutants, selected to represent oxidant gases, secondary pollutants, pollutants from traffic and coal-fired power plant sources, and criteria pollutants (Table 1). The "oxidant gases" combination included the major gaseous oxidant air pollutants (O_3, NO_2, and SO_2). The "secondary" pollutant combination included O_3 and secondary $PM_{2.5}$ (for which the concentration was calculated as the sum of the concentrations of the major inorganic $PM_{2.5}$ components SO_4^{2-}, NO_3^-, and NH_4^+). The pollutants in the "traffic" combination were those most closely associated with traffic pollution in Atlanta (CO, NO_2, and EC).[10] Organic carbon measurements were not used in these analyses because organic carbon originates from both primary (eg, traffic) and secondary sources, and the speciated organic data needed to apportion organic carbon to sources were available for only a limited time

period. The pollutants in the "power plant" combination (SO_2 and SO_4^{2-}) were selected to be relatively (although not completely) specific for pollution from coal-fired power plants.[26,27] The "criteria pollutants" combination included 5 of the pollutants for which NAAQS are set (including O_3, CO, NO_2, SO_2, and $PM_{2.5}$; excluding lead and PM less than 10 µm in diameter). The "criteria pollutants" combination was included because of its potential regulatory significance.

We examined joint effects of pollutant combinations on pediatric asthma emergency department visits using Poisson generalized linear models that accounted for overdispersion. Because previous analyses showed different warm- and cold-season effects,[22] analyses were season specific. We used the same general model form as Strickland et al.[22] The dependent variable was the hospital-specific daily pediatric asthma emergency department visit count. For each pollutant in a given combination, the primary models included a linear term for the 3-day moving average of pollutant concentrations (the average of the pollutant concentration on a given day [lag 0] and the previous 2 days [lags 1 and 2]). Models also included a linear term for the logarithm of the daily nonasthma pediatric emergency department visit count for acute upper respiratory infections; cubic polynomials for day-of-season, the moving average of dew point (lags 0–2), and the moving average of minimum temperature (lags 1 and 2); indicator variables for year, month, day of week or holiday (with holidays having a separate indicator), hospital and same-day (lag 0) maximum temperature (for each degree Celsius); and interaction terms between month and year, month and lag 0 maximum temperature, and month and day of week. We estimated joint effects for an interquartile range (IQR) increment in the 3-day moving average of each pollutant concentration as the exponentiated sum (across the pollutants in the combination) of the product of each pollutant's model coefficient and that pollutant's IQR. Standard errors for joint effects were calculated using the variance–covariance matrices for the individual-pollutant coefficients (for a mathematical representation of models and joint-effect calculations, see eAppendix, http://links.lww.com/EDE/A804).

Initial models included only the pollutants in the specified combination, without interaction terms. The results of these models were compared with the results of models that also included linear terms for all first-order multiplicative interactions between the pollutants in the combination (eg, for the oxidant gases combination, models included terms for O_3, NO_2, SO_2, and the product terms $O_3 \times NO_2$, $O_3 \times SO_2$, and $NO_2 \times SO_2$). In sensitivity analyses, we considered models with linear, quadratic, and cubic terms for each pollutant, to assess the adequacy of using linear pollutant terms. In interaction models and models with quadratic and cubic terms, joint effects were calculated for a concentration change equal in magnitude to each pollutant's IQR, starting from each pollutant's 15th, 25th, or 35th percentile levels. We also considered models that controlled for other potentially confounding pollutants.

TABLE 1. Pollutant Combinations for Calculation of Joint Effects

Combination Name	O_3	CO	NO_2	SO_2	$PM_{2.5}$	EC	SO_4^{2-}	Secondary $PM_{2.5}$[a]
Oxidant gases	X		X	X				
Secondary	X							X
Traffic		X	X			X		
Power plant				X			X	
Criteria pollutants	X	X	X	X	X			

[a]Secondary $PM_{2.5}$ was calculated as the sum of the concentrations of selected $PM_{2.5}$ components including SO_4^{2-}, NO_3^-, and NH_4^+.

Concurvity (the analogue of collinearity in nonlinear models) was calculated for each pollutant as the correlation between observed pollutant concentrations and predicted concentrations from linear models including all other model variables (ie, other pollutant terms, time variables, and meteorological variables).[28] We also calculated concurvity for each pollutant in relation to only the other pollutant terms in the models (without time and meteorological variables).

