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Multipollutant modeling issues in a study of ambient air quality and emergency department visits in Atlanta

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Multipollutant models are frequently used to differentiate roles of multiple pollutants in epidemiologic studies of ambient air pollution. In the presence of differing levels of measurement error across pollutants under consideration, however, they can be biased and as misleading as single-pollutant models. Their appropriate interpretation depends on the relationships among the pollutant measurements and the outcomes in question. In situations where two or more pollutant variables may be acting as surrogates for the etiologic agent(s), multipollutant models can help identify the best surrogate, but the risk estimates may be influenced by inclusion of a second variable that is not itself an independent risk factor for the outcome in question. In this paper, these issues will be illustrated in the context of an ongoing study of emergency visits in Atlanta. Emergency department visits from 41 of 42 hospitals serving the 20-county Atlanta metropolitan area for the period 1993–2004 ($n = 10{,}206{,}389$ visits) were studied in relation to ambient pollutant levels, including speciated particle measurements from an intensive monitoring campaign at a downtown station starting in 1998. Relative to our earlier publications, reporting results through 2000, the period for which the speciated data are available is now tripled (6 years in length). Poisson generalized linear models were used to examine outcome counts in relation to 3-day moving average concentrations of pollutants of *a priori* interest (ozone, nitrogen dioxide, carbon monoxide, sulfur dioxide, oxygenated hydrocarbons, PM_{10}, coarse PM, $PM_{2.5}$, and the following components of $PM_{2.5}$: elemental carbon, organic carbon, sulfate, and water-soluble transition metals). In the present analysis, we report results for two outcome groups: a respiratory outcomes group and a cardiovascular outcomes group. For cardiovascular visits, associations were observed with CO, NO_2, and $PM_{2.5}$ elemental carbon and organic carbon. In multipollutant models, CO was the strongest predictor. For respiratory visits, associations were observed with ozone, PM_{10}, CO, and NO_2 in single-pollutant models. In multipollutant models, PM_{10} and ozone persisted as predictors, with ozone the stronger predictor. Caveats and considerations in interpreting the multipollutant model results are discussed.
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Introduction

Epidemiologic studies assessing the roles of multiple ambient air pollutants are inherently limited by a number of interrelated issues including covariation of pollutants, potential confounding by mismeasured or unmeasured pollutants (or groups of pollutants), the possibility of complex interactions among pollutants in producing health effects, the subtlety of the associations of interest, extensive exposure uncertainty, and power constraints. In this context, multipollutant models are often used in an effort to distinguish the roles of various pollutants. In the presence of differing levels of measurement error across pollutants under consideration, however, they can be biased and as misleading as single-pollutant models. Their appropriate interpretation depends on the relationships among the pollutant measurements and the outcomes in question. In situations where two or more pollutant variables may be acting as surrogates for the etiologic agent(s), multipollutant models can help identify the best surrogate, but the risk estimates may be influenced by inclusion of a second variable that is not itself an independent risk factor for the outcome in question.

To illustrate some of the issues involved in multipollutant modeling in time series studies of acute outcomes in relation to central monitor ambient air quality data, we present work from an ongoing study of emergency department visits in Atlanta, the Study of Particles and Health in Atlanta (SOPHIA). We previously published results for the time period 1993–2000, 2 years of which included speciated $PM_{2.5}$ data (Metzger et al., 2004; Peel et al., 2005). We now have data through 2004, tripling the period for which the speciated $PM_{2.5}$ data are available. For the current assessment, we focus on two large outcome groups: a respiratory diseases (RDs) group and a cardiovascular diseases (CVDs) group

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(where each outcome group represents an aggregation of several diseases of *a priori* interest), and present updated single-pollutant and selected multipollutant model results. Considerations and caveats involved in the use of multipollutant modeling are highlighted.

Methods

Ambient Air Quality Data

The air quality data available for the study have been described previously (Van Loy et al., 2000; Metzger et al., 2004; Wade et al., 2006). Briefly, for the period January 1, 1993 through December 31, 2004, we obtained daily ambient air quality data for PM_{10} mass (PM with an aerodynamic diameter less than 10 μm), ozone (O_3), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and carbon monoxide (CO) from several existing monitoring networks, including the Air Quality System (AQS, formerly the Aerometric Information Retrieval System or AIRS). Meteorologic data, including temperature and dew point temperature, were obtained from the National Climatic Data Center network. Ozone levels were not monitored during the winter months when ozone levels are low in Atlanta; the remaining pollutants were measured year-round.

