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Regression calibration for models with two predictor variables measured with error and their interaction, using instrumental variables and longitudinal data

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SUMMARY

Regression calibration provides a way to obtain unbiased estimators of fixed effects in regression models when one or more predictors are measured with error. Recent development of measurement error methods has focused on models that include interaction terms between measured-with-error predictors, and separately, methods for estimation in models that account for correlated data. In this work, explicit and novel forms of regression calibration estimators and associated asymptotic variances are derived for longitudinal models that include interaction terms, when data from instrumental and unbiased surrogate variables are available but not the actual predictors of interest. The longitudinal data are fit using linear mixed models that contain random intercepts and account for serial correlation and unequally spaced observations.

The motivating application involves a longitudinal study of exposure to two pollutants (predictors) – outdoor fine particulate matter and cigarette smoke – and their association in interactive form with levels of a biomarker of inflammation, leukotriene E4 (LTE₄, outcome) in asthmatic children. Since the exposure concentrations could not be directly observed, measurements from a fixed outdoor monitor and urinary cotinine concentrations were used as instrumental variables, and concentrations of fine ambient particulate matter and cigarette smoke measured with error by personal monitors were used as unbiased surrogate variables. The derived regression calibration methods were applied to estimate coefficients of the unobserved predictors and their interaction, allowing for direct comparison of toxicity of the different pollutants. Simulations were used to verify accuracy of inferential methods based on asymptotic theory.

Keywords

measurement error; errors in variables; surrogate; PM_{2.5}; LTE₄; cotinine

1. Introduction

An important research study was conducted at National Jewish Health (NJH) in Denver, Colorado to examine the relationship between air pollution and health of children with persistent asthma who attended a school on the NJH campus [1]. One aim of this investigation was to determine effect on health after exposure to two pollutants, secondhand smoke (SHS) and fine particulate matter from outdoor sources (ambient particulate matter less than 2.5 microns in diameter, or ambient $PM_{2.5}$). Rabinovitch and colleagues demonstrated that although increasing one pollutant generally had a detrimental impact on health, the two pollutants had a negative interaction with each other such that changes in health outcomes per increase in one pollutant were greater when the second pollutant was lower. One limitation of the analysis was that instrumental variables were used rather than true exposure concentrations that could not be obtained. Specifically, urinary cotinine, a metabolite of nicotine, was used in place of SHS exposure, and $PM_{2.5}$ measured with a fixed outdoor monitor, was used instead of actual ambient $PM_{2.5}$ exposure. Since such instrumental variables may differ from the true variables of interest, there are limitations on how associated estimates can be interpreted. While the instrumental variables may suggest whether coefficients of true predictors of interest are positive or negative, an estimate of change in health outcomes per unit increase in exposure cannot be obtained with this approach, nor can direct comparisons be made between pollutant types. Although unbiased measures of personal exposure to SHS and ambient fine particulate matter were also available on a subset of days as surrogate measures of exposure, direct use of these measurements as predictors was not possible, due to the relatively small amount of data measured with error and lack of ability to reliably estimate the measurement error variances.

In this article, explicit forms of regression calibration estimators are derived for coefficients of unobserved predictors and their interaction in a longitudinal model, using surrogate and instrumental variables in place of the unobserved ones. Although the air pollution and asthma data presented above motivated the methods development, these estimators may apply to many longitudinal situations with two predictors measured with error that also have non-negligible interaction.

Regression calibration estimation procedures using instrumental variables and unbiased surrogate variables (RCIV) are well documented in the literature [2-4], and have been extended to multiple linear regression models [3-4]. There are several algorithms that can be used to accomplish RCIV. Two approaches that yield the same results for simpler models are described in the section entitled First Regression Calibration IV Algorithm by Carroll, et al. [3]. One approach uses a function of estimates from separate model fits to obtain calibration estimates (termed RCIV1 here), and another uses estimated expected values for the unobservable 'true' predictor variables (RCIV2). Thurston et al. [5] established equivalence of these approaches for independent data in generalized linear models.

Although an interaction term can be considered an additional predictor in a multiple regression model, explicit forms of estimators have only recently been derived for models with interaction terms involving measured-with-error variables. Murad and Freedman [6] examined models with two independent variables plus their interaction, using unbiased

measured-with-error independent variables, without any instrumental variables. They compared method of moments and regression calibration estimation methods and found a slight advantage for the regression calibration method. Wong et al. [7] and Huang, et al. [8] considered measurement error methods in models with one continuous predictor measured with error, one categorical predictor, plus their interaction. Others have applied structural equation modeling approaches (summarized in by Lee et al. [9]) to address measurement error in models with interaction. However, none of these approaches use mixed-effects models with 2 continuous variables or account for correlated data over time.