RESULTS

The distributions of the individual pollutants during the 1998–2004 warm and cold seasons are characterized in Table 2, and correlations between them are shown in Table 3. Warm-season correlations ranged from moderately high to high (Spearman correlation coefficient [r] = 0.62–0.98) among $PM_{2.5}$, secondary $PM_{2.5}$, and the $PM_{2.5}$ component SO_4^{2-}. There were moderately high correlations among the traffic-related pollutants CO, NO_2, and EC (r = 0.57–0.75) in both seasons and between $PM_{2.5}$ and O_3 (r = 0.66) in the warm season. Cold-season correlations were generally lower than warm-season correlations, except for correlations between $PM_{2.5}$ and CO and between $PM_{2.5}$ and EC, which were slightly higher in the cold season. For all of the pollutant combinations, all pollutants were simultaneously observed in their highest or lowest quartiles on some days in both seasons, and so effect estimates for IQR increments in each pollutant represent pollutant changes that actually occur (eTable 1, http://links.lww.com/EDE/A804). The mean daily number of pediatric asthma emergency department visits was 26 (standard deviation = 14.8) in the warm season and 33 (standard deviation = 14.1) in the cold season.

Daily increases in all of the selected pollutant combinations were associated with increases in daily warm-season pediatric asthma emergency department visit counts (Figure, eTable 2, http://links.lww.com/EDE/A804). Warm-season rate ratios (RRs) for the joint effect of an IQR change in the 3-day moving average of all pollutants in the selected combinations, in models without interactions, were 1.10 (95% confidence interval [CI] = 1.04–1.16) for oxidant gases, 1.09 (1.04–1.14) for secondary pollutants, 1.11 (1.06–1.16) for traffic pollutants, 1.06 (1.02–1.10) for power plant pollutants, and 1.13 (1.06–1.21) for criteria pollutants. Warm-season joint effects were stronger than any of the single-pollutant model effects for the pollutants in each combination (eTable 3, http://links.

lww.com/EDE/A804). If warm-season joint effects had been calculated using pollutant coefficients from single-pollutant models, joint-effect RRs would have been overestimated (calculated RR: for oxidant gases, 1.22; secondary, 1.12; traffic, 1.25; power plant, 1.07; and criteria pollutants, 1.41) because single-pollutant models do not control for potential confounding effects of covarying pollutants. Cold-season joint effects varied across pollutant combinations. These effects were highest for the secondary combination (RR per IQR change = 1.06 [95% CI = 0.99–1.14]) and the oxidant gases combination (RR per IQR change =1.05 [0.99–1.13]) (Figure, eTable 2, http://links.lww.com/EDE/A804). Comparison of cold-season joint effects based on single-pollutant model coefficients with those from the multipollutant models is complicated by some cold-season single-pollutant models suggesting protective effects (eTable 3, http://links.lww.com/EDE/A804). More detailed results from the single-pollutant and primary joint-effect models are shown in eTables 4 and 5 (pollutant coefficients and P values, http://links.lww.com/EDE/A804) and eTables 6 and 7 (variance–covariance matrix for estimates from primary multipollutant models, http://links.lww.com/EDE/A804).

Compared with joint-effect estimates from models without interactions, joint-effect estimates from models that included first-order interactions between pollutants, with evaluation of the joint effect for a change from the 25th to the 75th percentile level for each pollutant, were generally not substantially different (Figure, eTable 2, http://links.lww.com/EDE/A804). Sensitivity analyses evaluating joint effects at other points in the pollutant distributions yielded similar conclusions relative to no-interaction models (eFigures 1 and 2, http://links.lww.com/EDE/A804). Based on consideration of individual interaction terms or consideration of likelihood ratio tests for the interaction terms together, warm-season models including first-order pollutant interactions generally did not show strong statistical evidence of important interactions (eTables 2 and 4, http://links.lww.com/EDE/A804), but cold-season models for the oxidant gases and criteria pollutants combinations did (likelihood ratio test P values for interaction terms together <0.01, eTables 2 and 5, http://links.lww.com/EDE/A804).

