Journal of Exposure Science and Environmental Epidemiology (2006) 16, 30–38
© 2006 Nature Publishing Group All rights reserved 1559-0631/06/$30.00
www.nature.com/jes

Estimating effects of ambient $PM_{2.5}$ exposure on health using $PM_{2.5}$ component measurements and regression calibration

MATTHEW STRAND,[a] SVERRE VEDAL,[b] CHARLES RODES,[c] STEVEN J. DUTTON,[d] ERWIN W. GELFAND[e] AND NATHAN RABINOVITCH[e]

[a]*Division of Biostatistics, National Jewish Medical and Research Center, Denver, Colorado, USA*
[b]*Department of Environmental and Occupational Health Sciences, University of Washington School of Public Health and Community Medicine, Seattle, Washington, USA*
[c]*RTI International, Center for Aerosol Technology, Research Triangle Park, North Carolina, USA*
[d]*Department of Civil, Environmental and Architectural Engineering, University of Colorado, Boulder, Colorado, USA*
[e]*Department of Pediatrics, National Jewish Medical and Research Center, Denver, Colorado, USA*

Most air pollution and health studies conducted in recent years have examined how a health outcome is related to pollution concentrations from a fixed outdoor monitor. The pollutant effect estimate in the health model used indicates how ambient pollution concentrations are associated with the health outcome, but not how actual exposure to ambient pollution is related to health. In this article, we propose a method of estimating personal exposures to ambient $PM_{2.5}$ (particulate matter less than 2.5 μm in diameter) using sulfate, a component of $PM_{2.5}$ that is derived primarily from ambient sources. We demonstrate how to use regression calibration in conjunction with these derived values to estimate the effects of personal ambient $PM_{2.5}$ exposure on a continuous health outcome, forced expiratory volume in 1 s (FEV_1), using repeated measures data. Through simulation, we show that a confidence interval (CI) for the calibrated estimator based on large sample theory methods has an appropriate coverage rate. In an application using data from our health study involving children with moderate to severe asthma, we found that a 10 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with a 2.2% decrease in FEV_1 at a 1-day lag of the pollutant (95% CI: 0.0–4.3% decrease). Regressing FEV_1 directly on ambient $PM_{2.5}$ concentrations from a fixed monitor yielded a much weaker estimate of 1.0% (95% CI: 0.0–2.0% decrease). Relatively small amounts of personal monitor data were needed to calibrate the estimate based on fixed outdoor concentrations.
Journal of Exposure Science and Environmental Epidemiology (2006) **16,** 30–38. doi:10.1038/sj.jea.7500434; published online 6 July 2005

Keywords: *sulfate, asthma, measurement error, air pollution, particulate matter.*

Introduction

Many longitudinal studies have been conducted over the past decade to examine the relationship between air pollution and health indicators such as pulmonary function, respiratory symptoms, daily hospitalization and mortality counts. In most of these studies, pollution concentrations in health effects models have been based on fixed outdoor monitors. While the slope of the pollutant variable in such a fit model indicates the association between ambient pollution and the health outcome, it is not likely to be a good measure of the effect of the pollutant *to which subjects are exposed*. This is primarily due to the fact that people spend the majority of their time indoors, where they are exposed to a certain fraction of ambient pollution. As a result, the difference between the ambient pollutant concentration and the average personal exposure tends to increase as pollution increases, which we will refer to as *concentration-dependent measurement error*. Zeger et al. (2000) discuss more generally issues of exposure measurement error in time-series studies of air pollution and health, and point out that pollutant slope estimators in health effects models are biased when concentration-dependent measurement error (a type of non-Berksonian error) exists.

Recently, personal exposure monitors (henceforth called personal monitors) have been used in some air pollution studies to get a better idea of how ambient pollution concentrations relate to personal breathing zone exposures (Janssen et al., 1997, 1998, 1999; Ebelt et al., 2000; Rojas-Bracho et al., 2000; Williams et al., 2000; Liu et al., 2003). Some have argued that moderate to strong correlations between (average) personal

1. Abbreviations: CI, confidence interval; ETS, environmental tobacco smoke; FEV_1, forced expiratory volume in 1 second; F_{INF}, indoor concentration of a pollutant divided by the ambient level of that pollutant; MSE, mean-squared error; $PM_{2.5}$, particulate matter less than 2.5 μm in diameter; F_{PEX}, personal pollutant exposure concentration divided by the ambient level of that pollutant; RTI, Research Triangle Institute; REML, restricted maximum likelihood; SD, standard deviation; SE, standard error.

2. Address all correspondence to: Assistant Professor M. Strand, Division of Biostatistics, National Jewish Medical and Research Center, 1400 Jackson Street, M222a, Denver, CO 80206, USA. Tel.: +1 303 398 1862. Fax: +1 303 270 2131. E-mail: strandm@njc.org.
Received 8 December 2004; accepted 20 April 2005; published online 6 July 2005

concentrations and fixed monitor concentrations justify the use of the fixed monitors in place of personal monitors. However, such correlations do not indicate whether concentration-dependent measurement error exists.

Regression calibration and microenvironment models are two existing methodologies that can be used to obtain estimates of effect of direct pollution exposure on health, while still using fixed (surrogate) monitors and relatively little or no personal monitor data. In the context of pollution–health studies, regression calibration involves carrying out the regression between health outcomes and surrogate measures of pollution exposure, and then adjusting the pollutant slope estimate based on a known or observed relationship between the surrogate and actual (or personal) measures of pollution exposure. Carroll et al. (1995) and Fuller (1987) discuss regression calibration methods in general; Zeger et al. (2000) illustrate the methods with a pollution–health study application. Microenvironment models (Ozkaynak et al., 1996; Janssen et al., 1997; Liu et al., 2003) involve breaking down time that subjects spend within certain environments (e.g., outside, at work or school, at home) and then using a weighted average of concentrations from fixed monitors at these sites to estimate daily exposures, which can then be used in health effects regression models.

Since measured personal particulate matter (PM) is a mixture of pollution from both ambient and nonambient sources, there is difficulty in determining exactly what portion of it is based on one source or the other. One possible solution is to use a component of personal PM that is known to be derived from ambient sources only, and use this information to estimate ambient PM exposure concentrations. These derived concentrations can then be used to estimate effects of ambient PM on a health outcome.