Several articles have appeared that address measurement error in models that account for correlated data by employing linear mixed models [10], nonlinear mixed models [11,12], generalized linear mixed models [13-15], or other methods [16]. However, these articles do not specifically consider models with interaction terms.

In this work, we derive an explicit form of the RCIV1 estimators and associated asymptotic variances for coefficients of two continuous unobserved predictors and their interaction in longitudinal models using measured-with-error and instrumental variables. The form of the estimators is derived from a general expression for multiple regression models (see [3-4]). Linear mixed models with random intercepts and serially correlated errors are used to account for the correlated data. This method is applied to estimate the relationship between a biological mediator of asthma, urinary leukotriene E4 (LTE₄), and exposure to ambient PM_{2.5} and SHS, using the data described above. These estimators were tested for performance through Monte Carlo simulation.

2. Methods

2.1. Underlying models

Setting the framework for our methods, we consider a continuous outcome variable Y_{ij} (e.g., the health outcome variable) for subject i at time j , $i = 1, \dots, n$ and $j = 1, \dots, r_i$, that can be expressed through a linear mixed model as

$$Y_{ij} = \beta_0 + \beta_1 X_{1ij} + \beta_2 X_{2ij} + \beta_3 X_{1ij} X_{2ij} + b_i^Y + \mathbf{Z}_{ij} \boldsymbol{\tau} + \varepsilon_{ij} \quad (1)$$

where X_{1ij} and X_{2ij} are predictor variables that are not directly observable (e.g., the true pollutant exposure variables), $b_i^Y \sim N(0, \sigma_{b^Y}^2)$ is a random intercept term for subjects, $\mathbf{Z}_{ij} = (Z_{1ij}, Z_{2ij}, \dots, Z_{kij})$ are additional covariates with coefficients $\boldsymbol{\tau} = (\tau_1, \tau_2, \dots, \tau_k)^t$, and $\varepsilon_i = (\varepsilon_{i1}, \varepsilon_{i2}, \dots, \varepsilon_{ir_i})^t \sim N(\mathbf{0}, \mathbf{R}_{\varepsilon_i})$. The random intercept and error terms are assumed to be independent of each other, and subjects are assumed to be independent. The covariates $\mathbf{Z}_{ij}$ are assumed to be measured without error. In our application, we use the spatial power structure for $\mathbf{R}_{\varepsilon_i}$ to account for serial correlation in the data:

$Cov(\varepsilon_{ij}, \varepsilon_{ij'}) = \mathbf{R}_{\varepsilon_i}(j, j') = \phi_{\varepsilon}^{|t_{ij} - t_{ij'}|} \sigma_{\varepsilon}^2$, for days t_{ij} and $t_{ij'}$ in the study period associated with observations j and j' , respectively, for subject i . The parameters in this structure have the same interpretations as in the first-order autoregressive [AR(1)] structure, but the structure accounts for the intermittency of our data. The health outcome variable Y in our application is LTE₄, a biomarker of inflammation measured from urine in picograms per

milliter (pg/ml) and standardized per milligram/milliter (mg/ml) of creatinine [1]; X_1 is the exposure concentration of second-hand smoke (SHS) [also quantified as particulate matter less than 2.5 microns in diameter, but only from cigarette smoke; here we simply use SHS to denote this pollutant so as not to confuse it with $PM_{2.5}$ from ambient sources], and X_2 is the exposure concentration of $PM_{2.5}$ from outdoor sources such as automobile or industrial exhaust. Both X_1 and X_2 are measured in micrograms per cubic meter ($\mu\text{g}/\text{m}^3$).

Instead of X_1 and X_2 , we observe instrumental variables M_1 and M_2 that are linearly related to X_1 and X_2 :

$$\begin{aligned} X_{1ij} &= \theta_0 + \theta_1 M_{1ij} + \theta_2 M_{2ij} + b_i^{X_1} + \omega_{1ij} \\ X_{2ij} &= \pi_0 + \pi_1 M_{1ij} + \pi_2 M_{2ij} + b_i^{X_2} + \omega_{2ij} \end{aligned} \quad (2)$$

where $b_i^{X_p} \sim N(0, \sigma_{b^{X_p}}^2)$, $p = 1, 2$ are random intercept terms for subjects, and ω_1 and ω_2 are error terms that each may be correlated over time; we assume $\omega_{pi} = (\omega_{pi1}, \omega_{pi2}, \dots, \omega_{pir_i})^t \sim N(\mathbf{0}, \mathbf{R}_{\omega_{pi}})$ is independent of $b_i^{X_p}$ for all i , for $p = 1, 2$. In the application, M_1 is cotinine, a nicotine metabolite measured in the urine reflecting SHS exposure, measured in nanograms per milliliter (ng/ml) and standardized per mg/ml of creatinine, and M_2 is the one-hour morning maximum ambient $PM_{2.5}$ concentration measured in $\mu\text{g}/\text{m}^3$ from a fixed outdoor monitor.