Starting August 1, 1998, an extensive suite of pollutants, including PM size fractions and components, was also measured on a daily basis at the Aerosol Inhalation Epidemiology Study (ARIES) monitoring station in downtown Atlanta. From the ARIES measurements, we selected the following pollutants for this analysis *a priori*: $PM_{2.5}$ mass (PM with an aerodynamic diameter less than 2.5 μm), coarse PM (PM with an aerodynamic diameter between 2.5 and 10 μm), the $PM_{2.5}$ components sulfate, elemental carbon (EC), organic carbon (OC), and water-soluble transition metals, and oxygenated hydrocarbons (OHC).

In the data analyses performed for this study, the *a priori* metrics for the pollutants of interest were as follows: 1-h maxima for NO_2, SO_2, and CO; 8-h maximum for ozone; and 24-h averages for PM size fractions and components.

Emergency Department Data

Each of the 42 hospitals with emergency departments in the 20-county Atlanta metropolitan statistical area (MSA) agreed to contribute emergency department data for this study. Of these, 41 hospitals were able to provide usable electronic billing records for at least part of the study period.

Computerized billing records for all emergency department visits between January 1, 1993 and December 31, 2004 were collected, including the following data for each visit: primary International Classification of Diseases 9th Revision (ICD-9) diagnostic code, secondary ICD-9 diagnosis codes, age, date of birth, gender, race, and residential zip code. Only residents of the Atlanta MSA, determined by residential zip code at the time of the visit, were included in the analytic data set. Repeat visits within a single day were counted as a single visit.

For the present analysis, two outcome groups were formed: a combined CVDs group and a combined RDs group. The combined cardiovascular case group included the following groups of primary ICD-9 diagnostic codes (all two-digit extensions were used unless otherwise specified): ischemic heart disease (410–414), cardiac dysrhythmias (427), congestive heart failure (428), and peripheral vascular and cerebrovascular disease (433–437, 440, 443–445, and 451–453). The combined RDs group included: asthma (493, 786.07, and 786.09), COPD (491, 492, and 496), URI (460–465, 460.0, and 477), pneumonia (480–486), and bronchiolitis (466.1, 466.11, and 466.19).

Analytic Methods

All analyses were performed using SAS statistical software, version 9.1 (SAS Institute Inc., Cary, North Carolina, USA) unless otherwise indicated. We used Poisson generalized linear models (McCullagh and Nelder, 1989) to examine the association between ambient pollutants of *a priori* interest and counts of cardiovascular and respiratory emergency department visits. Risk ratios and 95% confidence intervals were calculated for increments of one interquartile range in the corresponding pollutant concentrations. The basic single-pollutant models had the following form:

$$\begin{aligned}\log(E(Y)) =& \alpha + \beta\,\text{pollutant} + \Sigma_k \lambda_k \text{DOW}_k + \Sigma_m \xi_m \text{season}_m \\ &+ \Sigma_n \upsilon_n \text{hospital}_n + \Sigma_p \zeta_p \text{holiday}_p + g(\gamma_1, \ldots, \gamma_N; \text{time}) \\ &+ g(\delta_1, \ldots, \delta_N; \text{temp}) + g(\eta_1, \ldots, \eta_N; \text{dew point}),\end{aligned}$$

where Y indicated the count of visits to participating emergency departments for a given day for the outcome of interest. The *a priori* models contained a 3-day moving average of pollution levels (average of 0-, 1-, and 2-day lags relative to the visits) (pollutant). Long-term temporal trends were accounted for using cubic splines with monthly knots [$g(\gamma_1,\ldots,\gamma_N$; time)]. Because ozone data were not available from November through March, models using the ozone measurements included separate time splines for each year. For the RDs outcome, additional season indicator variables (the 21st day of March, June, September, and December) were added to further control for seasonal trends (season). Cubic splines were also used to control for daily average temperature [$g(\delta_1,\ldots,\delta_N$; temp)] and dew point [$g(\eta_1,\ldots,\eta_N$; dew point)] with knots at the 25th and 75th percentiles (moving average of lags 0, 1, and 2). Indicator variables for day of week (DOW), federal holidays (holiday), and hospital entry and exit (hospital) were also included in the *a priori* model (as the hospitals provided data for varying amounts of time). The cubic splines, $g(x)$, were defined as follows:

