

Gaseous Pollutants in Particulate Matter Epidemiology: Confounders or Surrogates?

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Air pollution epidemiologic studies use ambient pollutant concentrations as surrogates of personal exposure. Strong correlations among numerous ambient pollutant concentrations, however, have made it difficult to determine the relative contribution of each pollutant to a given health outcome and have led to criticism that health effect estimates for particulate matter may be biased due to confounding. In the current study we used data collected from a multipollutant exposure study conducted in Baltimore, Maryland, during both the summer and winter to address the potential for confounding further. Twenty-four-hour personal exposures and corresponding ambient concentrations to fine particulate matter (PM_{2.5}), ozone, nitrogen dioxide, sulfur dioxide, and carbon monoxide were measured for 56 subjects. Results from correlation and regression analyses showed that personal PM_{2.5} and gaseous air pollutant exposures were generally not correlated, as only 9 of the 178 individual-specific pairwise correlations were significant. Similarly, ambient concentrations were not associated with their corresponding personal exposures for any of the pollutants, except for PM_{2.5}, which had significant associations during both seasons ($p < 0.0001$). Ambient gaseous concentrations were, however, strongly associated with personal PM_{2.5} exposures. The strongest associations were shown between ambient O₃ and personal PM_{2.5} ($p < 0.0001$ during both seasons). These results indicate that ambient PM_{2.5} concentrations are suitable surrogates for personal PM_{2.5} exposures and that ambient gaseous concentrations are surrogates, as opposed to confounders, of PM_{2.5}. These findings suggest that the use of multiple pollutant models in epidemiologic studies of PM_{2.5} may not be suitable and that health effects attributed to the ambient gases may actually be a result of exposures to PM_{2.5}. **Key words:** air pollution, carbon monoxide, confounding, exposure error, personal exposure, PM_{2.5}, nitrogen dioxide, ozone, sulfur dioxide. *Environ Health Perspect* 109:1053–1061 (2001). [Online 27 September 2001] <http://ehpnet1.niehs.nih.gov/docs/2001/109p1053-1061sarnat/abstract.html>

Daily variations in air pollution have been associated with daily variations in deaths and hospital visits in a large number of locations around the world (1–3). Of the criteria air pollutants, the strongest and most consistent associations have been found for ambient particulate matter. Because ambient particle levels are often correlated with ambient concentrations of other gaseous pollutants, it is possible that the observed associations between particles and adverse health effects may be due to confounding by other correlated pollutants and not to the fine particles themselves (4,5).

The issue of confounding in air pollution epidemiology has been examined in several large multicity studies (6,7). These studies proceeded on the assumption that the best way to assess the independent effects of two or more pollutants is to include the pollutants in the regression model at the same time. Samet et al. (6), for example, analyzed ambient air pollution [particulate matter $\leq 10 \mu\text{m}$ (PM₁₀), ozone, nitrogen dioxide, carbon dioxide, and sulfur dioxide] and daily mortality data from 20 cities with varying pollution profiles and found PM₁₀ to be a significant predictor of daily mortality controlling for the gaseous copollutants. Schwartz (7) examined 10 cities separately during the summer and

winter and reported identical associations between daily mortality and PM₁₀. Because the relationship among ambient PM₁₀ and its copollutants differed substantially by season, the observed identical summer and winter associations were offered as compelling evidence that particle associations were not affected by confounding from other pollutants. Similarly, Fairley (8) examined the relationship between ambient PM_{2.5}, PM₁₀, PM_{2.5–10}, sulfate, CO, O₃, and NO₂ and corresponding mortality. Fairley observed significant associations for numerous pollutants when the pollutants were examined individually. When the gaseous pollutants were examined along with PM_{2.5}, the significant associations for the gases disappeared, while the association for PM_{2.5} became stronger; this suggests that fluctuations in ambient PM_{2.5} concentrations are driving the health effect associations. All of these epidemiologic studies conducted to date, however, have investigated the potential for confounding using ambient pollutant concentrations, as none were able to include information about the personal exposures to the various air pollutants.

Information concerning personal exposures is critical to our ability to determine whether confounding is a potential problem within epidemiologic studies. The coefficient

for PM_{2.5} represents the independent effect of particles controlling for the other pollutant in a two-pollutant model, if each ambient pollutant measurement is a surrogate for actual exposures to that same pollutant. We began to examine the relationship between ambient pollutant concentrations and corresponding personal exposures and its copollutants in our exposure study of older adults living in Baltimore, Maryland (9). Results from this study showed that, despite significant associations among the ambient pollutant concentrations, personal exposures to PM_{2.5} were not significantly correlated with personal exposures to any of its copollutants, including O₃, NO₂, and PM_{2.5–10}. Moreover, personal PM_{2.5} exposures were significantly associated with its corresponding ambient concentrations, but the personal ambient associations were not significant for O₃, NO₂, or PM_{2.5–10}. These findings suggest that for this Baltimore cohort, true confounding of PM_{2.5} by its copollutants is implausible and that ambient PM_{2.5} concentrations are reasonable surrogates of their personal PM_{2.5} exposures.

In this study, we further evaluated the role of ambient O₃, NO₂, SO₂, and CO as confounders of ambient PM_{2.5} using data from the Baltimore study of older adults and using additional data collected in Baltimore for individuals with chronic obstructive pulmonary disease (COPD) and children. Our goal, in particular, was to understand for which exposure each ambient measurement was a surrogate.

Methods

Personal multipollutant exposures and corresponding ambient concentrations were measured for 56 subjects (three cohorts: 20 older adults, 21 children, and 15 individuals with COPD) living in the metropolitan Baltimore

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area. All subjects included in this analysis were nonsmokers and lived in nonsmoking private residences (i.e., either single-family houses or apartments). Sampling was conducted during the summer (29 June–23 August 1998) and winter (2 February–13 March 1999). Fourteen of 56 subjects participated in both sampling seasons. During both the summer and winter sampling periods, subjects included older adults and children. Subjects from the older adult cohort consisted of retired, healthy adults with an average age (\pm SD) of 75 ± 6.8 years. Subjects from the children's cohort consisted of healthy schoolchildren between 9 and 13 years of age. During the winter, personal exposures for individuals with COPD were also measured along with the older adults and children. Subjects from the COPD cohort consisted of individuals with physician-diagnosed moderate-to-severe COPD with an average age of 65 ± 6.6 years. Although the subjects were from a range of socioeconomic backgrounds and geographic locations within Baltimore, subject selection was random and was not intended to be representative of sensitive populations in general. Subjects completed and returned informed consent forms before their participation in the study.