In sensitivity analyses, compared with estimates from models with only linear pollutant terms, joint-effect estimates for an IQR change in each pollutant (starting at the

TABLE 2. Individual Pollutant Distributions by Season, Atlanta, August 1998–December 2004

Pollutant	Units	No. Measurements	Mean	Standard Deviation	Percentiles[a]		
					25th	50th	75th
WARM (May–October)							
O_3 (8-hour maximum)	ppb	1,196	53.9	19.2	39.8	53.3	67.7
CO (1-hour maximum)	ppm	1,186	0.7	0.4	0.5	0.7	0.9
NO_2 (1-hour maximum)	ppb	1,196	22.3	10.2	14.8	20.5	28.7
SO_2 (1-hour maximum)	ppb	1,196	8.3	7.4	2.9	6.0	11.4
$PM_{2.5}$ (24-hour average)	µg/m³	1,196	18.4	7.6	12.8	17.0	23.1
$PM_{2.5}$ elemental carbon (24-hour average)	µg/m³	1,190	0.8	0.6	0.4	0.7	1.1
$PM_{2.5}$ sulfate (24-hour average)	µg/m³	1,179	5.9	3.5	3.4	5.1	7.8
Secondary $PM_{2.5}$[b] (24-hour average)	µg/m³	1,178	8.6	4.7	5.1	7.5	10.9
COLD (November–April)							
O_3 (8-hour maximum)	ppb	1,148	33.6	13.9	23.4	32.6	42.7
CO (1-hour maximum)	ppm	1,137	0.9	0.5	0.5	0.7	1.1
NO_2 (1-hour maximum)	ppb	1,149	25.6	9.8	18.4	24.9	31.7
SO_2 (1-hour maximum)	ppb	1,149	10.8	9.0	4.1	8.2	14.6
$PM_{2.5}$ (24-hour average)	µg/m³	1,142	14.3	6.5	9.8	13.0	17.4
$PM_{2.5}$ elemental carbon (24-hour average)	µg/m³	1,144	0.9	0.6	0.4	0.7	1.2
$PM_{2.5}$ sulfate (24-hour average)	µg/m³	1,133	3.2	1.8	1.9	2.8	3.9
Secondary $PM_{2.5}$[b] (24-hour average)	µg/m³	1,133	5.6	2.7	3.7	5.1	6.9

[a]For comparability with previous analyses,[22] the IQRs used in calculation of joint effects were slightly different from those reflected here, due to use of the year-round IQR during 1993–2004 for O_3, NO_2, CO, and SO_2, and during 1 August 1998–31 December 2004 for $PM_{2.5}$ and $PM_{2.5}$ components.
[b]Secondary $PM_{2.5}$ was calculated as the sum of the concentrations of selected $PM_{2.5}$ components including SO_4^{2-}, NO_3^-, and NH_4^+.

25th percentile) from models including quadratic and cubic pollutant terms were slightly lower for the warm-season traffic and criteria pollutant combinations and notably higher for several cold-season combinations, particularly the oxidant gases, secondary, and criteria pollutant combinations (Figure). Evaluation of joint effects at other points in the pollutant distributions gave similar conclusions (eFigures 1 and 2, http://links.lww.com/EDE/A804). Dose–response curves based on the results of the models with and without nonlinear terms for the oxidant gases, secondary, and criteria pollutants combinations are shown in eFigure 3 (http://links.lww.com/EDE/A804). Statistical evidence for the importance of the quadratic and cubic terms was observed for the warm-season traffic combination, and the cold-season secondary, criteria pollutants, and power plant combinations (*P* values for likelihood ratio tests for nonlinear terms together <0.03; see eTable 8 for joint-effect estimates and eTables 9 and 10 for detailed model results, http://links.lww.com/EDE/A804).

Joint-effect estimates from models controlling for potentially confounding pollutants not included in calculation of joint effects were generally lower than joint-effect estimates from models including only the pollutants in the joint effect (except for the traffic combination in both seasons, and the oxidant gases combination in the cold season, for which estimates were not substantially different) (see eTable 8 for joint-effect estimates and eTables 9 and 10 for detailed model results, http://links.lww.com/EDE/A804). The difference was most marked for the warm-season secondary combination

when controlling for CO, NO_2, and SO_2 (RR = 1.02 [95% CI = 0.96–1.08] vs. 1.09 [1.04–1.14] in the model with only O_3 and secondary $PM_{2.5}$) and for the warm-season power plant combination when controlling for O_3, CO, NO_2, and EC (RR = 1.00 [0.96–1.05] vs. 1.06 [1.02–1.10] in the model with only SO_2 and SO_4^{2-}).