$$g(\gamma_1, \gamma_2, \ldots \gamma_N; x) = \gamma_1 x + \gamma_2 x^2 + \gamma_3 x^3 + \sum_{j=4}^{N} \gamma_j w_j(x),$$

where $w_j(x) = (x\text{-}\tau_j)^3$ if $x \geq \tau_j$, and $w_j(x) = 0$ otherwise. The cubic splines were defined so that the first and second derivatives were continuous.

Multipollutant models used the same basic structure as the single-pollutant models, with the inclusion of two or more pollutant variable terms. To have a consistent time series for comparison of the multipollutant results, we excluded days for which measurements of any of the pollutants included in the set of models for a given outcome group were missing.

Results

With 41 of 42 hospitals providing data, the final outcome database included data regarding 10,234,490 total emergency department visits, with 238,360 and 1,072,429 included in the CVD and RD groups, respectively. The average daily counts for CVD and RD groups were 54 and 244, respectively, providing robust numbers for the time-series analysis (Table 1). Descriptive statistics for the air quality variables of interest are presented in Table 2, and a Spearman's correlation matrix for pairs of the pollutants presented in Table 3.

Results of the *a priori* single-pollutant models are presented in Table 4. For CVD, significant positive associations were found with CO, NO_2, EC, OC, and TC. For RD, associations were observed with ozone, PM_{10}, CO, and NO_2.

Results of selected multipollutant models are presented in Figures 1 and 2, on the basis of the results of the single-pollutant models. In models predicting CVD, TC was used in place of EC and OC, as relationships for each type of carbon were similar in single-pollutant models, and the use of a single carbon metric reduced the number of parameters to be fit. Restricting our multipollutant analyses to days with no missing data among all pollutants of interest, multipollutant models predicting CVD visits were limited to the 1998–2004 time period when $PM_{2.5}$ component data were available. For CVD, CO was the strongest predictor in models with two-pollutant combinations of NO_2, CO, and TC, as well as in a model including all three pollutants.

Because we restricted our multipollutant analyses to days with no missing data among all pollutants of interest, models predicting RD visits were limited to non-winter months (as ozone was not measured in winter). For RD, results of a two-pollutant model with CO and NO_2 suggested that NO_2 was a stronger predictor of RD than CO (NB: this assessment was sensitive to the exclusion of the winter months; when winter was included, CO was a stronger predictor of RD than NO_2 (data not shown)). In two- and three-pollutant models of ozone, PM_{10}, and NO_2 (or alternatively CO (model results not shown)), PM_{10} and ozone remained predictive, with ozone the stronger predictor of the two. It should be noted that while the findings for PM_{10} predicting RD appeared more robust than those for $PM_{2.5}$, this result is likely a reflection of the longer time series for which PM_{10} measurements were available, that is, 1993–2004. In the 1998–2004 data, there was no indication that $PM_{2.5}$ was less

Table 1. Total counts and mean, SD, and selected percentiles of daily counts of emergency department visits at 41 participating hospitals for the period January 1, 1993 to December 31, 2004, Study of Particles and Health in Atlanta (SOPHIA).

	Total counts	Mean daily count	Min daily count	10th % daily count	25th % daily count	Median daily count	75th % daily count	90th % daily count	Max daily count
Total ED visits	10,234,490	2335	191	619	1167	2439	3368	3785	5453
Cardiovascular diseases group (ICD-9 410–414, 427–428, 433–437, 440, 443–444, 451–453)	238,360	54	1	12	29	57	77	90	123
Respiratory diseases group (ICD-9 460–465, 460.0, 461.1, 461.11, 461.19, 477, 491–493, 496, 786.07, 786.09)	1,072,429	244	22	77	145	224	327	423	1061

ED, emergency department; ICD-9, International Classification of Diseases, 9th Revision; SD, standard deviation.