Unbiased measures of X_{1ij} and X_{2ij} also exist, denoted as $W_{1ij} = X_{1ij} + U_{1ij}$ and $W_{2ij} = X_{2ij} + U_{2ij}$, respectively, where U_{pij} has mean 0 and is independent of $b_i^{X_p}$, $p = 1, 2$. In the application, these unbiased measures of SHS (W_1) and ambient $PM_{2.5}$ (W_2) exposure were obtained for a subset of days on each subject as described in [17-19]. First, total $PM_{2.5}$ exposure was estimated for a given subject and day [17]. This was accomplished by having children wear personal monitors that measured fine particle levels ($PM_{2.5}$) in their breathing zone over a 24 hour period. A portion of this total was then estimated to be from SHS, by methods described in [18], and another portion was estimated to be from outdoor (or ambient) sources using the 'Extrapolation 2' Method described in [19]. The SHS exposure estimates were obtained by a multiwavelength method that attributes a certain portion of the total personal $PM_{2.5}$ into SHS. The personal ambient $PM_{2.5}$ exposures were estimated by first separating the total personal ambient $PM_{2.5}$ concentrations into chemical components, and then using components within the total known to be either largely or exclusively derived from outdoor sources to extrapolate an estimate of exposure to total ambient $PM_{2.5}$, also using the portion of these components in outdoor concentrations. The specific components used were sulfate and iron, and the exposure estimates also adjusted for different infiltration rates of the components.

Incorporating the W_1 and W_2 variables into (2) yields

$$\begin{aligned} W_{1ij} &= \theta_0 + \theta_1 M_{1ij} + \theta_2 M_{2ij} + b_i^{X_1} + (\omega_{1ij} + U_{1ij}) \\ W_{2ij} &= \pi_0 + \pi_1 M_{1ij} + \pi_2 M_{2ij} + b_i^{X_2} + (\omega_{2ij} + U_{2ij}) \end{aligned} \quad (3)$$

In (3), let $\omega'_{pij} = \omega_{pij} + U_{pij}$ denote the new error term, and consider error vectors for subject i as $\omega'_{pi} = (\omega'_{pi1}, \omega'_{pi2}, \dots, \omega'_{pir_i})^t$, for $p = 1, 2$. The true structure for $Var(\omega'_{pi}) = R_{\omega'_{pi}}$ can become quite complex depending on assumptions about the individual error components ω_{pij} and U_{pij} . Furthermore, since (X_1, X_2) is unobserved, identifying and estimating the true error structure can be difficult. Covariance structures used in the data application are discussed in Section 2.4.

The variables W_1 , W_2 , M_1 and M_2 are assumed to have the surrogacy property. A random variable S is a surrogate variable for (X_1, X_2) in predicting Y if $E(Y|X_1, X_2, S) = E(Y|X_1, X_2)$, with Y and (X_1, X_2) as previously defined. If W_1 , W_2 , M_1 and M_2 are not surrogates for (X_1, X_2) , then the critical assumption of non-differential measurement error in the regression calibration does not hold and results may be inaccurate [3]. One difference between the two sets of variables is that W_1 and W_2 are assumed to be unbiased for X_1 and X_2 , respectively, while the instrumental variables M_1 and M_2 are not. For the covariates, we also assume that $E(X_p|M_1, M_2, Z_1, \dots, Z_k) = E(X_p|M_1, M_2)$ for $p = 1, 2$.

2.2. Regression calibration approaches

For the given models, there are two common approaches to estimate $\beta = (\beta_0, \beta_1, \beta_2, \beta_3)^t$, which are loosely described as follows.

Regression calibration instrumental variable method 1 (RCIV1)—Fit (3), then separately fit (1) using (M_1, M_2) in place of (X_1, X_2) , and then obtain final estimates of β as functions of estimated parameters in (1) and (3).

Regression calibration instrumental variable method 2 (RCIV2)—Fit (3) to obtain predicted values of W_1 and W_2 that are unbiased for X_1 and X_2 (denoted as $\hat{E}(X_1|M_1, M_2)$ and $\hat{E}(X_2|M_1, M_2)$, respectively), then fit (1), using these predicted values in place of the unknown X_1 and X_2 . For the interaction term, use $\hat{E}(X_1|M_1, M_2)\hat{E}(X_2|M_1, M_2)$ in place of $\hat{E}(X_1X_2|M_1, M_2)$ (see [6] for justification).