We use this proposed method in conjunction with regression calibration to estimate effects of ambient $PM_{2.5}$ on forced expiratory volume in 1 s (FEV_1), where personal ambient $PM_{2.5}$ exposure concentrations are derived using sulfate, a component of $PM_{2.5}$ that is known to be generated primarily from ambient sources. The models used for the regression calibration incorporate longitudinal (or repeated measures) data collected on study subjects. Data from a health study, collected as part of an EPA study of the effects of air pollution on children with severe asthma, conducted in Denver, Colorado from 1999 to the present (see Rabinovitch et al., 2004), are used to illustrate the methods. Finally, properties of the proposed estimation technique are examined through simulation.

Methods

Estimating Personal Ambient $PM_{2.5}$ Using Sulfate

Total $PM_{2.5}$ has both ambient and nonambient sources. Nonambient $PM_{2.5}$ is usually either generated from indoor or personal sources, while ambient sources include vehicular and industrial emissions, wood burning and crustal matter. If ambient sources can be clearly defined and differentiated from nonambient sources, then for subject i and time t, total personal $PM_{2.5}$ exposure can be expressed as:

$$X_{it}^{\mathrm{P}} = X_{it}^{\mathrm{N}} + X_{it}^{\mathrm{A}}$$

where the superscripts N and A denote nonambient and ambient sources of $PM_{2.5}$, respectively. In this article, we are interested in the effects of ambient sources of pollution on health. In practice, determining X_{it}^{A} is very difficult since the observable quantity, X_{it}^{P}, involves a mixture of ambient and nonambient $PM_{2.5}$. In particular, most people spend the majority of their time indoors, where they are exposed to a mixture of nonambient $PM_{2.5}$ and ambient $PM_{2.5}$ that has infiltrated indoors. The level of exposure to ambient $PM_{2.5}$ for a subject who is indoors is often less than for one who is outdoors (typically about half as much). Nevertheless, total $PM_{2.5}$ exposure may often be high for subjects that spend more time indoors if they are exposed to a significant indoor aerosol source, such as environmental tobacco smoke (ETS).

One possible approach to estimating personal exposure to ambient $PM_{2.5}$ is to consider components of $PM_{2.5}$ that are known to originate largely (if not entirely) from outdoor sources. Sulfate (SO_4) is one such compound (Wilson et al., 2000). Let S_t and X_t denote the ambient sulfate and $PM_{2.5}$ concentrations at time t, respectively. Also, let S_{it}^{A} denote the concentration of ambient sulfate that subject i is exposed to on day t. Then, if the composition of $PM_{2.5}$ remains relatively spatially homogeneous at a given time t, we have the approximate equivalence:

$$\frac{S_t}{X_t} \approx \frac{S_{it}^{\mathrm{A}}}{X_{it}^{\mathrm{A}}} \tag{1}$$

The "representative location" must be one for which nonambient sources are negligible (e.g., a fixed outdoor monitor that is not near nonambient sources such as smokers). If nonambient sources of sulfate are also negligible, then S_{it}^{A} can be approximated by the total personal sulfate exposure (S_{it}^{P}). Thus, with direct measures of S_t and X_t, and an approximate value of S_{it}^{A}, we can use (1) to obtain an estimate of personal exposure to ambient $PM_{2.5}$ (X_{it}^{A}).

The difficulty with (1) is that, even if the composition of ambient $PM_{2.5}$ is relatively homogeneous outside, the indoor infiltration efficiency of $PM_{2.5}$ depends on particle size within the $PM_{2.5}$ fraction. Sulfate particles are typically between 0.1 and 1 μm in diameter. Although $PM_{2.5}$ is primarily composed of particles within this size range, it may also contain coarse particles between 1 and 2.5 μm. Therefore, $PM_{2.5}$ collectively is not likely to infiltrate indoors as efficiently as sulfate. To account for this, a generalization of (1) is:

$$\frac{S_t}{X_t} \approx \lambda \frac{S_{it}^{\mathrm{A}}}{X_{it}^{\mathrm{A}}} \tag{2}$$

where λ accounts for the average difference in the proportion of ambient $PM_{2.5}$ that is made up of sulfate at the ambient and personal locations. If study subjects have similar living conditions (e.g., live in same types of housing), then differences in measured values of λ that occur between subjects and over time could be accounted for in statistical models with random error. If living conditions of study subjects vary significantly, then one may desire to estimate and use subject-specific λ values as opposed to one common value. We found the use of a common λ to be adequate. This issue is further addressed in Discussion.

Wilson et al. (2000) defined F_{INF} as the indoor concentration of a pollutant divided by the ambient level of that pollutant, and F_{PEX} as the personal pollutant exposure concentration divided by the ambient level of that pollutant. By manipulating (2), we can express λ as the ratio of $(X_{it}^{\mathrm{A}}/X_t)$ over $(S_{it}^{\mathrm{A}}/S_t)$, that is, the ratio of F_{PEX} for $PM_{2.5}$ to F_{PEX} for sulfate. Using our data, we obtained an average λ estimate of 0.78 (see section "Estimating the ratio of $PM_{2.5}$…" of Appendix A).

By considering two extremes, we can evaluate the validity of our estimate. Subjects who spend all their time outdoors would be expected to have λ near one. Subjects who spend all their time at one indoor site would be expected to have λ that is approximately equal to the ratio of F_{INF} for $PM_{2.5}$ to F_{INF} for sulfate, for that particular indoor location. At the school study location (see the Application section for details), we observed these two quantities to be 0.266 and 0.453, respectively, yielding a ratio of $0.266/0.453 = 0.59$, indicating that the infiltration rate of ambient $PM_{2.5}$ was 59% of that of sulfate, on average. These data suggest that a likely range for λ would be between 0.6 and 1, which contains our observed average estimate. Our data were collected in fall/winter, and there are likely to be seasonal differences between infiltration rates. Based on regression slopes, Sarnat et al. (2002) reported F_{INF} values of 0.47 for $PM_{2.5}$ and 0.83 for sulfur in fall/winter, for a ratio of $0.47/0.83 = 0.57$, similar to ours. (In spring/summer, the values were 0.72 and 0.77, respectively; ratio $= 0.935$.) It should be emphasized that F_{INF} ratios and estimates of λ may differ between regions and groups of study subjects, as well as between seasons; estimates obtained here may not necessarily apply to other studies.