Measures of concurvity between pollutants and all other variables in the joint-effect models were high in both seasons, ranging from 0.63 to 0.95 for the various pollutants in the models without interaction terms (eTables 4 and 5, http://links.lww.com/EDE/A804). Concurvity was generally lowest for SO_2 and highest for O_3. Lower but still substantial concurvity values were also seen for the pollutants in single-pollutant models (concurvities of 0.61–0.91), as well as for pollutants in multipollutant models in relation to only the other pollutants in the models (for warm season, 0.26–0.87, and for cold season, 0.05–0.83, in no-interaction models). As expected, concurvities increased when first-order interaction terms were included.

DISCUSSION

We calculated joint effects for several pollutant combinations selected based on shared pollutant properties, relevance to air quality standards, or shared sources. We observed warm-season joint effects representing increases of 6%–13% in daily pediatric asthma emergency department visit rates for an IQR change in all of the pollutants in the combinations. Warm-season pediatric asthma appears to be affected by a variety of

TABLE 3. Spearman Correlations Between Pollutants by Season, Atlanta, August 1998–December 2004

	O_3 (8-Hour Maximum)	CO (1-Hour Maximum)	NO_2 (1-Hour Maximum)	SO_2 (1-Hour Maximum)	$PM_{2.5}$ (24-Hour Average)	$PM_{2.5}$ Elemental Carbon (24-Hour Average)	$PM_{2.5}$ Sulfate (24-Hour Average)
WARM (May–October)							
O_3 (8-hour maximum)	1.00						
CO (1-hour maximum)	0.33	1.00					
NO_2 (1-hour maximum)	0.54	0.75	1.00				
SO_2 (1-hour maximum)	0.27	0.32	0.44	1.00			
$PM_{2.5}$ (24-hour average)	0.66	0.46	0.52	0.28	1.00		
$PM_{2.5}$ elemental carbon (24-hour average)	0.39	0.73	0.68	0.31	0.53	1.00	
$PM_{2.5}$ sulfate (24-hour average)	0.55	0.22	0.27	0.24	0.82	0.28	1.00
Secondary $PM_{2.5}$[a] (24-hour average)	0.55	0.27	0.31	0.24	0.86	0.33	0.98
COLD (November–April)							
O_3 (8-hour maximum)	1.00						
CO (1-hour maximum)	0.12	1.00					
NO_2 (1-hour maximum)	0.30	0.74	1.00				
SO_2 (1-hour maximum)	0.05	0.22	0.41	1.00			
$PM_{2.5}$ (24-hour average)	0.17	0.57	0.49	0.07	1.00		
$PM_{2.5}$ elemental carbon (24-hour average)	0.10	0.72	0.57	0.18	0.64	1.00	
$PM_{2.5}$ sulfate (24-hour average)	0.20	0.14	0.08	0.02	0.62	0.19	1.00
Secondary $PM_{2.5}$[a] (24-hour average)	0.07	0.16	0.12	0.08	0.67	0.24	0.92

[a]Secondary $PM_{2.5}$ was calculated as the sum of the concentrations of selected $PM_{2.5}$ components including SO_4^{2-}, NO_3^-, and NH_4^+.

pollutant combinations, particularly those including O_3 or NO_2. Joint effects for cold-season pediatric asthma showed more heterogeneity across mixtures, with strong effects observed for the oxidant gases, secondary, and criteria pollutants combinations when nonlinear effects were included in the models. Our results illustrated that calculation of joint effects from multi-pollutant models can avoid overestimation of joint effects that would result had their calculation been based on single-pollutant model effect estimates. Single-pollutant model estimates may include some of the effect of correlated pollutants due to mutual confounding, which can be substantial. Our results also illustrate some of the complexities involved in calculating and interpreting joint-effect estimates.