Theoretical equivalence of RCIV1 and RCIV2 estimators has been established for generalized linear models, without repeated measures [5]. We will also establish theoretical equivalence of these methods under certain conditions for linear mixed models that can handle longitudinal data, in Section 2.6. One advantage of RCIV2 is that it is easier to implement for more complex underlying models, such as those considered here. An advantage of RCIV1 is that it is somewhat easier to derive associated asymptotic variances (e.g., for confidence intervals), which was in fact our initial motivation for deriving the RCIV1 estimators below. These regression calibration approaches are both described in [3] under ‘First Regression Calibration IV Algorithm’; the ‘Second’ algorithm in that text refers to something completely different.

2.3. RCIV1 - point estimation

In this section we derive the RCIV1 estimators for models (1) and (3) following the logic of Buonaccorsi [4], who demonstrated the estimators for general linear models (e.g., multiple

linear regression, uncorrelated errors). In order to develop the theory, we define matrix quantities related to models (1) and (3). First let $\beta_0 + \beta_1 X_{1ij} + \beta_2 X_{2ij} + \beta_3 X_{1ij}X_{2ij} = \mathbf{X}_{ij}\boldsymbol{\beta}$ where $\mathbf{X}_{ij} = (1, X_{1ij}, X_{2ij}, X_{1ij}X_{2ij})$ and $\boldsymbol{\beta} = (\beta_0, \beta_1, \beta_2, \beta_3)^t$. Corresponding to $\mathbf{X}_{ij}$, let $\mathbf{W}_{ij} = (1, W_{1ij}, W_{2ij}, W_{1ij}W_{2ij})$. We consider elements of $\mathbf{X}_{ij}$ and $\mathbf{W}_{ij}$ as predictors, with the first element being a dummy predictor for the intercept. Let $\mathbf{M}_{ij} = (1, M_{1ij}, M_{2ij})$ denote the surrogate predictors meaningful to model (3), and let

$\mathbf{M}_{ij}^{full} = (1, M_{1ij}, M_{2ij}, M_{1ij}^2, M_{2ij}^2, M_{1ij}M_{2ij})$ denote the surrogate predictors meaningful to model (1). (The second-order terms are induced due to the interaction term, $W_{1ij}W_{2ij}$.) Subject-specific data matrices are obtained by stacking rows of the vector of interest. For example,

$$\mathbf{X}_i = \begin{pmatrix} \mathbf{X}_{i1} \\ \mathbf{X}_{i2} \\ \vdots \\ \mathbf{X}_{ir_i} \end{pmatrix}$$

Also, let $\mathbf{Y}_i = (Y_{i1}, \dots, Y_{ir_i})^t$ denote vector of the responses for subject i , such that

$E(\mathbf{Y}_i | \mathbf{X}_i, \mathbf{Z}_i) = \mathbf{X}_i\boldsymbol{\beta} + \mathbf{Z}_i\boldsymbol{\tau}$. For the full model based on (1) and (3), we let $\mathbf{C}$ denote the matrix of coefficients such that

$$E(\mathbf{W}_i | \mathbf{M}_i) = \mathbf{M}_i^{full} \mathbf{C} = \begin{pmatrix} 1 & M_{1i1} & M_{2i1} & M_{1i1}^2 & M_{2i1}^2 & M_{1i1}M_{2i1} \\ 1 & M_{1i2} & M_{2i2} & M_{1i2}^2 & M_{2i2}^2 & M_{1i2}M_{2i2} \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ 1 & M_{1ir_i} & M_{2ir_i} & M_{1ir_i}^2 & M_{2ir_i}^2 & M_{1ir_i}M_{2ir_i} \end{pmatrix} \begin{pmatrix} 1 & \theta_0 & \pi_0 & \theta_0\pi_0 \\ 0 & \theta_1 & \pi_1 & \theta_0\pi_1 + \theta_1\pi_0 \\ 0 & \theta_2 & \pi_2 & \theta_0\pi_2 + \theta_2\pi_0 \\ 0 & 0 & 0 & \theta_1\pi_1 \\ 0 & 0 & 0 & \theta_2\pi_2 \\ 0 & 0 & 0 & \theta_2\pi_1 + \theta_1\pi_2 \end{pmatrix}$$

Now based on our models and assumptions,

$$\begin{aligned} E(\mathbf{Y}_i | \mathbf{M}_i) &= E_{\mathbf{X}}(E(\mathbf{Y}_i | \mathbf{X}_i, \mathbf{M}_i, \mathbf{Z}_i) | \mathbf{M}_i, \mathbf{Z}_i) \\ &= E_{\mathbf{X}}(E(\mathbf{Y}_i | \mathbf{X}_i, \mathbf{Z}_i) | \mathbf{M}_i, \mathbf{Z}_i) \\ &= E_{\mathbf{X}}(\mathbf{X}_i\boldsymbol{\beta} + \mathbf{Z}_i\boldsymbol{\tau} | \mathbf{M}_i, \mathbf{Z}_i) \\ &= E_{\mathbf{X}}(\mathbf{X}_i | \mathbf{M}_i)\boldsymbol{\beta} + E_{\mathbf{X}}(\mathbf{Z}_i | \mathbf{M}_i, \mathbf{Z}_i)\boldsymbol{\tau} \\ &= E_{\mathbf{X}}(\mathbf{W}_i | \mathbf{M}_i)\boldsymbol{\beta} + \mathbf{Z}_i\boldsymbol{\tau} \\ &= \mathbf{M}_i^{full}\mathbf{C}\boldsymbol{\beta} + \mathbf{Z}_i\boldsymbol{\tau} \end{aligned}$$