Given the λ estimate ($\hat{\lambda} = 0.78$), estimated values of personal ambient $PM_{2.5}$ exposure can then be calculated as:

$$X_{it}^{\mathrm{A}*} = \hat{\lambda}\frac{S_{it}^{\mathrm{A}}}{S_t}X_t \tag{3}$$

A simple additive error model that accounts for differences between the actual personal ambient exposure to $PM_{2.5}$ (X_{it}^{A}) and the estimated amount ($X_{it}^{\mathrm{A}*}$) is:

$$X_{it}^{\mathrm{A}*} = X_{it}^{\mathrm{A}} + u_{it} \tag{4}$$

where u_{it} is random error. The assumption for the standard linear model would be $u_{it} \sim N(0, \sigma_u^2)$ independently for all i and t.

The Health Effects (or Main Study) Model

A model relating a health outcome to personal ambient $PM_{2.5}$ exposure in a longitudinal panel study is:

$$Y_{it} = \beta_0 + \beta_1 X_{it}^{\mathrm{A}} + \{\alpha_1 W_{it}^1 + \alpha_2 W_{it}^2 + \cdots + \alpha_k W_{it}^k\} + \gamma_i + \varepsilon_{it} \tag{5}$$

where Y_{it} is the health outcome, X_{it}^{A} is the true ambient $PM_{2.5}$ exposure level, ε_{it} is random error, i denotes the subject and t time (e.g., days). The terms β_0 and β_1 are the fixed y-intercept and slope parameters, respectively, the latter of which is used to indicate the effect of the pollutant on the health outcome. The set of terms within brackets are covariates with fixed coefficients, α_j, $j = 1, \ldots, k$, and γ_i is a subject-specific random intercept. An appropriate covariance of errors structure can be used to account for correlated responses within subjects over time. A model such as (5) is often referred to as the "main study" model in regression calibration and measurement error studies.

The Personal Exposure (or Validation Study) Model

To quantify the relationship between daily personal ambient $PM_{2.5}$ concentrations and fixed monitor concentrations, we consider the model,

$$X_{it}^{\mathrm{A}} = \theta_0 + \theta_1 X_t + \phi_i X_t + \omega_{it} \tag{6}$$

where ϕ_i is a random slope for subject i that indicates a specific ambient to personal $PM_{2.5}$ exposure relationship, and differs by subject primarily due to type of housing ($\phi_i \sim N(0, \sigma_\phi^2)$, $i = 1, \ldots, n$), and ω_{it} is random error. The parameters θ_0 and θ_1 are the fixed y-intercept and slope, respectively. In terms of regression calibration terminology, (6) is often referred to as the "validation study" model. The model (6) may also be used in regression calibration when X_t is replaced with any variable that is linearly related to X_{it}^{A}. For details, see sections on *instrumental variables* in Fuller (1987) and Carroll et al. (1995).

Unfortunately, the outcome variable in (6) is unobservable. However, by incorporating (4), we can express (6) in terms of the imperfect measure of ambient personal $PM_{2.5}$ exposure:

$$X_{it}^{\mathrm{A}*} = \theta_0 + \theta_1 X_t + \phi_i X_t + \omega_{it} + u_{it} \tag{7}$$

The errors ω_{it} and u_{it} in (7) can be combined into one general error term, ω_{it}'. We first determined $X_{it}^{\mathrm{A}*}$ values based on (3). We then used standard mixed model analysis to fit (7). More details for the fits are given in the Application section.

Regression Calibration

Considering model (5), where the actual personal ambient exposure X_{it}^{A} is replaced with its equation given in (6), yields:

$$\begin{aligned} Y_{it} &= \beta_0 + \beta_1 X_{it}^{\mathrm{A}} + \varepsilon_{it} \\ &= [\beta_0 + \beta_1\theta_0] + [\beta_1\theta_1]X_t + [\beta_1\gamma_i] + [\beta_1\omega_{it} + \varepsilon_{it}] \end{aligned}$$

Since the true slope of X_t in the regression model for Y_{it} is $\beta_1\theta_1$, one can expect a corresponding estimate from a mixed

model analysis to be closer to that quantity than to β_1. In other words, bias is expected in estimating β_1 if X_t (ambient $PM_{2.5}$ concentration at the fixed outdoor site) is used in place of X_{it}^{A} (personal ambient $PM_{2.5}$). Let $\hat{\beta}_1$ denote the estimate obtained from the mixed model analysis when modeling Y as a function of X_t. If one has a validation study to produce an unbiased estimate of θ_1, call it $\hat{\theta}_1$, a logical point estimator of β_1 would be:

$$\hat{\beta}_1^{\text{adj}} = \hat{\beta}_1/\hat{\theta}_1 \tag{8}$$

which corrects for the systematic linear difference between X_{it}^{A} and X_t. This procedure is one common form of regression calibration. Fuller (1987) showed that $\hat{\beta}_1^{\text{adj}}$ is a consistent estimator of β_1 and gave the form of the asymptotic distribution of $\hat{\beta}_1^{\text{adj}}$ in the case where errors (ε_{it}) are independent and no random terms (other than error) are considered for (5) and (7).

Inference for Calibrated Estimators

The estimator $\hat{\beta}_1^{\text{adj}}$ is based on the ratio of two slope estimators, so an appropriate confidence interval needs to take into account the variability in both these statistics. Most of the existing theory for confidence intervals of calibrated estimators is based on large sample (or asymptotic) theory (e.g., Fuller, 1987; Rosner et al., 1989) or resampling methods (e.g., Carroll et al., 1995; Haukka, 1995). An asymptotic distribution of $\hat{\beta}_1^{\text{adj}} = \hat{\beta}_1/\hat{\theta}_1$ can be derived relatively easily using the delta method (e.g., see Agresti, 2002). Specifically, if it can be shown that $\hat{\beta}_1$ and $\hat{\theta}_1$ are each asymptotically normal with a certain mean and variance, then the delta method shows that a function of these statistics (such as the ratio) is asymptotically normal with a mean and variance that can be calculated.