All subjects were monitored for 12 consecutive days in each of the one or two seasons, with the exception of children who, during the summer, were measured for 8 consecutive days. We measured 4–16 subjects during each 12-day monitoring period. A total of 800 person-days of exposure data were collected for some of the following pollutants: $PM_{2.5}$, PM_{10} , O_3 , NO_2 , SO_2 , elemental carbon (EC), organic carbon (OC), and volatile organic compounds (VOCs; Table 1). Because PM_{10} and VOCs were only sampled for the older adult cohort and there were questions concerning the precision of the OC measurements, these exposures were not included in this analysis.

A subset of $PM_{2.5}$ filters was analyzed for SO_4^{2-} concentration. For these filters, personal exposure to $PM_{2.5}$ of ambient origin was estimated using the expression:

$$\left(\frac{[SO_4^{2-}]_{\text{personal},ij}}{[SO_4^{2-}]_{\text{ambient},j}} \right) \cdot [PM_{2.5}]_{\text{ambient},j}$$

where $personal_{ij}$ represents the personal exposure to SO_4^{2-} for subject i on day j , and $ambient_j$ represents the ambient concentration measured at the stationary site on day j . The effective penetration of ambient $PM_{2.5}$ to personal exposures for all fine particles was assumed to equal that for SO_4^{2-} . Since recent studies have shown that fine particle deposition rates and penetration efficiencies

vary by particle size and other factors such as air exchange rates (10), SO_4^{2-} -based estimates used in the current study provide only an indication of exposure to $PM_{2.5}$ of ambient origin rather than a definitive value. With the exception of NO_2 , the gaseous copollutants measured during the study were primarily (if not exclusively) ambient in origin. To estimate exposures to NO_2 of ambient origin, analyses involving personal NO_2 exposures were performed by controlling for the potential nonambient contributions from gas stoves, the primary nonambient source of NO_2 for these cohorts.

Personal exposure samples were collected using a specially designed multipollutant sampler that consisted of personal environmental monitors (PEMs) to collect $PM_{2.5}$, PM_{10} , EC, and OC; sorbent tubes filled with activated carbon to collect VOCs; and passive samplers to collect O_3 , NO_2 , and SO_2 . Subjects were permitted to remove the sampler during prolonged periods of inactivity (i.e., sleeping, watching television) and during activities when the sampler could be damaged (i.e., showering, intense physical activity). When the sampler was removed from the subject's body, subjects were instructed to keep the sampling inlets as close as possible to their breathing zone. The design and performance of this sampler have been described, in detail, elsewhere (9,11).

We measured 24-hr integrated ambient $PM_{2.5}$ and PM_{10} concentrations using Harvard Impactors at a centrally located site. Continuous ambient $PM_{2.5}$ mass concentrations were obtained from a pair of $PM_{2.5}$ tapered element oscillating microbalances (TEOMs; model 1400A; Rupprecht & Patashnick, Co., Inc., Albany NY) operated by the Maryland Department of the Environment. Ambient O_3 , NO_2 , SO_2 , CO, and VOC data were obtained from local stationary ambient monitoring sites operated by the Maryland Department of the Environment for monitoring citywide pollutant concentrations. Additional ambient $PM_{2.5}$ concentrations were obtained from the U.S. Environmental Protection Agency that was collected as part of a personal exposure study (12). O_3 , NO_2 , SO_2 , and CO were measured using UV photometric analyzers, chemiluminescence monitors, pulsed fluorescent monitors, and nondispersive infrared monitors, respectively. All of the participants' residences were located within an approximately 40-km radius from each of the stationary sites which were located either within the city of Baltimore or Baltimore County. $PM_{2.5}$ concentrations were obtained from the Old Town monitoring station; O_3 from the Living Classroom, and Essex monitoring stations during the summer and from the Essex monitoring stations during the winter;

NO_2 from the Old Town, Living Classroom, and Essex stations during the summer and from the Old Town and Essex stations during the winter; SO_2 from the Rivera Beach monitoring station; and CO from the Old Town monitoring station. In cases where pollutant concentrations were measured at multiple sites, concentrations were averaged across the sites. Additional data collected included daily time-activity diaries and household characteristic surveys that provided supplemental information relating to pollutant exposures.

Standard quality assurance procedures were followed for this study (13). We assessed collected data for bias, precision, and completeness. Completeness for personal $PM_{2.5}$, O_3 , NO_2 , SO_2 , SO_4^{2-} , and EC was 92, 83, 90, 91, 91 and 91%, respectively. Completeness for the ambient pollutant concentrations was > 98% for all of the sampled pollutants. Precision, accuracy, and limit of detection information are detailed in Chang et al. (11) and Sarnat et al. (9). All samples were field-blank corrected. Teflon PEM filters were also corrected for barometric pressure.

Sampler measurement error (sampler error) was calculated by collocating replicate, fully configured sampling packs for 24 hr (\pm 10%). Sampler error was estimated as the root mean squared difference of the collocated samplers, divided by the square root of two, divided by the mean concentration of the samples. Based on precision data from this study and previous studies, we assumed that precision was relative and that sampler error values for the outdoor range of concentrations applied to the entire range of personal exposure concentrations (9).

Correlation of sampler error in the dependent and independent variables was assumed to be independent of each other, a valid assumption based on previous laboratory and field characterization tests (14). In univariate regression analysis (such as the mixed-model approach used in the current analysis) sampler error in the dependent

Table 1. Sampling plan.

Cohort	Older adults	COPD	Children
Season			
Summer (<i>n</i>)	15		10
Winter (<i>n</i>)	15	15	15
Sampling duration (days and season)	12	12	8 (summer) 12 (winter)
Pollutants			
$PM_{2.5}$	✓	✓	✓
PM_{10}	✓		
O_3	✓	✓	✓
NO_2	✓	✓	✓
SO_2	✓	✓	✓
VOCs	✓		
EC/OC		✓	✓(winter only)
CO	(ambient measurements only)		

variable may lead to biased correlations between the variables but will not bias the estimates of slope or intercept (15). Sampler error in the independent variable, on the other hand, may bias estimates of the slope and intercepts as well as reduce model sensitivity. To account for the effects of this error, we corrected the slope by adjusting the variance associated with the sampler error:

$$\hat{\beta}_{\text{true}} = \hat{\beta}_{\text{obs}} \left(\frac{\hat{\sigma}_{\text{obs}}^2}{\hat{\sigma}_{\text{true}}^2} \right), \quad [1]$$

where $\hat{\beta}_{\text{true}}$ is the slope of the regression corrected for sampler error, $\hat{\beta}_{\text{obs}}$ is the slope of the observed or naïve regression results, $\hat{\sigma}_{\text{obs}}^2$ is the variance of the observed exposures or concentrations, and $\hat{\sigma}_{\text{true}}^2$ is the estimated observed variance of the exposures or concentrations minus the estimated variance attributable to sampler error. The true standard error of the mixed-model slope (i.e., the estimated standard error minus the fraction attributable to sampler error) can be estimated using the delta method, which is expressed in Equation 2 (15) where $\hat{SE}(\hat{\beta}_{\text{true}})$ is the estimated standard error of the true slope of the regression, $\hat{Var}(\hat{\beta}_{\text{true}})$ is the estimated variance of the true slope of the regression, and $\hat{Var}(\hat{\beta}_{\text{obs}})$ is the estimated variance of the observed slope of the regression. The true significance of the slope was subsequently determined as the $(\hat{\beta}_{\text{true}})$ divided by $\hat{SE}(\hat{\beta}_{\text{true}})$.