We will denote $\mathbf{C}\boldsymbol{\beta}$ as $\boldsymbol{\gamma} = (\gamma_0, \gamma_1, \gamma_2, \gamma_3, \gamma_4, \gamma_5)^t$; these are the coefficients of $\mathbf{M}_i^{full}$ that are estimated when model (1) is fit, replacing unknown $\mathbf{X}_i$ with $\mathbf{M}_i^{full}$. There are at most 4 linearly independent rows in $\mathbf{C}\boldsymbol{\gamma}$, and the constraints can be expressed as $\gamma_3 = \gamma_5(\theta_1\pi_1)/(\theta_2\pi_1 + \theta_1\pi_2)$ and $\gamma_4 = \gamma_5(\gamma_2\pi_2)/(\theta_2\pi_1 + \theta_1\pi_2)$. Thus, we can re-express

$$E(\mathbf{W}_i | \mathbf{M}_i) = \mathbf{M}_i^{red} \mathbf{C}^{red} = \begin{pmatrix} 1 & M_{1i1} & M_{2i1} & M_{i1}^* \\ 1 & M_{1i2} & M_{2i2} & M_{i2}^* \\ \vdots & \vdots & \vdots & \vdots \\ 1 & M_{1ir_i} & M_{2ir_i} & M_{ir_i}^* \end{pmatrix} \begin{pmatrix} 1 & \theta_0 & \pi_0 & \theta_0 \pi_0 \\ 0 & \theta_1 & \pi_1 & \theta_0 \pi_1 + \theta_1 \pi_0 \\ 0 & \theta_2 & \pi_2 & \theta_0 \pi_2 + \theta_2 \pi_0 \\ 0 & 0 & 0 & \theta_1 \pi_2 + \theta_2 \pi_1 \end{pmatrix}$$

where $M_{ij}^* = \frac{M_{1ij}^2 \theta_1 \pi_1 + M_{2ij}^2 \theta_2 \pi_2}{\pi_2 \theta_1 + \pi_1 \theta_2} + M_{1ij} M_{2ij}$, $j = 1, \dots, r_i$. The term M_{ij}^* essentially collects all of the higher order terms associated with the instrumental variables into one composite variable. In order to use M_{ij}^* , the θ and π parameters can be replaced with their unbiased estimators. (The forms of variance presented later do not account for the added variability in M^* due to replacement of parameters with estimators, but there was no apparent negative impact on calculated standard errors in the simulations conducted.) For this new model, $\beta = (\mathbf{C}^{red})^{-1} \gamma^{red}$, where $\gamma^{red} = (\gamma_0, \gamma_1, \gamma_2, \gamma_5)^t$ and

$$(\mathbf{C}^{red})^{-1} = \begin{pmatrix} 1 & \frac{(\pi_2 \theta_0 - \pi_0 \theta_2)}{c_1} & -\frac{(\pi_1 \theta_0 - \pi_0 \theta_1)}{c_1} & \frac{\pi_0 \theta_0}{c_2} \\ 0 & -\frac{\pi_2}{c_1} & \frac{\pi_1}{c_1} & -\frac{\pi_0}{c_2} \\ 0 & \frac{\theta_2}{c_1} & -\frac{\theta_1}{c_1} & -\frac{\theta_0}{c_2} \\ 0 & 0 & 0 & \frac{1}{c_2} \end{pmatrix} \quad (4)$$

where $c_1 = \pi_1 \theta_2 - \pi_2 \theta_1$ and $c_2 = \pi_1 \theta_2 + \pi_2 \theta_1$. The inverse holds as long as rows or columns in $\mathbf{C}^{red}$ are not linearly dependent [e.g., $(\theta_0, \theta_1, \theta_2)$ cannot be a scalar multiple of (π_0, π_1, π_2)]. For nonzero c_1 and c_2 , then the RCIV1 estimator is

$$\hat{\beta} = (\hat{\mathbf{C}}^{red})^{-1} \hat{\gamma}^{red}$$

where $(\hat{\mathbf{C}}^{red})^{-1}$ is obtained by replacing unknown parameters with their estimates based on the fit of (3) and $\hat{\gamma}^{red}$ is obtained from the regression of $\mathbf{Y}_i$ on $\mathbf{M}_i^{red}$ (and covariates).