Richardson and Welsh (1994) showed that restricted maximum likelihood (REML) estimators of regression coefficients in mixed models were asymptotically normal with certain mean and variance as the number of independent subjects was increased. These results can be applied to both $\hat{\beta}_1$ and $\hat{\theta}_1$. If the correlation between these estimators is negligible, then $\hat{\beta}_1^{\text{adj}} \sim N(\beta_1, \sigma^2_{\hat{\beta}_1^{\text{adj}}})$, where

$$\sigma^2_{\hat{\beta}_1^{\text{adj}}} = \frac{1}{\hat{\theta}_1^2}\sigma^2_{\hat{\beta}_1} + \frac{\hat{\beta}_1^2}{\hat{\theta}_1^4}\sigma^2_{\hat{\theta}_1} \tag{9}$$

An estimate of $\sigma^2_{\hat{\beta}_1^{\text{adj}}}$ (namely, $\hat{\sigma}^2_{\hat{\beta}_1^{\text{adj}}}$), can be determined when the unknown variances ($\sigma^2_{\hat{\beta}_1}$ and $\sigma^2_{\hat{\theta}_1}$) are replaced with robust estimates of variance. Using SAS PROC MIXED, robust estimates of variance can be obtained with the "EMPIRICAL" option. Using this estimated variance, an approximate 95% CI for β_1 is then

$$\hat{\beta}_1^{\text{adj}} \pm 2\hat{\sigma}_{\hat{\beta}_1^{\text{adj}}} \tag{10}$$

Rosner et al. (1989) also considered estimators based on (8)–(10), but where the main study model was a logistic regression model, the validation study model was a linear model, and where both involved independent errors.

Application

EPA Study in Denver: Background and Methods

The data for the application of these methods are from an EPA study in Denver (see Rabinovitch et al., 2004). This ongoing project involves studying the effects of air pollution on children (ages between 6 and 12 years) with moderate and severe asthma. The children attend a school at the National Jewish Medical & Research Center, where the research is conducted; this facilitates data collection and monitoring.

Personal and fixed monitor concentrations for the validation study were recorded within the fall and winter months of 2002–2003 and 2003–2004. The fixed monitors were located at the school the children attended, one indoors and one outdoors, and up to 10 children wore personal monitors on a given day. A daily reading was based on an entire 24 h period, for all monitor types. Subjects wore the personal monitor for an entire day, including time at home, to reflect their actual daily level of exposure. Research Triangle Institute (RTI) monitors (see Rodes et al., 2001; Lawless, 2003) were used at the fixed sites as well as for subject personal monitors for the validation study. (The RTI personal sampling system for children is a compact version of the adult personal system described by Rodes et al., 2001.) Total $PM_{2.5}$ was further broken into measured amounts of specific components such as elemental carbon, sulfate, nitrate and ETS. Lawless et al. (2004) describe methods of deriving ETS concentrations from $PM_{2.5}$.

After removing flagged data (due to subject noncompliance and/or monitor error), there were 567 daily personal sulfate concentration values available for analysis among 50 subjects, on days when fixed monitor concentrations were also available. There were 111 daily readings available for analysis for both the fixed indoor and outdoor monitors, after removing flagged values due to monitor error.

The health data and ambient pollution measures used to fit the main study model were taken in the winter seasons of 1999–2000 and 2000–2001 (same time of year as validation study). There were 75 subjects in the 2 years of the study (some in only the first or second study year, and some in both), and subjects had an average of 57 days with recorded FEV_1 on days when fixed monitor pollution concentrations were also available. Subjects had several FEV_1 values recorded in the morning (0700–0900) and evening (1700–2300). Daily FEV_1 levels were then obtained for subjects by averaging the morning and evening means. For more description of the data collection and methods, see Rabinovitch et al. (2004).

Sulfate and $PM_{2.5}$ Concentrations

Generally, sulfate concentrations are lower in Denver than in some other regions of the US, and sulfate composes a relatively small fraction of total ambient $PM_{2.5}$ (8% on average, based on data collected within the validation study

period). Still, daily concentrations of ambient $PM_{2.5}$ and sulfate were moderately well correlated ($r = 0.63$). Other $PM_{2.5}$ components had similar correlations with $PM_{2.5}$: $r = 0.72$ between elemental carbon (EC) and $PM_{2.5}$; $r = 0.66$ between nitrate and $PM_{2.5}$. However, we chose sulfate to predict personal ambient $PM_{2.5}$ exposures because there are few if any nonambient sources of sulfate, while for EC and nitrate, this is not as clear.

Table 1 displays summary statistics for daily pollutant concentrations. Although sulfate concentrations relative to $PM_{2.5}$ indoors and outdoors were within 1% (last two rows), it should be noted that significant amounts of $PM_{2.5}$ are generated indoors, but not sulfate. Therefore, the similar percentages does not reflect equal infiltration rates of sulfate and $PM_{2.5}$. Figure 1 shows time-series graphs for daily mean personal sulfate and fixed outdoor sulfate (panel a), and daily mean personal sulfate and fixed indoor sulfate (panel b), both for fall and winter, 2002–2003. The correlation of daily values for the two series in (a) was $r = 0.96$, and for the two series in (b) it was $r = 0.97$. However, the data clearly show that fixed outdoor sulfate levels were generally about twice as large as mean personal levels, whereas fixed indoor levels were similar to mean personal levels. Figure 2 shows the differences in mean personal sulfate and fixed outdoor sulfate more clearly. The solid line is the least-squares regression fit to the data (y-intercept = 0.079, slope = 0.453), while the dotted line indicates equal concentrations (y-intercept = 0, slope = 1). Note that the absolute difference between average personal sulfate and outdoor sulfate increases as concentration increases.

Table 1. Summary statistics for daily pollutant concentrations in validation study period, fall and winter, 2002–2003 and 2003–2004.