Data analysis. Units for $\text{PM}_{2.5}$, SO_4^{2-} and EC concentrations and exposures are reported in micrograms per cubic meter. Units for O_3 , NO_2 , and SO_2 concentrations and exposures are reported in parts per billion. Units for CO concentrations and exposures are reported in parts per million. Negative values for the gaseous pollutants as well as values less than their respective limits of detection were included in the data analyses as measured to avoid bias in estimating relations among measurements (16). Graphical techniques and Shapiro-Wilks tests for normality indicated that most of the pollutants were normally or nearly normally distributed.

We examined four sets of associations to assess the relationship between $\text{PM}_{2.5}$ and its copollutants, including the association between a) ambient $\text{PM}_{2.5}$ concentrations

and ambient copollutant concentrations; b) ambient pollutant (both $\text{PM}_{2.5}$ and copollutants) concentrations and their respective personal exposures; c) personal $\text{PM}_{2.5}$ exposures and personal copollutant exposures; and d) ambient copollutant concentrations and personal $\text{PM}_{2.5}$ exposures. In addition, models using $\text{PM}_{2.5}$ components, such as SO_4^{2-} , EC, and $\text{PM}_{2.5}$ of ambient origin were examined to identify factors that may affect the above associations.

Analyses of the associations between ambient $\text{PM}_{2.5}$ concentrations and ambient pollutant concentrations were conducted using univariate time-series regression analysis assuming a first-order autoregressive structure for the error. Because personal exposures were measured repeatedly for each subject, analyses of personal exposure data were conducted using mixed models and individual-specific Spearman's correlation coefficients (r_s). Pollutant exposures and concentrations were modeled as fixed-effects variables, and subjects were modeled as random variables to account for between subject variation. Models were fitted using a compound symmetry covariance matrix which yielded the lowest Akaike Information Criteria diagnostic values compared with other covariance matrices examined (e.g., autoregressive, banded toeplitz). Data from the three cohorts were analyzed in aggregate, with the exception of cases where significant differences in associations among the cohorts were found. It should be noted that, due to the intrasubject correlation, coefficients of determination (R^2) or other measures of scatter are not statistically valid and are, therefore, not reported. Consequently, strength of association was determined by the significance of the slope of the mixed models. Distributions of individual-specific r_s values are also reported as another indicator of the strength of the observed associations. The primary objective of the analysis was to examine the predictive power of a single pollutant exposure or concentrations for other exposures or concentrations. Therefore, the models are almost exclusively univariate models with the sole exception being models that control for the impact of indoor NO_2 contributions from gas stoves, which have a cooking-fuel interaction term. All of the above analyses were

computed using SAS software (SAS Institute, Cary, NC). Statistical significance is reported at the 0.05 level unless otherwise specified.

Exclusion of data points. Data points were voided due to sampling problems (e.g., pump or battery failures, tube disconnection) or laboratory analysis irregularities. Time-activity data indicated that two subjects (one older adult who participated during both sampling periods and one child who participated during the summer sampling period) were heavily exposed to environmental tobacco smoke (ETS) throughout the course of their participation in the study. Days of heavy or prolonged exposure to ETS were not included in the analyses, since collected samples did not typify exposures for a nonsmoker or someone living in a residence with nonsmokers.

Results

Summary statistics for the measured ambient concentrations and personal exposures, stratified by season and by cohort are presented in Figure 1. A summary of household characteristic and time activity data is presented in Table 2. In general, cohort-specific differences in household characteristics and time-activity patterns were not apparent, which may be due to the relatively small size of each cohort. There were, however, a number of observed differences that varied by cohort, but these were probably not specifically related to cohort affiliation. Most of the monitored children and individuals with COPD lived in single-family houses (35 of 40 subjects), whereas subjects from the older adult cohort lived equally in apartments (18 of 30 subjects) and single-family homes. Approximately one-half of the subjects (34 of 69) lived in residences with gas stoves, a potential source of NO_2 and CO, although few participants spent substantial periods of time cooking. Time-activity diary results showed that older adult subjects spent less than 2% of the day, on average, engaged in stove-related cooking activities. Only three of the subjects lived in residences with attached garages, another potential source of $\text{PM}_{2.5}$, CO, and NO_2 . Similarly, there were approximately an equal number of subjects from each cohort living near (100 yards) busy roads. Few subjects indicated on their time-activity diaries any exposure to ETS during their respective sampling periods. Older adults and children spent similar fractions of time outdoors during the summer (4.7% and 5.7% of the day, respectively). Time spent outdoors during the winter was not examined but was assumed to be limited for all subjects.

Are ambient copollutant concentrations significantly associated with ambient $\text{PM}_{2.5}$ concentrations? Significant associations were found between ambient $\text{PM}_{2.5}$ and corresponding ambient copollutant concentrations

$$\begin{aligned} \hat{SE}(\hat{\beta}_{\text{true}}) &= \sqrt{\hat{Var}(\hat{\beta}_{\text{true}})} \\ &= \sqrt{\left(\frac{\hat{\sigma}_{\text{obs}}^2}{\hat{\sigma}_{\text{true}}^2} \right)^2 \hat{Var}(\hat{\beta}_{\text{obs}}) + \left(\frac{\hat{\beta}_{\text{obs}}}{\hat{\sigma}_{\text{true}}^2} \right)^2 \hat{Var}(\hat{\sigma}_{\text{obs}}^2) + \frac{(\hat{\beta}_{\text{obs}} \cdot \hat{\sigma}_{\text{obs}}^2)^2}{(\hat{\sigma}_{\text{true}}^2)^4} \hat{Var}(\hat{\sigma}_{\text{true}}^2)} \end{aligned}$$

Equation 2.

during both the summer and winter. For O₃ and CO, the strength and the direction of this association varied by season (Tables 3 and 4). During the summer, ambient PM_{2.5} was significantly and positively associated with ambient O₃ and NO₂ ($r_s = 0.67$ and 0.37 , respectively). During the winter, ambient PM_{2.5} was significantly and positively associated with ambient NO₂ and CO ($r_s = 0.75$ and 0.69 , respectively). A significant, negative association was found between ambient PM_{2.5} and O₃ during the winter ($r_s = -0.72$). Ambient PM_{2.5} and SO₂ were not significantly associated during the winter ($r_s = -0.17$).