For applications where M_1 is the primary instrumental variable for W_1 and M_2 is the primary instrumental variable for W_2 , the terms associated with θ_2 or π_1 may be negligible, in which case they can be dropped from model (3). In this case, the model reduction method is not required as M_{1ij}^2 and M_{2ij}^2 terms are eliminated and $\mathbf{C}$ no longer has linear dependencies; call this new matrix $\mathbf{C}^{simp}$, which can be inverted to obtain

$$(\mathbf{C}^{simp})^{-1} = \begin{pmatrix} 1 & -\frac{\theta_0}{\theta_1} & -\frac{\pi_0}{\pi_2} & \frac{\pi_0 \theta_0}{\pi_2 \theta_1} \\ 0 & \frac{1}{\theta_1} & 0 & -\frac{\pi_0}{\pi_2 \theta_1} \\ 0 & 0 & \frac{1}{\pi_2} & -\frac{\theta_0}{\pi_2 \theta_1} \\ 0 & 0 & 0 & \frac{1}{\pi_2 \theta_1} \end{pmatrix}$$

The form of $(\mathbf{C}^{simp})^{-1}$ can also be obtained by setting $\theta_2 = \pi_1 = 0$ in (4). Let

$\hat{\gamma}^{simp} = (\hat{\gamma}_0, \hat{\gamma}_1, \hat{\gamma}_2, \hat{\gamma}_3)^t$ be the estimated coefficients of the intercept, M_{1ij} , M_{2ij} , and $M_{1ij}M_{2ij}$, respectively, in the regression of Y_{ij} on these predictors, plus covariates. The

estimators of interest become $\hat{\beta}^{simp} = (\hat{\mathbf{C}}^{simp})^{-1} \hat{\gamma}^{simp}$, where as before, $(\hat{\mathbf{C}}^{simp})^{-1}$ is obtained by replacing individual parameters in $(\mathbf{C}^{simp})^{-1}$ with their ML estimators via mixed model fits of (3). The requirement becomes that θ_1 and π_2 are nonzero, which is highly likely since they are associated with the primary instrumental variables.

Note that the results in this section follow similarly if more random effect terms are added to (1), as long as all random effects have mean 0. Note also that although the covariates and associated parameters τ are fit in the same model, they are not used directly in computing estimates of β .

2.4. Covariance structures and approximations

Determining and fitting covariance structures using models (1)-(3) is quite difficult for a number of reasons. First, observed ‘errors’ in model (3) are the sum of two random error processes. Since values of X variables are not observed, it is difficult or impossible to estimate covariance parameters separately for these processes. Also, for RCIV1, since $\mathbf{Y}_i$ is regressed on $\mathbf{M}_i$, rather than $\mathbf{X}_i$, elements of (3) become embedded into the regression model, making $\text{Var}(\mathbf{Y}_i|\mathbf{M}_i)$ quite complex. (For the remainder of this article, conditioning on $\mathbf{Z}_i$ is implied but suppressed to simplify notation.) The following describes assumptions about covariance structures in the models, along with descriptions about approximations used for the covariance structures. Simulations were conducted in order to determine the accuracy of approximations, presented later.

For (3), one plausible set of assumptions is that errors U_{pij} and ω_{pij} are independent for all i and j , where ω_{pi} follows an AR(1) process over time, and measurement errors

$U_{pi} \sim N(0, \sigma_{U_p}^2 \mathbf{I})$, for each of $p = 1, 2$, which we term the ‘AR(1) plus ME variance’

structure (ME for measurement error). In this case, the $(j, j')^{th}$ element of $\mathbf{R}_{\omega'_{pi}}$ is

$\mathbf{R}_{\omega'_{pi}}(j, j') = \phi_{\omega_p}^{|t_{ij} - t_{ij'}|} \sigma_{\omega_p}^2$ $j \neq j'$, for off-diagonal elements and $\mathbf{R}_{\omega'_{pi}}(j, j) = \sigma_{\omega_p}^2 + \sigma_{U_p}^2$ for all j for diagonal elements, where t_{ij} is ordered day in the study that is associated with the j^{th} observation for subject i . We initially fit models using this set of assumptions. We then fit a second set of models assuming that the sum of the error components could be reasonably approximated by a single AR(1) process. Asterisks were added to covariance parameters in

these models $(\phi_{\omega_p}^*, \sigma_{\omega_p}^{*2}, \sigma_{\omega_{X_p}}^{*2}, p=1, 2)$ to distinguish them from covariance parameters in a true, or at least more realistic structure. For example, if the first set of assumptions held for the errors, but the single AR(1) structure were used to model it, parameters in the approximated structure could differ in value and interpretation from the first. Fits with our data demonstrated little difference in estimated effects of interest and associated standard errors between these two approaches, and goodness-of-fit statistics did not clearly favor one or the other. Thus we used the single AR(1) (plus random intercept) structure in final models. Note that for unequally spaced data such as with our data application, the AR(1) structure discussed above is actually fit with the spatial power structure, as with the model for $\mathbf{Y}$ in (1).