Variable	n (days)	Mean	SD	Minimum	Maximum
Mean personal sulfate[a]	113	0.594	0.506	0.000	3.035
Outdoor sulfate	111	1.037	1.080	0.000	6.303
Indoor sulfate	111	0.575	0.557	0.000	2.759
Outdoor $PM_{2.5}$	111	12.699	6.426	0.660	32.290
Indoor $PM_{2.5}$	111	8.148	4.348	2.750	32.130
Sulfate/$PM_{2.5}$: outdoor	111	0.079	0.067	0.000	0.529
Sulfate/$PM_{2.5}$: indoor	111	0.074	0.060	0.000	0.257

Units for sulfate and $PM_{2.5}$ are $\mu g/m^3$.
[a]Values were based on the mean of 1 to 9 subjects per day.

The SD of daily mean personal sulfate values (0.51 $\mu g/m^3$) was greater than the mean of the daily SD (0.17 $\mu g/m^3$). This indicates that sulfate was relatively homogeneous at fixed times (across subject locations), compared with how it changed over time.

Validation Study Model Fit

Using the methods described in the Methods section, personal ambient $PM_{2.5}$ values (X_{it}^{A*}) were calculated for each subject on days when data were available; a total of 567 observations were generated for 50 subjects. Averages were computed for each subject within the study period. The grand

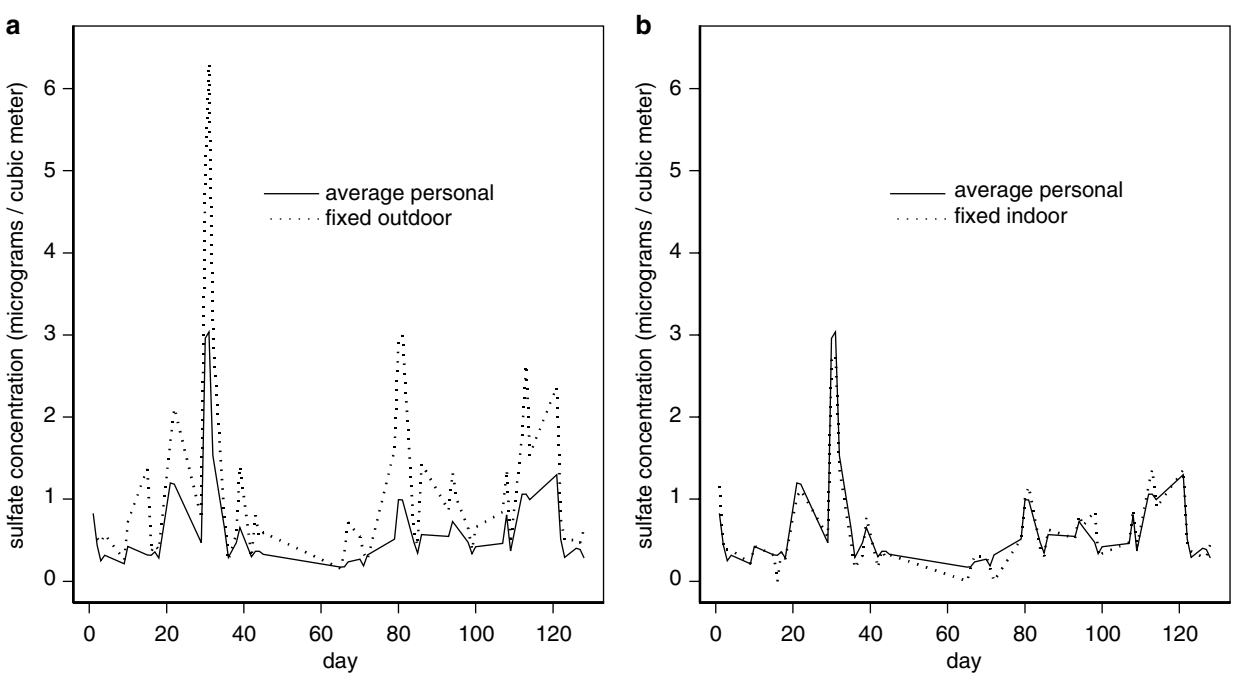

Figure 1. Daily average personal sulfate exposure *versus* (a) fixed outdoor sulfate and (b) fixed indoor sulfate. Fixed monitors were placed at the school the study subjects attended. Day 1 is November 4, 2002; day 128 is March 11, 2003. Similar patterns were observed for fall and winter, 2003–2004 data (not plotted).

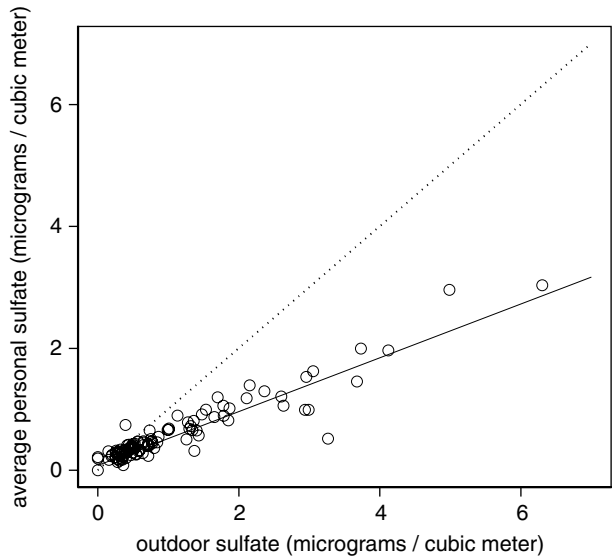

Figure 2. Daily average personal sulfate plotted *versus* outdoor sulfate, for fall and winter, 2002–2003 and 2003–2004 (each circle represents concentrations for 1 day). The solid line is the least-squares regression fit (y-intercept = 0.079, slope = 0.453) and the dotted line is the line of equal concentrations (y-intercept = 0, slope = 1).

mean of these averages across subjects was 6.38 $\mu g/m^3$ (SD = 1.60, min = 3.20, max = 10.97). Next, daily F_{PEX} values were calculated for each subject as (X_{it}^{A*}/X_t). The grand mean of subject averages for this variable was 0.51 (SD = 0.14, min = 0.19, max = 0.92).