Are personal exposures to copollutants significantly associated with personal exposures to PM_{2.5}? In contrast to the ambient concentrations, virtually none of the personal copollutant exposures were significantly associated with corresponding personal PM_{2.5} exposures (Table 5). The summertime association between personal PM_{2.5} and NO₂ (slope = 0.18, $p < 0.01$) was the sole exception to this finding. There was some evidence that the strength of the personal PM_{2.5}–NO₂ association was largely driven by older adult subjects (slope = 0.21, $p = 0.01$), as results using data only from the children were not significant (slope = 0.06, $p = 0.62$). Conversely, although insignificant when data from all the cohorts were analyzed together, summertime personal PM_{2.5} and O₃ were significantly associated for children (slope = 0.37, $p = 0.03$), but not for older adults (slope = 0.07, $p = 0.73$). The fraction of time spent outdoors during the summer differed little by cohort, so reasons for these cohort differences are not known but may result from different activity patterns.

Similar, yet slightly stronger, associations were found when personal exposures to PM_{2.5} of ambient origin, as opposed to total PM_{2.5}, were regressed on personal copollutant levels (Table 5). During both the summer and winter, the significance of the slope (as evidenced by the t -statistics for the mixed model slopes) between personal PM_{2.5} of ambient origin and both personal O₃ and NO₂ increased, as compared to models using total personal PM_{2.5}, but remained insignificant. Results from models that included a cooking-fuel interaction term showed that gas stoves did not significantly affect the strength of the personal PM_{2.5}–NO₂ associations (summertime $p = 0.61$; wintertime $p = 0.44$). During the summer, cooking fuel was shown to interact significantly with the strength of the association between personal exposure to PM_{2.5} of ambient origin and personal NO₂ (0.02), with subjects living in residences with gas stoves having stronger associations as compared to those living in residences with electric stoves. Cooking fuel was not shown to

influence the wintertime association between personal exposures to PM_{2.5} of ambient origin and NO₂ significantly ($p = 0.22$).

An analysis of the individual-specific pairwise correlation coefficients showed similar weak associations between personal PM_{2.5} and corresponding personal copollutant exposures. Only 9 of the 178 individual-specific pairwise correlations were significant (3 during the summer and 4 in the winter for PM_{2.5}–NO₂; 1 during the summer for PM_{2.5}–O₃; and 1 during the winter for PM_{2.5}–SO₂; Figure 2). Of these significant

correlations, three between personal PM_{2.5} and personal NO₂ were negative, an inverse relationship from that observed between the ambient concentrations of these two pollutants. Similar results were found for personal PM_{2.5} of ambient origin. Of 115 total correlations examined using personal PM_{2.5} of ambient origin, only 5 were significant.

Are ambient pollutant concentrations associated with their respective personal exposures? The weaker associations among the personal pollutant exposures as compared to associations among the ambient pollutant

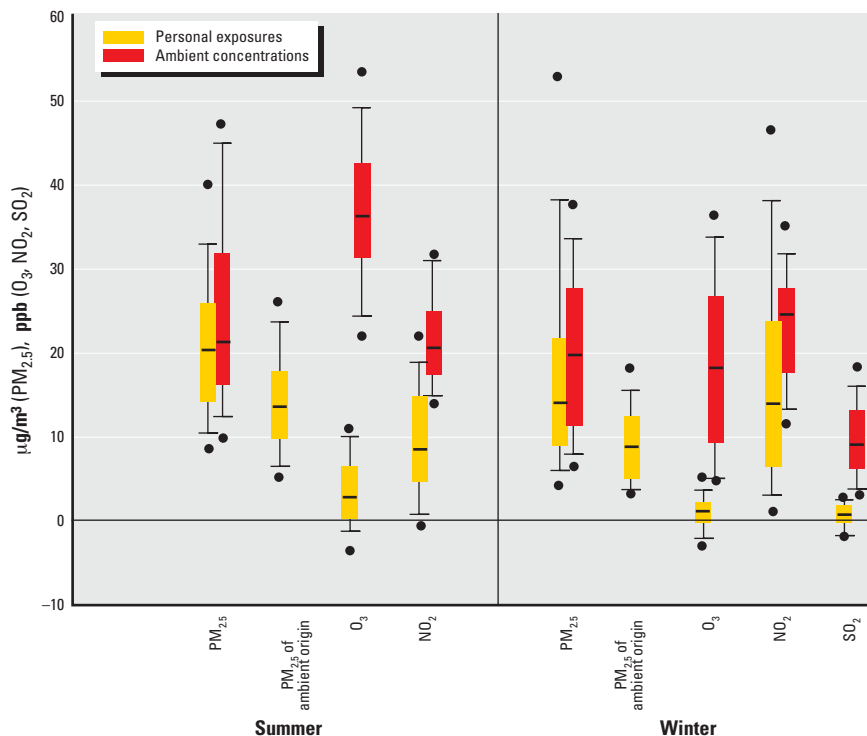


Figure 1. Boxplots showing the distribution (5th, 10th, 25th, median, 75th, 90th, and 95th percentiles) of ambient concentrations and personal exposures by season and pollutant.

Table 2. Summary of cohort-specific household characteristics and time–activity data.

	Older adults		Children		COPD
	Summer (n = 15)	Winter (n = 15)	Summer (n = 10)	Winter (n = 15)	Winter (n = 15)
Single-family houses	5	7	10	14	11
Gas stoves	4	8	5	8 ^a	9
Attached garages	0	1	0	1 ^a	1
Percentage of time outdoors	4.7% ^b	—	5.7%	—	—
Storm windows	—	10	—	8 ^a	8
Near (100 yards) busy road	4	5	5	8 ^a	7

^aIncludes data for 11/15 subjects only. ^bIncludes data for 9/10 subjects only.

Table 3. Correlations among ambient concentrations (Spearman's r).

	PM _{2.5}	O ₃	NO ₂	SO ₂	CO
PM _{2.5}	1.00	0.67*	0.37*	—	0.15
O ₃	-0.72*	1.00	0.02	—	-0.06
NO ₂	0.75*	-0.71*	1.00	—	0.75*
SO ₂	-0.17	0.41*	-0.17*	1.00	-0.32*
CO	0.69*	-0.67*	0.76*	-0.12	1.00

Top right represents summertime correlations. Lower left represents wintertime correlations.