Table 2. Mean, SD, and selected percentiles of daily ambient air quality measurements for criteria pollutants from AQS/MAI during the period January 1, 1993 to December 31, 2004 and for other pollutants from ARIES during the period August 1, 1998 to December 31, 2004.

	No. of days	Mean	Minimum	10th %	25th %	Median	75th %	90th %	Maximum
January 1, 1993 to December 31, 2004									
24-h PM_{10} ($\mu g/m^3$)	4264	26.6	0.5	12.3	17.5	24.8	33.8	42.8	98.4
8-h Ozone (p.p.b.)	2935	53.0	2.9	26.1	37.3	51.0	67.0	82.1	147.5
1-h Nitrogen dioxide (p.p.b.)	4351	43.2	1.0	22.0	31.0	41.0	54.0	66.0	181.0
1-h Carbon monoxide (p.p.m.)	4275	1.6	0.1	0.5	0.8	1.3	2.0	3.0	7.7
1-h Sulfur dioxide (p.p.b.)	4358	14.9	1.0	2.0	4.0	9.0	20.0	35.0	149.0
Average temperature (°C)[a]	4383	17.1	−10.8	5.6	10.6	18.1	24.4	26.9	32.5
Average dew point (°C)[a]	4383	10.4	−19.1	−2.6	3.8	12.3	18.5	20.8	23.7
August 1, 1998 to December 31, 2004									
24-h $PM_{2.5}$ ($\mu g/m^3$)	2291	17.1	0.8	7.9	11.0	15.6	21.9	28.8	65.8
24-h coarse PM ($\mu g/m^3$)	2183	9.0	0.5	3.6	5.6	8.2	11.5	15.1	50.3
24-h $PM_{2.5}$ sulfate ($\mu g/m^3$)	2135	4.9	0.5	1.7	2.4	3.9	6.2	9.5	21.9
24-h $PM_{2.5}$ organic carbon ($\mu g/m^3$)	2259	4.4	0.4	2.1	2.7	3.8	5.3	7.2	25.9
24-h $PM_{2.5}$ elemental carbon ($\mu g/m^3$)	2258	1.6	0.1	0.6	0.9	1.3	2.0	3.0	11.9
24-h $PM_{2.5}$ water-soluble metals ($\mu g/m^3$)	2138	0.030	0.003	0.009	0.014	0.023	0.039	0.059	0.202
24-h oxygenated hydrocarbon (p.p.b.)	1890	29.2	0.7	12.2	18.4	27.6	37.8	48.6	91.6

AQS, Air Quality System; ARIES, Aerosol Research and Inhalation Epidemiology Study; PM, particulate matter.
[a]For temperature and dew point: average of minimum and maximum values recorded at Hartsfield-Atlanta International Airport.

Table 3. Spearman's correlation coefficients for pollutant measurements, 1993–2004, study of particles and health in Atlanta (SOPHIA).

	PM_{10}	O_3	NO_2	CO	SO_2	Coarse PM	$PM_{2.5}$	SO_4	EC	OC	TC	Water-sol metals	OHC
PM_{10} (24-h)	1.00												
O_3 (8-h)	0.59	1.00											
NO_2 (1-h)	0.53	0.44	1.00										
CO (1-h)	0.51	0.27	0.70	1.00									
SO_2 (1-h)	0.21	0.21	0.36	0.28	1.00								
Coarse PM (24-h)	0.67	0.36	0.48	0.38	0.16	1.00							
$PM_{2.5}$ (24-h)	0.84	0.62	0.47	0.47	0.17	0.47	1.00						
$PM_{2.5}$ SO_4 (24-h)	0.69	0.56	0.14	0.14	0.09	0.32	0.76	1.00					
$PM_{2.5}$ EC (24-h)	0.61	0.40	0.64	0.66	0.22	0.49	0.65	0.32	1.00				
$PM_{2.5}$ OC (24-h)	0.65	0.54	0.62	0.59	0.17	0.49	0.70	0.33	0.82	1.00			
$PM_{2.5}$ TC (24-h)	0.67	0.52	0.65	0.63	0.19	0.51	0.71	0.34	0.91	0.98	1.00		
$PM_{2.5}$ water-sol metals (24-h)	0.73	0.43	0.32	0.35	0.06	0.50	0.69	0.65	0.52	0.49	0.52	1.00	
OHC (24-h)	0.53	0.37	0.24	0.29	0.05	0.41	0.50	0.47	0.35	0.37	0.38	0.48	1.00

CO, carbon monoxide; EC, elemental carbon; NO_2, nitrogen dioxide; O_3, ozone; OC, organic carbon; OHC, oxygenated hydrocarbons; PM, particulate matter; SO_2, sulfur dioxide; SO_4, sulfate; TC, total carbon.

associated with respiratory outcomes than coarse PM. In addition, the association of PM_{10} with respiratory outcomes was weaker when analyses were restricted to the 1998–2004 time period.