To calculate a joint effect, one has to calculate the effect of some specified change in each pollutant in the combination. The degree of change in each pollutant used in the calculation could be determined in several ways. We calculated the joint effect of an IQR change in each pollutant because that has a basis in actual pollutant distributions. However, the IQR is specific to the location and time period and may vary for a given pollutant depending on the metric used (eg, central monitor vs. population-weighted average). Use of the IQR could also lead to combinations of pollutants with greater variability appearing more harmful (ie, having a higher effect estimate per IQR change in pollutant concentrations) than combinations of pollutants with less variability, even if those combinations are not inherently more harmful. In addition, contrasts other than an IQR change may be of interest to risk assessors. To allow examination of other contrasts of interest, we

have included information in the supplemental material about the individual parameter estimates (eTables 4 and 5, http://links.lww.com/EDE/A804) and the corresponding covariance matrix (eTables 6 and 7, http://links.lww.com/EDE/A804).

In sensitivity analyses, we explored the impact of several model specification decisions on the joint-effect estimates. One decision relates to the approach to potential confounding by pollutants not included in the joint effect of interest. In our sensitivity analyses, models controlling for common, potentially confounding pollutants other than those in the joint effect often showed lower joint-effect estimates than models that included only pollutants in the joint effect. Changes in joint-effect estimates observed when including additional pollutants in the model could be due to control for confounding but could also be due to differential measurement error. In a multipollutant model, measurement error can cause the effect estimate for a better-measured pollutant to represent some of the effect of a correlated but less well-measured pollutant, making individual pollutant effect estimates less accurate.[29,30] In the presence of differential measurement error, adding other pollutants to the model could decrease the accuracy of the joint-effect estimate. Differential measurement error may have affected our joint-effect estimates, with the degree of the impact depending on true pollutant effects, correlations between pollutants, relative degrees of measurement error, and correlations between measurement errors.[29,31]

Other model-specification issues relate to how pollutants are included in the model. Pollutants are often included in models as linear terms, as in our primary analyses. Our
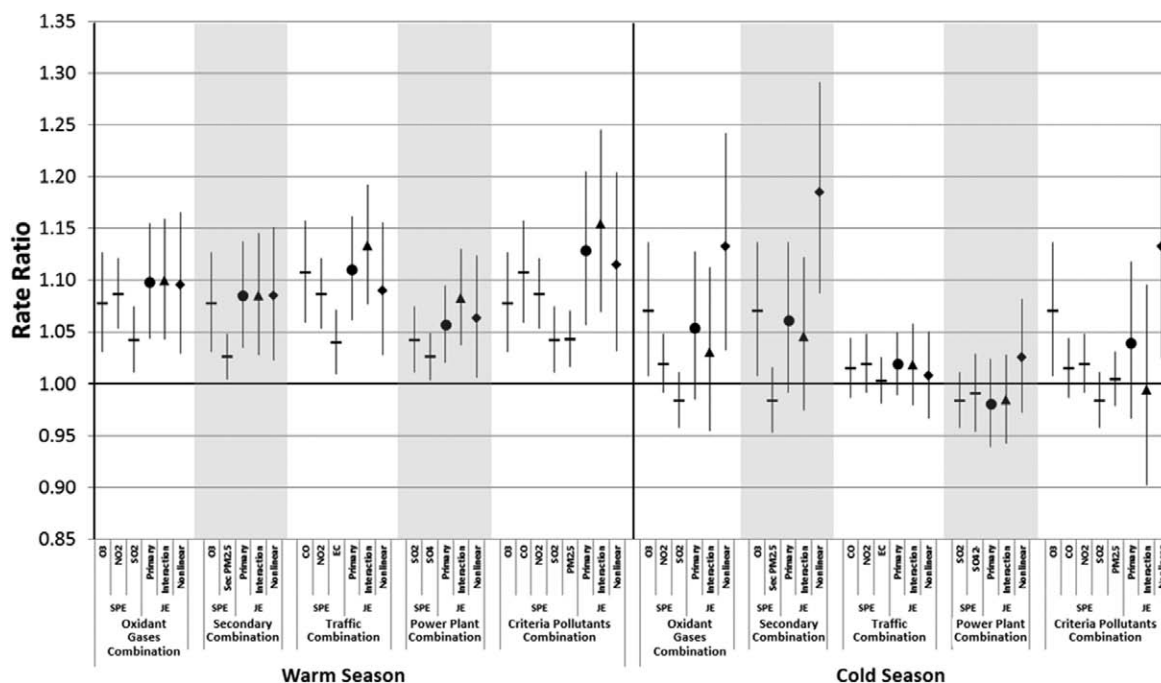
FIGURE. RRs and 95% CIs for single-pollutant effects per IQR increment in each pollutant from single-pollutant models and for corresponding joint effects from multipollutant models. For each combination of pollutants, single-pollutant RRs (shown with horizontal line markers) are followed by joint-effect RRs from the primary multipollutant models, which had linear pollutant terms and no interactions ("Primary," circle markers), multipollutant models with linear pollutant terms and first-order interactions between pollutants, with IQR increments evaluated starting at the 25th percentile for each pollutant ("Interaction," triangle markers), and multipollutant models with linear, quadratic, and cubic pollutant terms and no interactions, with IQR increments evaluated starting at the 25th percentile for each pollutant ("Nonlinear," diamond markers). For comparability with previous analyses,[22] this analysis used the year-round IQR during 1993–2004 for O_3, NO_2, CO, and SO_2, and during 1 August 1998–31 December 2004 for $PM_{2.5}$ and $PM_{2.5}$ components. The IQRs used in the analysis were: O_3, 29.18 ppb; CO, 0.66 ppm; NO_2, 12.87 ppb; SO_2, 10.51 ppb; $PM_{2.5}$, 9.18 $\mu g/m^3$; EC, 0.69 $\mu g/m^3$; SO_4^{2-}, 3.45 $\mu g/m^3$; and secondary $PM_{2.5}$, 4.52 $\mu g/m^3$. EC indicates elemental carbon component of $PM_{2.5}$; Sec PM, secondary $PM_{2.5}$; and SO_4, sulfate component of $PM_{2.5}$. Secondary $PM_{2.5}$ was calculated as the sum of the concentrations of selected $PM_{2.5}$ components including NO_3^-, NH_4^+, and SO_4^{2-}.