*Significant at the 0.05 level.

concentrations were not unexpected given that ambient concentrations for gaseous pollutants were not associated with their respective personal exposures (Table 6), as also shown in our previous paper (9) as well as in other exposure studies (17,18). Of the measured pollutants, PM_{2.5} was the only pollutant for which ambient concentrations were significantly (and positively) associated with their respective personal exposures. (Although personal SO₂ was significantly associated in the winter with corresponding ambient concentrations, their association was negative: slope = -0.05, $p = 0.005$). The strong personal-ambient associations for PM_{2.5} were found during both the summer and winter ($p < 0.0001$), providing further evidence of the strong longitudinal association between ambient PM_{2.5} and corresponding personal exposures (9,19,20). Personal-ambient associations for personal PM_{2.5} of ambient origin were similarly strong and with increased significance during the winter (the t -value rose from 3.56 to 14.11; Table 6). The presence of gas stoves did not significantly affect the personal-ambient NO₂ associations (summertime interaction with cooking-fuel type, $p = 0.56$; wintertime $p = 0.57$).

The interpersonal variability of the personal-ambient association varied by pollutant (Figure 2). For both seasons, the median correlation between ambient concentrations and personal exposures was highest for PM_{2.5} (summer median $r_s = 0.65$, 13 of 24 significant correlations; winter median $r_s = 0.22$, 10 of 44 significant correlations). Even higher correlations were shown for SO₄²⁻, a component of PM_{2.5} that is predominantly of ambient origin (summer median $r_s = 0.88$, 13 of 14 significant correlations; winter median $r_s = 0.71$, 16 of 29 significant correlations). Among the gaseous copollutants, the wintertime personal-ambient association for NO₂

was the strongest with 7 of 44 subjects having significant correlations between ambient NO₂ and their personal NO₂ exposures.

Are ambient copollutant surrogates for personal exposure to PM_{2.5}? Although ambient copollutant concentrations were generally not associated with their respective personal exposures, they were associated with personal PM_{2.5} during both seasons (Table 7). The sole exception was summertime ambient CO, which was not significantly associated with personal PM_{2.5}. The direction of the associations between personal PM_{2.5} and the ambient copollutant concentrations mirrored those of the corresponding ambient associations between PM_{2.5} and its respective copollutants. Results from cohort-specific models examining these associations were not consistently significant, which may be due to the relatively small sample size since the slope and intercepts were relatively stable. The children's summertime association between ambient O₃ and total personal PM_{2.5} was the sole exception, being both insignificant ($p = 0.99$) and significantly different from results involving the older adults ($p = 0.03$).

The associations between ambient copollutant concentrations and personal PM_{2.5} of ambient origin were consistently stronger than those for total personal PM_{2.5}. Additionally, all of the cohort-stratified associations between ambient copollutant concentrations and personal PM_{2.5} of ambient origin were significant. [The wintertime association between ambient SO₂ and personal PM_{2.5} of ambient origin for the older adults was significant, but at the 0.1 level ($p = 0.09$).] Furthermore, when associations were examined using maximum 1-hr averages for O₃ and CO instead of the integrated 24-hr averages of these pollutants, model results were comparable (Table 8). Finally,

ambient PM_{2.5} was not associated with exposures to any of its gaseous copollutants during either season.

Are ambient copollutant concentrations surrogates for personal exposure to PM_{2.5} from specific sources? Personal EC and SO₄²⁻ were also measured during the winter for the cohort of COPD patients, and we used data from this cohort and season to identify factors that affected the association between the ambient copollutant concentrations and personal PM_{2.5} exposures from different ambient sources (Table 9). Specifically, SO₄²⁻, a secondary pollutant formed from coal-fired power plants, was used as a marker of regional pollution, and EC was used as an indicator of mobile source pollution. For the COPD cohort, ambient NO₂, SO₂, and CO were significantly associated with personal PM_{2.5} of ambient origin with t -values that were consistently higher than those observed for models using exposure to total PM_{2.5}. These results suggest that personal exposures to the copollutants for this cohort were primarily surrogates for ambient particles. The associations between the ambient copollutants and the personal SO₄²⁻ and EC varied by pollutant. Personal SO₄²⁻ was significantly and negatively associated with ambient O₃ and SO₂ ($p = 0.0009$ and 0.0125 , respectively), and personal EC was significantly associated with ambient O₃, NO₂, and CO ($p < 0.0001$ for all). This suggests that ambient O₃ is primarily a surrogate for secondary particle exposures, whereas ambient CO and NO₂ is primarily a surrogate for particles from traffic.

Estimating the effects of sampler measurement error on the results. The relative precision for a given sampler (i.e., the percentage of variability attributable to sampler and analytical error) varied by pollutant, season, and filter batch (Table 10). During the summer, relative precision for the personal exposure samplers was similar (range: 8% for PM_{2.5} to 14% for NO₂), whereas during the winter the precision was more variable (range: 5% for PM_{2.5} to 39% for NO₂). The relative precision of the ambient monitors (under 5% for all pollutants) was consistently lower than that observed for the personal samplers. Table 10 shows that although sampler error may have elevated the degree of overall variability in the exposures, true

Table 4. Association between ambient PM_{2.5} concentrations and ambient copollutant concentrations.

Season	Model	No.	Slope	t -Value	Intercept
Summer	Ambient PM _{2.5} = ambient O ₃	48	0.84*	5.98	-5.61
Winter	Ambient PM _{2.5} = ambient NO ₂	37	-0.67*	-5.56	32.31*
Summer	Ambient PM _{2.5} = ambient CO	48	0.65*	2.21	11.12
Winter	Ambient PM _{2.5} = ambient SO ₂	37	1.02*	6.22	-2.74
Summer	Ambient PM _{2.5} = ambient O ₃	48	6.50	0.57	21.95*
Winter	Ambient PM _{2.5} = ambient NO ₂	37	15.93*	5.56	5.84*
Winter	Ambient PM _{2.5} = ambient SO ₂	37	-0.34	-0.93	23.05*

Estimates generated using time series regression analysis.

*Significant at the 0.05 level.

Table 5. Association between personal PM_{2.5} exposures and personal copollutant exposures.