Discussion

The uses and interpretation of multipollutant models vary depending on the relationship of pollutants to each other and to the outcome of interest. For example, consider several possible scenarios with respect to two-pollutant models. If the two pollutants are thought to be independent risk factors for the outcome in question, and are correlated with each other (positively or negatively), then it may be appropriate to use a two-pollutant model to adjust the effect estimate of each pollutant for confounding by the other pollutant. While it should be kept in mind that there may be residual confounding as a result of model mis-specification or measurement error, the risk estimates from this model are likely to be more valid than those from each pollutant's single-pollutant model. In a second scenario, if one of the pollutants is etiologically linked to the outcome and the second pollutant is a surrogate for the first pollutant,

Table 4. Results of *a priori* models[a] for the association of emergency department visits for cardiovascular disease and respiratory disease with daily ambient air quality measurements, 1993–2004, Study of Particles and Health in Atlanta (SOPHIA).

Pollutant (IQR)[b]	IQR	CVD	RD
		RR per IQR (95% CI)	*RR per IQR (95% CI)*
January 1, 1993 to December 31, 2004			
24-h PM_{10}	16.30 $\mu g/m^3$	1.008 (0.997–1.020)	1.015 (1.006–1.024)
8-h ozone	29.75 p.p.b.	1.000 (0.982–1.019)	1.039 (1.027–1.052)
1-h nitrogen dioxide	23.00 p.p.b.	1.015 (1.004–1.025)	1.015 (1.004–1.025)
1-h carbon monoxide	1.22 p.p.m.	1.020 (1.010–1.030)	1.016 (1.009–1.022)
1-h sulfur dioxide	16.00 p.p.b.	1.003 (0.994–1.011)	1.003 (0.997–1.009)
August 1, 1998 to December 31, 2004			
24-h $PM_{2.5}$	10.96 $\mu g/m^3$	1.005 (0.993–1.017)	1.005 (0.995–1.015)
24-h coarse PM	5.89 $\mu g/m^3$	1.004 (0.990–1.019)	0.983 (0.972–0.995)
24-h $PM_{2.5}$ sulfate	3.82 $\mu g/m^3$	0.999 (0.987–1.011)	1.007 (0.996–1.018)
24-h $PM_{2.5}$ total carbon	3.63 $\mu g/m^3$	1.016 (1.005–1.026)	1.001 (0.993–1.008)
24-h $PM_{2.5}$ organic carbon	2.61 $\mu g/m^3$	1.015 (1.005–1.026)	1.003 (0.995–1.011)
24-h $PM_{2.5}$ elemental carbon	1.15 $\mu g/m^3$	1.015 (1.005–1.025)	0.996 (0.989–1.004)
24-h $PM_{2.5}$ water-soluble metals	0.03 $\mu g/m^3$	1.009 (0.997–1.021)	1.005 (0.995–1.015)
24-h oxygenated hydrocarbon	19.40 $\mu g/m^3$	1.009 (0.991–1.028)	0.990 (0.975–1.004)

CI, confidence interval; CVD, cardiovascular disease; IQR, inter-quartile range; PM, particulate matter; RD, respiratory disease; RR, risk ratio.
[a]Single-pollutant generalized linear models including indicators for day-of-week, hospital entry and holidays; cubic splines for time, temperature and dew point temperature.
[b]Three-day moving average.