sensitivity analyses showed that an assumption of linear pollutant effects (on the log scale) may be inadequate. We observed statistical evidence for the importance of the quadratic and cubic terms in some cases (particularly the secondary, oxidant gases, and criteria pollutants combinations in the cold season). Violation of the assumption of a log-linear effect of pollutant concentration across each pollutant's concentration range could be magnified in a joint-effect model because the assumption is made for several pollutants. Decisions also need to be made about which interactions to consider and how to include those interactions in the model (ie, linear terms or flexible forms). In some of our models, there was statistical evidence of important interactions. Models that include interaction terms may more accurately represent joint effects than models without interaction terms, but estimates from them may be less precise due to high correlations between model terms.

Our goal was to evaluate the joint-effects approach as a method for examining air pollution mixture effects, but our analyses have limitations. Direct comparison of joint-effect magnitudes across our pollutant combinations requires caution. Our combinations were carefully selected, and provided a good framework for examining issues surrounding quantification of joint effects, but they were selected for different reasons and included different numbers of pollutants (which alone can affect joint-effect magnitudes). Some pollutants were in multiple combinations, which can contribute to similarities in observed joint effects. In addition, for combinations selected based on common sources, our results should be viewed as estimates of the joint effects of selected pollutants from shared sources and not as the total effects of those sources per se. Finally, results of time-series studies of acute air pollution health effects can be sensitive to model specification decisions other than those related to air pollutants. Our basic model was used in a previous study of acute air pollution effects on pediatric asthma;[22] that paper presented several sensitivity analyses (controlling for pollen levels, not controlling for nonasthma upper respiratory infection emergency department visit counts, and using 3 alternate methods for time trend control), which indicated that the basic model was robust.[22]

Some previous studies have used multipollutant models to calculate joint effects of pollutant combinations on pediatric respiratory outcomes, using approaches similar to ours. An analysis of prerandomization phase data from an asthma management study included estimation of the joint effect of pairs of common air pollutants on pediatric asthma exacerbations.[20] In that study, the strongest single-pollutant model effect estimates were observed for CO and NO_2. Joint-effect estimates from models including CO and NO_2 were closer to the strongest single-pollutant model effect estimates than to an effect estimate based on the sum of single-pollutant model effects. A study of the associations of $PM_{2.5}$ and of O_3 with peak expiratory flow among children in Mexico City found that both pollutants were associated with decreased peak expiratory flow, but the joint effect (per IQR change) of the 2 pollutants was lower than the sum of their effects from single-pollutant models.[17]