Season	Model	Subjects (n)	Total personal PM _{2.5} exposure			Personal exposure to PM _{2.5} of ambient origin			
			Slope	t -Value	Intercept	Subjects (n)	Slope	t -Value	Intercept
Summer	Personal PM _{2.5} = personal O ₃	24 (193)	0.21	1.31	19.78*	15 (130)	0.22	1.56	13.12*
Winter	Personal PM _{2.5} = personal NO ₂	45 (434)	-0.05	-0.20	18.51*	30 (282)	-0.18	-1.66	9.01*
Summer	Personal PM _{2.5} = personal NO ₂	24 (213)	0.18*	2.51	18.65*	15 (150)	0.17*	3.03	12.77*
Winter	Personal PM _{2.5} = personal NO ₂	45 (467)	-0.02	-0.68	19.04*	30 (289)	-0.16	-0.83	9.23*
Winter	Personal PM _{2.5} = personal SO ₂	45 (465)	-0.19	-0.65	18.68*	30 (289)	0.03	0.18	8.98*

*Significant at the 0.05 level.

variability in the exposures accounted for the majority of overall variability (> 66%), even for exposures whose mean concentrations were extremely low (e.g., O₃ and SO₂). These results suggest that true variability contributed more to the overall variability in exposures than sampler error. As a result,

there was likely sufficient variability in exposures to detect significant associations when they truly existed.

Because sampler error increases the likelihood of type II errors, we conducted further analyses to quantify its effect on models with insignificant results. For models examining

the association between ambient copollutant concentrations and personal PM_{2.5} exposures, reduced model sensitivity was not likely to affect the interpretation of the results, as the slopes were highly significant in spite of any sampler error. Furthermore, the estimates of slope for the models examining

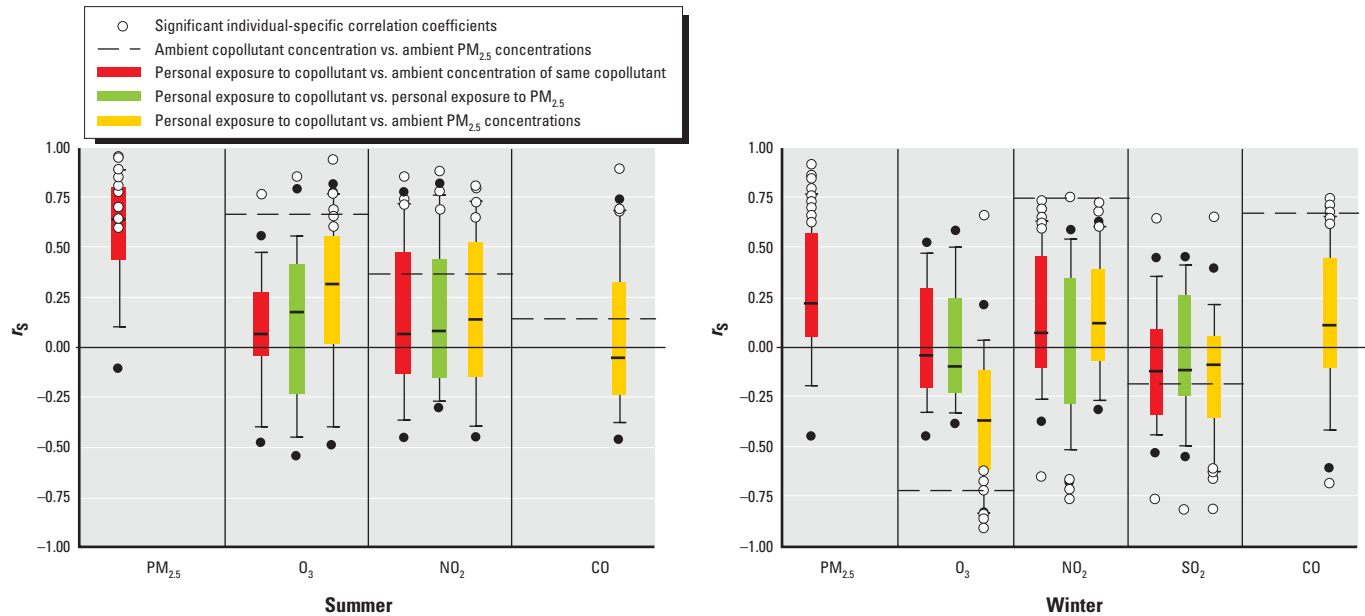


Figure 2. Boxplots showing the distribution (5th, 10th, 25th, median, 75th, 90th, and 95th percentiles) of individual specific Spearman's correlation coefficients (r_s) for (A) summertime and (B) wintertime plots ($n = 24$ and 44 , respectively).

Table 6. Association between ambient concentrations and respective personal exposures.

Season	Model	Total personal PM _{2.5} exposure			Personal exposure to PM _{2.5} of ambient origin				
		Subjects (<i>n</i>)	Slope	<i>t</i> -Value	Intercept	Subjects (<i>n</i>)	Slope	<i>t</i> -Value	Intercept
Summer	Personal PM _{2.5} = ambient PM _{2.5}	24 (225)	0.46*	9.96	10.20*	15 (154)	0.34*	11.12	5.56*
Winter		45 (481)	0.26*	4.36	13.27*	30 (301)	0.39*	19.88	1.19*
Summer	Personal O ₃ = ambient O ₃	24 (196)	0.01	1.21	1.84				
Winter		45 (449)	0.00	0.03	0.46				
Summer	Personal NO ₂ = ambient NO ₂	24 (217)	0.04	0.37	9.52*				
Winter		45 (484)	-0.05	-0.53	18.16*				
Winter	Personal SO ₂ = ambient SO ₂	45 (487)	-0.05*	-2.82	0.54*				

*Significant at the 0.05 level.

Table 7. Association between personal PM_{2.5} exposures and ambient copollutant concentrations.

Season	Model	Total personal PM _{2.5} exposure			Personal exposure to PM _{2.5} of ambient origin				
		Subjects (<i>n</i>)	Slope	<i>t</i> -Value	Intercept	Subjects (<i>n</i>)	Slope	<i>t</i> -Value	Intercept
Summer	Personal PM _{2.5} = ambient O ₃	24 (225)	0.28*	4.00	10.94*	15 (150)	0.37*	6.23	0.04
Winter		45 (487)	-0.29*	-4.68	23.86*	30 (301)	-0.36*	-14.04	15.60*
Summer	Personal PM _{2.5} = ambient NO ₂	24 (225)	0.42*	3.83	12.38*	15 (154)	0.38*	3.79	6.27*
Winter		45 (487)	0.24*	3.44	13.16*	30 (301)	0.26*	7.30	3.06*
Summer	Personal PM _{2.5} = ambient CO	24 (225)	5.36	1.34	18.30*	15 (150)	1.87	0.50	13.42*
Winter		45 (487)	3.99*	3.17	15.00*	30 (301)	6.30*	10.97	3.24*
Winter	Personal PM _{2.5} = ambient SO ₂	45 (487)	-0.24*	-2.06	20.75*	30 (301)	-0.17*	-2.74	10.38*

*Significant at the 0.05 level.