The random component of $Y_{ij}|M_{1ij}, M_{2ij}$ implied through models (1) and (3) is

$$\lambda_{1ij} \left(b_i^{X_1} + \omega_{1ij} \right) + \lambda_{2ij} \left(b_i^{X_2} + \omega_{2ij} \right) + \beta_3 \left(b_i^{X_1} b_i^{X_2} + b_i^{X_1} \omega_{2ij} + b_i^{X_2} \omega_{1ij} + \omega_{1ij} \omega_{2ij} \right) + b_i^Y + \varepsilon_{ij}$$

where

$$\begin{aligned} \lambda_{1ij} &= \beta_1 + \beta_3 \pi_0 + \beta_3 \pi_1 M_{1ij} + \beta_3 \pi_2 M_{2ij} \\ \lambda_{2ij} &= \beta_2 + \beta_3 \theta_0 + \beta_3 \theta_1 M_{1ij} + \beta_3 \theta_2 M_{2ij}. \end{aligned}$$

The $(j, j')^{th}$ element of the covariance matrix for subject i (corresponding to observations j and j') is

$$\begin{aligned} \mathbf{V}_{Y_i|M_i}(j, j') &= \sigma_{b^Y}^2 + \mathbf{R}_{\varepsilon_i}(j, j') + \lambda_{1ij} \lambda_{1ij'} \left(\sigma_{b^{X_1}}^2 + \mathbf{R}_{\omega_{1i}}(j, j') \right) + \lambda_{2ij} \lambda_{2ij'} \left(\sigma_{b^{X_2}}^2 + \mathbf{R}_{\omega_{2i}}(j, j') \right) \\ &\quad + \beta_3^2 \left(\sigma_{b^{X_1}}^2 \sigma_{b^{X_2}}^2 + \sigma_{b^{X_1}}^2 \mathbf{R}_{\omega_{2i}}(j, j') + \sigma_{b^{X_2}}^2 \mathbf{R}_{\omega_{1i}}(j, j') + \mathbf{R}_{\omega_{1i}}(j, j') \mathbf{R}_{\omega_{2i}}(j, j') \right) \end{aligned}$$

The form of $\mathbf{V}_{Y_i|M_i}$ is obviously very complicated and one question that arises is how well a simpler structure would approximate it. In this work, we simplified the structure so that the

$(j, j')^{th}$ element of the model-based $\text{Var}(Y_i|M_i)$ was approximated as $\phi_Y^{*|t_{ij}-t_{ij'}|} \sigma_{\varepsilon}^{*2} + \sigma_{b^Y}^{*2}$, the ‘AR(1) plus random intercept’ model. As before, asterisks are included on parameters to indicate they are from an approximated structure.

In summary, for model fitting and computation of estimates, structural forms for $\mathbf{V}_{Y_i|M_i}$, $\mathbf{V}_{W_{1i}|M_i}$ and $\mathbf{V}_{W_{2i}|M_i}$ were simplified so that they each contained a random intercept term for subject plus an AR(1) process. The simplification of the structure of models was assessed by examining coverage and accuracy statistics based on simulations.

2.5. RCIV1 - Variance of $\hat{\beta}$

One straightforward approach to obtain an approximate variance of $\hat{\beta}$ employs the delta method. Since $\hat{\gamma}$, $\hat{\theta}$, and $\hat{\pi}$ are obtained by fitting linear mixed models, we know that if the errors are normally distributed, then these estimators are also normal. Even if the errors are not normally distributed, ML estimators of fixed-effect parameters are asymptotically normal under a wide range of conditions as the number of independent subjects increases [20]. Asymptotic normality has also been established for estimators of fixed-effect parameters in certain linear mixed models using the generalized least squares (or ML) form but that employ REML estimates of covariance parameters [21]. Although the algebraic expression of variance derived from the delta method is quite messy, obtaining it is straightforward.

If $\left(\hat{\theta}^t, \hat{\pi}^t, \left(\hat{\gamma}^{red} \right)^t \right)^t$ is asymptotically multivariate normal, then it can be shown that $\hat{\beta}$ is asymptotically multivariate normal via the delta method. Let $\mathbf{J}$ be the matrix of first order

partial derivatives for with respect to $\left(\hat{\theta}^t, \hat{\pi}^t, (\hat{\gamma}^{red})^t\right)^t$, and let Σ be the asymptotic covariance matrix of $\left(\hat{\theta}^t, \hat{\pi}^t, (\hat{\gamma}^{red})^t\right)^t$. Then the asymptotic covariance matrix for $\hat{\beta}$ is Σ^{-1} ; algebraic forms of Σ and Σ^{-1} are given in the Appendix.