Other studies have considered air pollutant joint effects in relation to other outcomes. Roberts[18] and Roberts and Martin[19] modeled the total acute effect of PM_{10}, O_3, NO_2, SO_2, and CO on mortality using time-series models that calculated the overall effect of the pollutants (per standard deviation change in each pollutant), estimating the relative contribution of each pollutant to the overall effect through pollutant weights. Burnett et al[16] studied the associations of particulate and gaseous air pollutants with cardiorespiratory hospitalizations in Toronto, Canada, and calculated the total effect (for a change in each pollutant equal to its mean value) of pollutants selected using a forward-selection procedure. In a separate study, Burnett et al[15] examined the association between daily ambient air pollution and mortality in 8 Canadian cities. They presented single-pollutant and joint effects (for a change in each pollutant equal to its mean value) for $PM_{2.5}$ and $PM_{10-2.5}$ and for a combination of 4 gases (O_3, CO, SO_2, and NO_2). They reported that the joint effect for the gases calculated in this way was greater than the joint effects for the particles. Jerrett et al[21] examined the "cumulative risk index" (calculated as for our joint effects) for long-term exposure to O_3, $PM_{2.5}$, and NO_2 in relation to cardiovascular mortality. They found that the joint effect from a 2-pollutant model was larger than the joint effect calculated based on single-pollutant model results. Many other studies have considered multipollutant models but have focused on single-pollutant effects, controlling for other pollutants, rather than on joint effects.[23,30,32,33]

One reason the approach used in our analyses has not been more commonly used is concern that collinearity (also called concurvity in nonlinear models) can lead to instability in effect estimates.[1] Collinearity can lead to inflation of the estimated variances of effect estimates,[34] and the degree of collinearity in time-series models of air pollution health effects can be substantial.[28] Given the need to control for confounding by variables, such as temperature, that are highly correlated with pollutant concentrations, some degree of

collinearity is inevitable in time-series studies of air pollution health effects. However, collinearity must be considered in relation to power.[35] Our study used a long time series (6 years) with fairly high daily event counts, leading to ample power.[36] This may allow for a higher degree of collinearity with less adverse impact on model performance than would be the case for a study with a shorter time series or lower average daily counts. Effect-estimate variances in our models did not appear severely inflated, providing some reassurance that concurvity was not excessive in relation to our study size. Nevertheless, when considering our results, one should recognize that pollutants vary in the degree to which they demonstrate collinearity with other variables in the model.[28] This can lead to better power for detection of effects of some pollutants, or pollutant combinations, than others.[36]

Recognition of the importance of air pollution mixtures has led to increased interest in air pollution cumulative risk assessments (eg, a recent risk assessment for $PM_{2.5}$ and O_3).[37] Cumulative risk assessment considers the combined impact of multiple stressors on health outcomes, with consideration of potential interactions between stressors.[38,39] Epidemiologic studies like this one can contribute to cumulative risk assessments,[40] by providing dose–response functions. To be most useful for risk assessments, epidemiologic studies must present dose–response estimates for the same multipollutant contrasts considered in the risk assessment or pollutant effect estimates from multipollutant models with their variance–covariance matrix to allow adaptation of results to other contrasts.[14,40] Our consideration of only commonly measured pollutants may facilitate use of our results in risk assessment. We have included information relevant to risk assessment in our supplementary material (http://links.lww.com/EDE/A804). However, individual-pollutant effect estimates presented in our supplementary material are subject to the issues discussed above relating to confounding and measurement error.

In summary, our analyses illustrate the feasibility of a straightforward approach to modeling joint effects in a study of acute air pollution health effects with a long time series and fairly high average daily outcome counts. Our results shed light on pollutant combinations that may have important acute effects on pediatric asthma emergency department visits and provide estimates (potentially useful for risk assessments) of the joint effects of those combinations. They also illustrate some of the complexities involved in calculating and interpreting joint effects of multiple pollutants. If the complexities are appropriately considered, calculation of joint effects is appealing because it transparently and explicitly specifies the contributions of various pollutants to the health effects of mixtures. This approach has promise for application to time-series analyses of joint effects of multiple pollutants in relation to various health end points in studies with sufficient power.

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