Table 8. Association between personal PM_{2.5} exposures and hourly maximum ambient O₃ and CO concentrations.

Season	Model	Total personal PM _{2.5} exposure			Personal exposure to PM _{2.5} of ambient origin				
		Subjects (<i>n</i>)	Slope	<i>t</i> -Value	Intercept	Subjects (<i>n</i>)	Slope	<i>t</i> -Value	Intercept
Summer	Personal PM _{2.5} = ambient O ₃	24 (225)	0.26*	6.22	4.33	15 (154)	0.27*	8.02	-3.66
Winter		45 (487)	-0.30*	-5.23	28.31*	30 (301)	-0.27*	-10.57	17.54*
Summer	Personal PM _{2.5} = ambient CO	24 (225)	2.66	1.61	18.16*	15 (154)	-0.69	-0.40	14.94*
Winter		45 (487)	1.50*	2.64	15.94*	30 (301)	2.09*	7.97	5.12*

*Significant at the 0.05 level.

the associations between ambient pollutant concentrations and their respective personal exposures were essentially unbiased given the relatively high precision of the ambient pollutant monitors. As shown in Table 11 for the older adult cohort, the true significance of the models did not change, with all of the models remaining insignificant. For each model, estimates of both the true slope and true standard error increased, resulting in no appreciable difference in statistical significance. It should be noted that our ability to examine statistical significance may be limited by our relatively small sample size. With a larger sample size, it is possible that the corrected parameter estimates might become more statistically significant due to correcting the attenuation bias in the uncorrected estimates.

Discussion and Conclusions

For copollutants to be confounders of the epidemiologic associations between particles and adverse health effects, two conditions must be satisfied. They must be correlated with exposure to particles, and they must be correlated with the health outcome. We have shown that personal exposures to the gaseous air pollutants are not correlated, at least in our cohorts, with personal exposures to PM_{2.5}. Hence the gaseous copollutants cannot be confounders of PM_{2.5} associations. Yet several studies have reported that ambient concentrations of gaseous air pollutants did confound observed associations between ambient particles and health. Why did this happen?

Ambient PM_{2.5} concentrations were strongly associated with corresponding ambient concentrations of several gaseous

copollutants in Baltimore, although the strength and direction of these associations differed by season. These results are consistent with findings from other studies and likely reflect common sources and meteorological conditions (4,20). Based on ambient results alone, therefore, it is possible that confounding by gaseous copollutants may impact observed associations between ambient PM_{2.5} and adverse health.

With the exception of PM_{2.5}, however, ambient pollutant concentrations were weak indicators of their respective personal exposures. In many respects, these weak associations were not surprising given findings from earlier single-pollutant exposure studies that showed similarly strong longitudinal personal-ambient associations for particulate matter (19,21,22) and weak associations for the gases (17,18,23,24). For the gases, these weak associations can be attributed in part to low personal exposures, where personal exposures to O₃ and SO₂, in particular, were extremely low. Additionally, weak personal-ambient associations for the gases may be because variations in time spent outdoors, rather than variations in ambient concentrations, are the principal factor driving fluctuations in exposures to reactive gaseous pollutants over time. For a less reactive gas, such as NO₂, indoor sources may also weaken the association. This did not appear to affect the current results unduly, as similar results were shown for subjects living in residences with gas stoves as compared to electric stoves.

As could be expected from the previous pollutant relationships, the associations among the personal PM_{2.5} and gaseous pollutant exposures were also weak and did not change in direction or significance when personal exposures to PM_{2.5} of ambient origin were used in the analyses. These weak associations among personal PM_{2.5}, O₃, NO₂ and SO₂, together with the strong personal-ambient associations for PM_{2.5}, provide evidence that the observed PM_{2.5}-associated health effects are not due to confounding by the gaseous pollutants, at least for individuals with similar exposure profiles and living in similar urban locations. Additionally, differential sampler error, while present in varying amounts, accounted for at most 39% of overall exposure variability for the samplers used. This finding suggests that the reported associations were not unduly affected by reduced statistical power due to sampler error.

While exposures to the gaseous copollutants are unlikely to be potential confounders of PM_{2.5}, ambient copollutant concentrations were surrogates of personal PM_{2.5}. For all of the measured copollutants during both seasons, ambient copollutant

Table 9. Associations between ambient copollutant concentrations and personal exposure to PM_{2.5} and its components for individuals with COPD, winter 1999.

Dependent variable	Independent variable	Slope	t-Value	p-Value
Ambient SO ₄ ²⁻	Ambient O ₃			
Personal exposure to total PM _{2.5}	Ambient O ₃	-0.25	-3.43	0.0008
Personal exposure to PM _{2.5} of ambient origin	Ambient O ₃	-0.27	-9.63	0.0001
Personal SO ₄ ²⁻	Ambient O ₃	-0.02	-3.38	0.0009
Personal EC	Ambient O ₃	-0.04	-5.34	0.0001
Ambient SO ₄ ²⁻	Ambient NO ₂			
Personal exposure to total PM _{2.5}	Ambient NO ₂	0.09	0.96	0.3376
Personal exposure to PM _{2.5} of ambient origin	Ambient NO ₂	0.29	8.3	0.0001
Personal SO ₄ ²⁻	Ambient NO ₂	0.00	-0.09	0.9321
Personal EC	Ambient NO ₂	0.05	5.06	0.0001
Ambient SO ₄ ²⁻	Ambient SO ₂			
Personal exposure to total PM _{2.5}	Ambient SO ₂	-0.20	-1.44	0.1524
Personal exposure to PM _{2.5} of ambient origin	Ambient SO ₂	-0.16	-2.49	0.0139
Personal SO ₄ ²⁻	Ambient SO ₂	-0.03	-2.53	0.0125
Personal EC	Ambient SO ₂	-0.01	-0.54	0.5927
Ambient SO ₄ ²⁻	Ambient CO			
Personal exposure to total PM _{2.5}	Ambient CO	1.36	0.88	0.3823
Personal exposure to PM _{2.5} of ambient origin	Ambient CO	4.42	6.74	0.0001
Personal SO ₄ ²⁻	Ambient CO	-0.05	-0.32	0.7529
Personal EC	Ambient CO	1.02	6.38	0.0001

Table 10. Estimating the effects of sampler error.

Season	Pollutant	Personal COV (%)	Sampler error (%)	Percent of true variability ^a	Ambient COV (%)
Summer	PM _{2.5}	44	8	92	48
	O ₃	104	9	91	25
	NO ₂	81	14	86	27
Winter	PM _{2.5}	54	5	95	47
	O ₃	566	9	91	57
	NO ₂	73	39 (28) ^b	61	32
	SO ₂	2,071	31	69	51

COV, coefficient of variation.