Using the constructed X_{it}^{A*} values and ambient $PM_{2.5}$ concentrations, the personal exposure model (7) was fit using a mixed model analysis (using the default restricted maximum likelihood (REML) estimators). Since the outcome represented the fraction of ambient $PM_{2.5}$ that a subject was exposed to on a given day, we further constrained the model by setting $\theta_0 = 0$. Estimates obtained for the remaining parameters were $\hat{\theta}_1 = 0.46$ (SE = 0.02), $\hat{\sigma}_\phi^2 = 0.014$, $\hat{\sigma}_\omega^2 = 10$ (with an independent error structure for time and subject). A plot of residuals *versus* $PM_{2.5}$ indicated some right skewness, which is not surprising since the distribution of X_{it}^{A*} values were also somewhat right skewed. It is not expected that this apparent slight violation of the normally distributed errors assumption greatly affected estimates and standard errors.

The observed slope value of 0.46 for ambient $PM_{2.5}$ in the validation study model regression reflected concentration-dependent measurement error between outdoor and average personal pollution concentrations.

Unadjusted and Adjusted Health Effects from the EPA Study

Using data collected from our health study (also see Rabinovitch et al., 2004), we determined $\hat{\beta}_1$ and $\hat{\beta}_1^{adj}$ after fitting the main (5) and validation study (7) models. For the main study model, daily FEV_1 was the outcome, with outdoor $PM_{2.5}$ as the predictor of interest. There were several covariates in this model: height, temperature, barometric pressure, humidity and linear trend for time as continuous variables; weekend, holiday and upper respiratory illness as daily indicator variables; year as a class variable (1 or 2). A 1-day lag of the pollutant to the health outcome was used. A spatial exponential covariance structure was used to model correlated responses within subjects over time; this structure allowed us to account for gaps between days with available data, including data between years. A total of 4282 subject-day observations were used to fit the main study model, which produced $\hat{\beta}_1 = -0.002$ litres per $\mu g/m^3$ (empirical SE = 0.001), which corresponded to a 1% decrease in FEV_1 per 10 $\mu g/m^3$ increase in total ambient $PM_{2.5}$.

Using the estimated slope for the validation study model (based on generated personal ambient $PM_{2.5}$ values using constant λ), the adjusted estimate based on (8) was found to be:

$$\hat{\beta}_1^{adj} = \hat{\beta}_1/\hat{\theta}_1 = -0.002/0.46 = -0.00435 \text{ liters per } \mu g/m^3$$

This corresponds to an average decrease in FEV_1 of 2.2% per 10 $\mu g/m^3$ increase in ambient $PM_{2.5}$ for the study subjects.

Using (9) and (10), we calculated the asymptotic 95% CI for the corrected estimate to be (−4.3%, 0.0%). The CI for the unadjusted estimate (−2.0%, 0.0%) did not contain the adjusted point estimate of −2.2%. Since data were combined across years, one of our key assumptions was that the general relationship between the ambient pollutants remained consistent. Based on our observations this seemed reasonable.

Equation (9) leads to the inequality $\sigma_{\hat{\beta}_1^{adj}} \geq \sigma_{\hat{\beta}_1}/\hat{\theta}_1$. If contribution from the second term on the right-hand side of (9) is negligible, then $\sigma_{\hat{\beta}_1^{adj}} \approx \sigma_{\hat{\beta}_1}/\hat{\theta}_1$. Consequently, the significance of the calibrated estimate will be roughly the same as for the uncalibrated estimate. So when concentration-dependent measurement error exists, regression calibration will have a strong effect on the magnitude of the estimate, but not the P-value. In our case, the second term on the right-hand side of (9) was indeed negligible, and the P-values of uncalibrated and calibrated estimates (using z-statistics) were 0.0455 and 0.0462, respectively. In terms of statistical power and future studies, Equation (9) and our data also indicate that increasing the sample size in the main study model will reduce the variance of $\hat{\beta}_1^{adj}$ more efficiently than increasing the sample size in the validation study model.

Simulated Properties of Estimation Techniques

In order to verify the effectiveness of the regression calibration methods, 1000 simulations were conducted assuming our estimates of β_1 and θ_1 to be true. Within each simulation, the fit personal exposure and health models were employed to generate new outcomes. (The generated outcomes included error, so they were not predicted values.) The health and personal exposure models were then refit, yielding simulated values of $\hat{\beta}_1$, $\hat{\theta}_1$ and $\hat{\beta}_1^{adj}$. Within each simulation, data were generated to yield roughly the same sample sizes

that were obtained in the actual study. The simulations were carried out using a created SAS macro-program and employing the "Output Delivery System" (ODS) to obtain output for each simulation. More details about these simulations are given in section "Details for Simulation" for Appendix A.

The average estimate, percentage error (i.e., bias), mean-squared error (MSE) and confidence interval coverage rates were all determined for the unadjusted and adjusted estimates and are displayed in Table 2. The percentage error in the mean estimate is calculated relative to the true slope. The MSE is calculated by squaring the difference between each simulated estimate and true slope, and then averaging these values. The CI coverage rate is the proportion of constructed CIs that contain the true slope. This calculation was particularly important since the CI procedure is not based on exact methods, but rather on large sample theory.

Results for the adjusted estimates were as expected and desired; the difference in actual CI coverage and nominal coverage (95%), as well as bias for the adjusted estimates, was small and could possibly be due to sampling error in the 1000 simulations. The MSE was roughly twice as large for the unadjusted estimates than the adjusted ones. The MSE can also be calculated as the variance plus the squared bias for the simulated estimates, which are also reported in Table 2. These quantities show that the MSE was primarily due to variance for the adjusted estimates, and primarily due to squared bias for the unadjusted ones. However, the MSE indicates that the added variability in the adjusted estimates does not outweigh the gain in unbiasedness that this estimation technique has.

Discussion

Consideration of Nonambient $PM_{2.5}$

In our regressions, we estimated the effects of personal ambient $PM_{2.5}$ on FEV_1. Since personal ambient $PM_{2.5}$ is only a portion of the total $PM_{2.5}$ to which subjects are exposed, a question arises as to how estimates would change if nonambient $PM_{2.5}$ was also included in the model. Using simple calculations, our data indicated that ambient and nonambient personal $PM_{2.5}$ exposures were not correlated. (Nonambient personal $PM_{2.5}$ exposures were estimated as $X_{it}^{N*} = X_{it}^{P} - X_{it}^{A*}$.) These findings are consistent with those reported from Wilson and Suh (1997), and this suggests that bias is not introduced in estimating effects of X^A on health when X^N is not included in the model (Zeger et al., 2000).