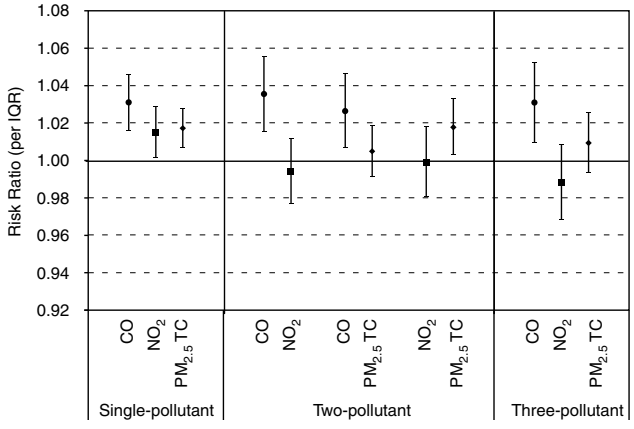

Figure 1. Results of selected multipollutant models for combined cardiovascular diseases group, 1998–2004, Study of Particles and Health in Atlanta (SOPHIA). CO, carbon monoxide; IQR, inter-quartile range; NO_2, nitrogen dioxide; PM, particulate matter; TC, total carbon. Models shown include only days on which CO, NO_2, $PM_{2.5}$, and TC are all non-missing. The single-pollutant results therefore are not identical to the single-pollutant results presented in Table 4.

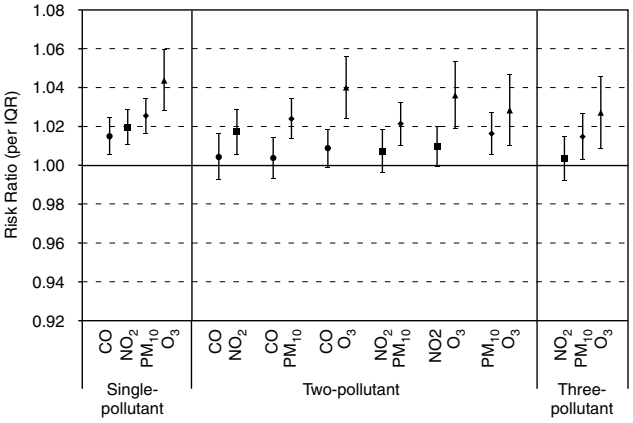

Figure 2. Results of selected multipollutant models for combined respiratory diseases group, 1993–2004, Study of Particles and Health in Atlanta (SOPHIA). CO, carbon monoxide; IQR, inter-quartile range; NO_2, nitrogen dioxide; O_3, ozone; PM, particulate matter. Models shown include only days on which CO, NO_2, PM_{10}, and O_3 are all non-missing. The single-pollutant results therefore are not identical to the single-pollutant results presented in Table 4.

the two-pollutant model is only useful for determining which pollutant is the better predictor of the outcome. If the etiologic agent is measured with substantially more error than the surrogate (e.g., because of spatial variation or analytic error), measurements of this agent may be less predictive than those of the surrogate, leading to potentially misleading conclusions if the model is interpreted causally. Finally, in a third scenario in which both pollutants are thought to be surrogates for an etiologic agent, a multipollutant model may be helpful in determining which of the two pollutants is the better surrogate. The risk estimates from models in both the second and third scenarios, however, are biased by the inclusion of the second pollutant variable that is correlated with the first pollutant, but is not an independent risk factor; thus, in these scenarios, risk estimates obtained from

single-pollutant models will be better estimates of the relationship of the risk factor (or surrogate) with the health outcome.