^aRepresents COV minus variability attributable to sampler error. ^bIndicates values after removing three outliers likely caused by filter contamination.

Table 11. Association between personal PM_{2.5} exposures and personal copollutant exposures using slopes corrected for sampler error: models for older adults

Season	Personal PM _{2.5} vs.	True slope	True SE	True t-value
Summer	Personal O ₃	0.08	0.22	0.3
	Personal NO ₂	0.24	0.09	2.6
Winter	Personal O ₃	-0.29	0.36	-1.0
	Personal NO ₂	-0.10	0.11	-1.4
	Personal SO ₂	-0.85	0.93	-0.9

concentrations were shown to be better predictors of personal $PM_{2.5}$ than of their respective personal exposures. Associations involving personal $PM_{2.5}$ of ambient origin were even stronger. One-hour maximum ambient concentrations of O_3 and CO, which have also been associated with adverse health in epidemiologic studies, were similarly strongly correlated with personal exposures to both total $PM_{2.5}$ and that of ambient origin, indicating that the results were insensitive to the averaging time of these gaseous pollutants. In contrast, ambient $PM_{2.5}$ was a poor predictor of personal exposures to the gaseous copollutants. Together, these results demonstrate that the ambient concentrations of $PM_{2.5}$, O_3 , NO_2 , CO, and SO_2 are serving as surrogates for personal exposures to $PM_{2.5}$ alone.

Gaseous pollutants were stronger surrogates for $PM_{2.5}$ of ambient origin, as evidenced by the higher *t*-statistics for these comparisons. These stronger associations may be due to shared outdoor sources for the gaseous pollutants and $PM_{2.5}$ of ambient origin. Furthermore, some of the gaseous pollutants appear to be acting as surrogates for specific $PM_{2.5}$ components, as shown by the observed associations between ambient gaseous pollutant concentrations and personal EC and SO_4^{2-} exposures. For subjects with COPD, ambient CO and NO_2 were not significantly associated with total personal $PM_{2.5}$, but were associated with personal exposures to $PM_{2.5}$ of ambient origin and also to personal EC. These significant associations may be due to the fact that motor vehicles are a major source of CO, NO_2 , EC, and, to a lesser degree, to $PM_{2.5}$ of ambient origin. Conversely, ambient CO and NO_2 were not significantly associated with personal SO_4^{2-} , a pollutant not associated with motor vehicle emissions. O_3 , in contrast, was predominantly associated with personal SO_4^{2-} , an indicator of long-range transport and secondary particles.

The differences in significance among the cohorts may be attributable to differences in cohort-specific exposure patterns. For example, it is possible that although the total fraction of time spent outdoors was comparable, children spent more time outside during the peak O_3 - $PM_{2.5}$ afternoon hours than older adults. This could account for the significance of the summertime association between personal O_3 and personal $PM_{2.5}$ for children but not for older adults. Observed cohort differences may also be due to differences in statistical power for each cohort.

If ambient copollutant concentrations are surrogates, as opposed to confounders, of $PM_{2.5}$, the results suggest that using multiple pollutant models in epidemiologic studies of $PM_{2.5}$ may not be suitable. As discussed by

Breslow and Day (25), it is inappropriate to treat one variable as a confounder of another when both variables are actually surrogates of the same thing. In Baltimore, this would apply to epidemiologic models that incorporate ambient $PM_{2.5}$ as well as ambient O_3 , NO_2 , SO_2 , or CO which have been shown in our analyses to be surrogates of personal $PM_{2.5}$. Depending on the strength of the true epidemiologic association, models that include these collinear, yet nonconfounding variables, will yield slopes for the causal pollutant factor ($PM_{2.5}$) that are underestimated (5). Likewise, the models will yield a misleading significant association for the collinear copollutant. Consequently, the correct modeling approach may be to exclude the gaseous pollutant concentrations for pollutants that are surrogates for particles rather than gaseous exposures and to employ single-pollutant regression models instead.

Additionally, results from this analysis clarify findings from epidemiologic studies. For example, in the recently published National Morbidity, Mortality, and Air Pollution Study (NMMAPS), data from 90 cities were compiled to assess the percentage change in mortality associated with changes in ambient air pollutant concentrations (6). The authors found that during the summer, increases of 10 ppb in ambient O_3 was associated with a 0.4% increase in mortality (95% CI; -0.20-1.01). Conversely, wintertime data indicated that the same increase in ambient O_3 led to a mean decrease of 1.86% in mortality (95% CI; -2.70-0.96), implying a protective effect from exposure to O_3 . The peculiar wintertime results were described by the authors as "puzzling and may reflect some unmeasured confounding factor" (6). The results from the current analysis suggest that these results could be due to the fact that ambient O_3 is a surrogate for personal $PM_{2.5}$, where the observed negative wintertime associations between ambient O_3 and mortality reflect the negative association between ambient O_3 and corresponding personal $PM_{2.5}$.

Other recent studies have reported positive associations between ambient CO and respiratory hospital visits (26). Yet CO is neither a respiratory irritant nor a moderator of immune response in the respiratory tract, making those associations biologically implausible. $PM_{2.5}$, in contrast, has been shown to exacerbate respiratory infections (27) as well as produce an inflammatory response (28). The findings showing that ambient CO is a surrogate for personal $PM_{2.5}$ of ambient origin may, therefore, provide a biologically plausible explanation for the observed association between CO and respiratory hospital visits as well.

Our results were obtained in only one location, which is a limitation of this analysis.

However, modulators of these associations between ambient concentrations and personal exposures, such as the amount of time spent outdoors and degree of ventilation in the home, were variable. Our sample included subjects who spent more time than average outdoors as well as subjects who spent less time than average outdoors. In addition, we had a wide range of indoor ventilation conditions in the homes sampled. We therefore believe that although different associations might be found in other cities, the qualitative results we report are unlikely to change.

In summary, the above results highlight the importance of properly characterizing associations among ambient pollutant concentrations and their personal exposures to air pollution epidemiologic studies. Studies conducted in locations with strong associations among ambient pollutant concentrations should not assume that associations observed among ambient pollutant concentrations necessarily persist among personal exposures to these pollutants, nor should they assume that relationships among ambient pollutant concentrations are consistent across seasons. In particular, ambient concentrations of gaseous air pollutants cannot be considered as surrogates for their respective personal exposures without site-specific evidence to support that assumption. Future research should focus on how specific factors, such as ventilation, time spent outdoors, and household characteristics, affect the strength of these associations for certain individuals and cohorts.

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