Table 2. Properties of unadjusted and adjusted estimators, determined through Monte Carlo simulation.

Quantity	Unadjusted estimator, $\hat{\beta}_1$	Adjusted estimator, $\hat{\beta}_1^{adj}$
95% CI coverage rate	154/1000 (15.4%)	939/1000 (93.9%)
True slope	−0.00435	−0.00435
Mean estimate	−0.00206	−0.00449
% error in mean estimate	+53%	−3%
MSE × 10^6	5.81	2.75
Variance × 10^6	0.56	2.73
Bias^2 × 10^6	5.25	0.02

All quantities are based on 1000 simulations. True slope and mean estimate entries represent the change in raw FEV_1 (l) per 1 $\mu g/m^3$ increase of ambient $PM_{2.5}$. The units for MSE, variance and squared bias are the same, but squared.

Fixed versus Subject-Specific λ

The use of a common λ to generate personal ambient $PM_{2.5}$ is preferred for several reasons. First, subject-specific estimates vary so much that more error is introduced into the model, making estimation more difficult. This could be as much due to high variability in the pollutant concentrations (in time and/or space) as it is in different subject lifestyles and housing characteristics. Second, by using a common λ, we can estimate personal ambient $PM_{2.5}$ exposures for subjects for whom estimation of personal λ values are more difficult (e.g., high-ETS-exposed subjects). Lastly, if a random slope for the ambient pollutant is included in the validation study model, we would expect that differences in λ values between subjects would be accounted for by this term, with little or no effect on the estimate of θ_1. Examination of our data verified this. Thus, although estimates of personal ambient $PM_{2.5}$ exposure will be different for these two methods, it is not expected that using the common infiltration factor will lead to bias in estimating θ_1.

General Conclusions

The slope (θ_1) in the validation study regression model (6) indicates whether concentration-dependent measurement error exists, and it is this quantity that is used in regression calibration to adjust estimates. Specifically, values of θ_1 that differ substantially from one indicate bias in associated health-effects estimators. Recent articles (Janssen et al., 1997, 1998, 1999; Ebelt et al., 2000; Rojas-Bracho et al., 2000; Williams et al., 2000; Liu et al., 2003) reported slope estimates for regressions of personal PM concentrations on fixed monitor PM concentrations: mean or median slopes were as low as 0.4 and as high as 0.8 for fixed outdoor monitors. These findings underscore the importance of calibrating estimates if fixed monitors are used to measure exposure levels in health effect studies, when the relationship between level-of-exposed ambient PM and health is of interest. Once a reliable value of λ is obtained, our proposed methods will allow researchers to analyze this relationship without using total personal PM, which has been shown to pose modeling problems for certain subjects such as those with high-ETS exposure.

Fortunately, it is possible for past studies to calibrate estimates if adequate validation study data that are still

relevant can be obtained, and our results suggest that relatively small amounts of validation study data are needed in order to adjust pollutant slope estimates from the main study model, making cost less of an issue. The regression calibration methods described here can be applied whether ambient PM components are of interest, or total PM. In the latter case, extrapolating estimates of exposure is not needed; one simply uses the observed PM as the outcome in the personal exposure (or validation study) model.

Acknowledgements

This work was funded in part by three grants: EPA R825702, Thrasher Research Fund 02816-8 and, Colorado Tobacco Research Program R2-001.

References

Agresti A. *Categorical Data Analysis*, 2nd edn. John Wiley & Sons, New Jersey, 2002.

Carroll R.J., Ruppert D., and Stephanski L.A. *Measurement Error in Nonlinear Models*. Chapman and Hall, London, 1995.

Ebelt S.T., Petkau A.J., Vedal S., Fisher T.V., and Brauer M. Exposure of chronic obstructive pulmonary disease patients to particulate matter: relationships between personal and ambient concentrations. *J Air Waste Manage Assoc* 2000: 50: 1081–1094.

Fuller W.A. *Measurement Error Models*. John Wiley & Sons, New York, 1987.

Haukka J.K. Correction for covariate measurement error in generalized linear models — a bootstrap approach. *Biometrics* 1995: 51: 1127–1132.

Janssen N.A.H., Hoek G., Brunekreef B., Harssema H., Mensink I., and Zuidhof A. Personal sampling of particles in adults: relation among personal, indoor, and outdoor air concentrations. *Am J Epidemiol* 1998: 146: 537–547.

Janssen N.A.H., Hoek G., Harssema H., and Brunekreef B. Childhood exposure to PM_{10}: relation between personal, classroom, and outdoor concentrations. *Occup Environ Med* 1997: 54: 888–894.

Janssen N.A.H., Hoek G., Harssema H., and Brunekreef B. Personal exposure to fine particles in children correlates closely with ambient fine particles. *Arch Environ Health* 1999: 54: 95–101.

Lawless P.A. Portable air sampling apparatus including non-intrusive activity monitor and methods of using same, US Patent 6,502,469 B2, awarded 1/7/2003, Research Triangle Institute, Research Triangle Park, NC 27709.

Lawless P.A., Rodes C.E., and Ensor D.S. Multiwavelength absorbance of filter deposits for determination of environmental tobacco smoke and black carbon. *Atmos Environ* 2004: 38: 3373–3383.

Liu L.-J.S., Box M., Kalman D., Kaufman J., Koenig J., Larson T., Lumley T., Sheppard L., and Wallace L. Exposure assessment of particulate matter for susceptible populations in Seattle, WA. *Environ Health Perspect* 2003: 111: 909–918.

Ozkaynak H., Xue J., Spengler J., Wallace L., Pellizzari E., and Jenkins P. Personal exposure to airborne particles and metals: results from the Particle TEAM Study in Riverside, CA. *J Exposure Anal Environ Epidemiol* 1996: 6: 57–78.

Rabinovitch N., Zhang L., Murphy J., Vedal S., Dutton S.J., and Gelfand E.W. Health effects of wintertime ambient air pollution on children with moderate to severe asthma. *J Allergy Clin Immunol* 2004: 114: 1131–1137.

Richardson A.M., and Welsh A.H. Asymptotic properties of restricted maximum likelihood (REML) estimates for hierarchical mixed models. *Aust J Stat* 1994: 36: 31–43.