The Atlanta emergency department study provides the opportunity to apply this type of assessment to epidemiologic model results. The predictors of interest for multipollutant models of CVD were based on significant positive single-pollutant model results and included NO_2, CO, and fine particle EC, OC, and TC. TC was chosen as a combined EC and OC metric in all CVD multipollutant models, as described earlier. The three resulting predictors, NO_2, CO, and TC, are all known to be markers of motor vehicle emissions. While diesel and gas engines both emit all three pollutants, gas engines emit relatively more CO and diesel exhaust is richer in EC and NO_x. Spearman's correlation coefficients between NO_2, CO, and TC concentrations were moderate, in the range of 0.60–0.70. While it is conceivable that all three pollutants are independent risk factors for CVD, it is also plausible that some or all of these pollutants are related to CVDs only through their correlation with other agents in vehicle exhaust. In such a case, the two- or three-pollutant models can assist in identifying which of the predictors is the best surrogate for traffic emissions, as evidenced by the strongest association with the outcome. In our analysis, we found that for CVD, CO was the strongest predictor in models with two-pollutant combinations of NO_2, CO, and TC, as well as in a model including all three pollutants. Several scenarios are consistent with this observation. For instance, these results could have been obtained if TC is etiologically linked to the outcome and CO is associated with the outcome only by virtue of being a marker of TC, and ambient CO levels measured at a central monitor are more correlated with personal exposure to TC of ambient origin than ambient TC. Spatial variation for these motor vehicle-related pollutants is substantial, but because traffic tends to have citywide temporal variation, there is at least moderate temporal correlation in levels of each of these pollutants across space (Wade et al., 2006). Of these three pollutants, CO appears to be most reliably measured in the Atlanta data based on collocation studies (Wade et al., 2006), suggesting that differential measurement error may partly explain our multipollutant CVD results. Rather than being itself responsible for the CVD association, CO may be operating as the best surrogate of vehicular emissions in this context. USEPA's most recent carbon monoxide criteria document concluded that ambient carbon monoxide at levels typically found in US cities is unlikely to have detrimental effects in healthy individuals, based largely on evidence from controlled-exposure studies (USEPA, 2000). Levels such as those observed in Atlanta (mean 1-h level of 1.6 p.p.m. and maximum 1-h level of 7.7 p.p.m. during our study period) would not be expected to impact carboxy-hemoglobin levels appreciably. Thus, while some subpopulations, such as those with coronary heart disease, may be particularly susceptible to reduction of oxygen-carrying capacity of the blood, and certain microenvironments can have substantially higher levels than those reported at AQS monitoring sites, there is a reasonable possibility that ambient carbon monoxide is operating as a surrogate of other components of traffic emissions.

For RD, multipollutant analyses included combinations of CO, NO_2, PM_{10}, and ozone, based on positive single-pollutant model results for these pollutants. These analyses, therefore, included two pollutants associated with vehicle exhaust (i.e., CO and NO_2), a heterogeneous pollutant comprised of both primary and secondary species (i.e., PM10), and a secondary pollutant formed largely from photooxidation of other pollutants, including NO_2 (i.e., ozone). These pollutants were weakly to moderately positively correlated with each other in our data, with Spearman's correlation coefficients ranging from 0.27 for ozone and CO to 0.70 for NO_2 and CO. In multipollutant models, PM_{10} and ozone remained predictive, with ozone the stronger predictor of the two. Ozone is the least spatially varying of all the pollutants under consideration in the RD models, and measurements at the central monitor are broadly representative of ozone levels throughout the study area (Wade et al., 2006). As such, differential measurement error among the four pollutants of interest may also partly explain our multipollutant RD results. In addition, it is possible that at least part of the observed association of ozone with respiratory outcomes is mediated through ambient ozone measurements operating as a surrogate for personal PM exposure (Sarnat et al., 2001), and may explain the stronger association of ozone with RD compared to PM_{10}. On the other hand, ozone is known to have direct adverse pulmonary effects based on chamber studies with human volunteers (e.g., Adams, 2002), and thus an association with ozone itself is biologically plausible. These results highlight the uncertainty and potential for misinterpretation associated with multipollutant modeling.

Generally, the extension of the time series for an additional 4 years led to more stable risk estimates, and the observed associations are consistent with those observed in the earlier analysis (Metzger et al., 2004; Peel et al., 2005). For the two case groups examined here, we found no additional pollutant associations compared to our previous analyses. As before, EC and OC continued to be the fine particle species most strongly associated with the combined CVD outcome group.

Source apportionment has been proposed as an approach for dealing with some of the challenges of studying the roles of multiple pollutants, particularly in the case of PM components. While source apportionment introduces an additional layer of uncertainty into epidemiologic analyses and results in a loss of specificity, it is complementary to more traditional modeling approaches. In the Atlanta study, $PM_{2.5}$ source apportionment work corroborates the

impression provided by the single-pollutant models that CVD visits are related to vehicular emissions (both diesel and gasoline) (Kim et al., 2003, 2004; Marmur et al., 2005, 2006; Sarnat et al., 2006). Reports on these and a number of other analyses of the Atlanta data, including spatial subanalyses and assessment of measurement error impacts, are forthcoming.

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