Rodes C.E., Lawless P.A., Evans G.F., Sheldon L.S., Williams R.W., Vette A.F., Creason J.P., and Walsh D. The relationships between personal PM exposures for elderly populations and indoor and outdoor concentrations for three retirement center scenarios. *J Exposure Anal Environ Epidemiol* 2001: 11: 103–115.

Rojas-Bracho L., Suh H.H., and Koutrakis P. Relationship among personal, indoor, and out-door particle concentrations for individuals with COPD. *J Exposure Anal Environ Epidemiol* 2000: 10: 294–306.

Rosner B., Willett W.C., and Spiegelman D. Correction of logistic regression relative risk estimates and confidence intervals for systematic within-person measurement error. *Stat Med* 1989: 8: 1051–1069.

Sarnat J.A., Long C.M., Koutrakis P., Coull B.A., Schwartz J., and Suh H.H. Using sulfur as a tracer of outdoor fine particulate matter. *Environ Sci Technol* 2002: 36: 5305–5314.

Williams R., Suggs J., Zweidinger R., Evans G., Creason J., Kwok R., Rodes C., Lawless P., and Sheldon L. The 1998 Baltimore Particulate Epidemiology — Exposure Study: Part 1. Comparison of ambient, residential outdoor, indoor and apartment particulate matter monitoring. *J Exposure Anal Environ Epidemiol* 2000: 10: 518–532.

Wilson W., Mage D., and Grant L. Estimating separately personal exposure to ambient and nonambient particulate matter for epidemiology and risk assessment: why and how. *J Air Waste Manage Assoc* 2000: 50: 1167–1183.

Wilson W., and Suh H. Fine particles and coarse particles: concentration relationships relevant to epidemiologic studies. *J Air Waste Manage Assoc* 1997: 47: 1238–1249.

Zeger S., Thomas D., Dominici F., Samet J.M., Schwartz J., Dockery D., and Cohen A. Exposure measurement error in time-series studies of air pollution: concepts and consequences. *Environ Health Perspect* 2000: 108: 419–426.

Appendix A

Estimating the Ratio of $PM_{2.5}$ to Sulfate Exposure Factors (λ)

A general approach to estimating λ (i) Perform a mixed model regression of total personal $PM_{2.5}$ on ambient $PM_{2.5}$, where fixed and subject-specific random terms for both the y-intercept and slope of ambient $PM_{2.5}$ are included in the model. If nonambient and ambient $PM_{2.5}$ exposures are approximately independent of each other, which our data suggested (also see Wilson and Suh, 1997), then the personal slope (fixed slope plus subject-specific random slope) indicates the average fraction of ambient $PM_{2.5}$ that the subject is exposed to within the study period, while the y-intercept indicates average exposure to nonambient sources. (ii) Repeat the previous step, with personal sulfate and ambient sulfate. (iii) The estimate of λ for a given subject is then obtained by dividing the personal $PM_{2.5}$ slope by the personal sulfate slope. (iv) The common λ can be obtained by averaging subject-specific estimates.

Notes on Calculations Data for the 21 "low-ETS" children were used to estimate subject-specific λ values. (A "low-ETS" subject was defined as one who (i) claimed to not live in a home with a smoker, and (ii) infrequently had days with high measured personal ETS exposure within the study period.) The average estimated value across subjects ($(\hat{\lambda} = (1/n)\sum_i \hat{\lambda}_i)$ was 0.78 (median = 0.75, SD = 0.285, min = 0.44, max = 1.59). The regression of total personal $PM_{2.5}$ on ambient $PM_{2.5}$ for the remaining 29 subjects produced counterintuitive results; the slope estimate for the group was near zero, with no strong outliers apparent in the data. But slope estimates were similar between ETS groups for the sulfate regressions (and confirmed when analyzing

another strong ambient-sourced $PM_{2.5}$ component, elemental carbon). This reaffirmed our belief that exposures to ambient $PM_{2.5}$ were probably more similar between ETS groups and that more complex statistical methods were necessary to model accurately those not in the low-ETS group.

Details for Simulations

Based on observed fits, we assumed $\omega_{it}' \sim N(0,10)$ (i.e., ω_{it}' has a normal distribution with mean = 0, variance = 10), $u_{it} \sim N(0,2)$, $\omega_{it} \sim N(0,8)$, $\varepsilon_{it} \sim N(0,0.14)$ and $\phi_i \sim N(0, 0.014)$ for all i and t, and that the correlation between FEV_1 responses within an individual on two consecutive days was 0.44. For the models below, values for the random terms were sampled independently from these distributions for all i and t, except for ε_{it}, which were autocorrelated within subjects (AR(1) model) with $\rho = 0.44$. The variance of u was estimated by examining differences in estimated exposures between subjects within days since we did not have true ambient exposures for subjects. The variance for ω_{it} was then determined using $\sigma_{\omega}^2 = \sigma_{\omega'}^2 - \sigma_u^2$. Within each simulation, the following steps were taken.

The Health Model (i) Ambient exposures were simulated as $X_{it}^{A} = 0.46Z_t + \phi_i Z_t + \omega_{it}$. (ii) FEV_1 outcomes were then simulated as $Y_{it} = 2\text{–}0.00435X_{it}^{A} + \varepsilon_{it}$. (iii) Some FEV_1 outcomes were randomly set to missing values so that the pattern and amount of responses were similar to actual data. (Subjects missed having FEV_1 values on certain days due to absence or because the recorded FEV_1 values were flagged as invalid.) (iv) The generated FEV_1 data were then fit as a simple linear function of actual ambient $PM_{2.5}$ concentrations (with correlated errors) to obtain a simulated estimate of β_1.

The Personal Exposure Model (i) Ambient exposures were simulated (independently of those for the health model) using $X_{it}^{A} = 0.46Z_t + \phi_i Z_t + \omega_{it}$ for the same subjects and days that personal monitor information was available in the actual study. (ii) Exposures with measurement error were then created as $X_{it}^{A*} = X_{it}^{A} + u_{it}$. (iii) The generated ambient $PM_{2.5}$ exposures and actual ambient $PM_{2.5}$ concentrations were then used to fit model (7), yielding a simulated estimate of θ_1.