In order to determine $Var(\hat{\beta})$, random terms (including random intercepts and errors) between models were assumed to be independent, in addition to being independent within models. The numerical calculation of Σ requires $Cov(\mathbf{Y}_i|\mathbf{M}_i, \mathbf{W}_{pi}|\mathbf{M}_i)$, for $p = 1, 2$, and $Cov(\mathbf{W}_{1i}|\mathbf{M}_i, \mathbf{W}_{2i}|\mathbf{M}_i)$, which are ‘between-model’ covariances. Based on models (1) and (3) and the independence assumptions, the true form of

$Cov(\mathbf{Y}_i|\mathbf{M}_i, \mathbf{W}_{pi}|\mathbf{M}_i) = diag(\lambda_{pi}) \left(\sigma_{bX_1}^2 \mathbf{J} + \mathbf{R}_{\omega_{pi}} \right)$, for $p = 1, 2$, where $diag(\lambda_{pi})$ is a matrix with $\lambda_{pi1}, \dots, \lambda_{pir_i}$ along the diagonal and $\mathbf{J}$ is a $r_i \times r_i$ matrix of ones, while $Cov(\mathbf{W}_{1i}|\mathbf{M}_i, \mathbf{W}_{2i}|\mathbf{M}_i) = \mathbf{0}$. However, since approximated forms for ‘within-model’ variance structures were used as described in the previous subsection, we found that using the true form of $Cov(\mathbf{Y}_i|\mathbf{M}_i, \mathbf{W}_{pi}|\mathbf{M}_i)$ and the resulting nonzero matrices for $\Sigma_{\gamma\theta}$ and $\Sigma_{\gamma\pi}$ often resulted in

problems such as non-positive definite matrices or negative variances in $Var(\hat{\beta})$. Thus, in actual calculations of model-based variance, all off-block diagonal matrices in Σ were set to $\mathbf{0}$.

Empirical (also called sandwich or robust) estimators of $Var(\hat{\beta})$ were also determined by using estimates of variance and covariance forms that employed sums of squares and cross products of residuals (see Appendix). In this case, it was not necessary to set the off-block-diagonal elements Σ of to zero since the use of data-based forms of middle ‘Var’ and ‘Cov’ quantities in (5) did not result in non-conforming matrices. Hence, for a sufficient number of subjects, we suspect the empirical variance estimators will be more reliable than the model-based ones when the covariance approximations are used. Even if it was not necessary to set off-block-diagonal elements of Σ to $\mathbf{0}$ for the model-based approach, empirical estimators are likely to be less affected by use of approximations to ‘true’ covariance structures as well as to violations of independence assumptions in the models, relative to the model-based approach. Both model-based and empirical variance estimators were calculated in simulation runs in order to determine their accuracies. Parameters in model-based and empirical variance forms were replaced with their estimates for numerical calculation.

2.6. Inference for β using RCIV2, and equivalency of RCIV1 and RCIV2

The RCIV2 algorithm previously described is less complicated and does not need theoretical development as for RCIV1. Essentially, the RCIV2 method fits model (1), where estimated expected (or predicted) values from fits of (3) are used in place of unknown X variables, for each pollutant surrogate variable. The coefficients of the variables for this fit are the estimates of elements of β ; it is not necessary to further manipulate them.

Although estimates are derived more easily for RCIV2, obtaining standard errors of these estimates is less straightforward using asymptotic methods. One possible approach would be

to estimate the standard errors based on resampling methods. In this work, we constructed confidence intervals for elements of β by simply using the naive standard errors obtained from the linear mixed model fits that ignored the variability of the estimates used in place of the true, measured-without-error (X) variables. Although we did not expect these confidence intervals to be optimal, we were interested in determining just how well they would perform relative to the RCIV1 approach, and whether CI coverage would be reasonable. It should be noted that the predicted values used with this approach are the predicted means that do not include random effect estimates. (In SAS, these are obtained by using OUTPM option in PROC MIXED; in R, they are obtained by specifying 'level=0' within the 'fitted' function that is applied to the *lme* object, using the *nlme* package.)

RCIV1 and RCIV2 yield equivalent estimates for β when fitting the linear mixed models (1) and (3) using maximum likelihood estimation, provided the same covariance structure is used for both approaches. To show this, we first introduce notation to clarify and expedite the proof. Let $\mathbf{X}$ denote the study-wide data matrix obtained by stacking subject data:

$$\mathbf{X} = \begin{pmatrix} \mathbf{X}_1 \\ \mathbf{X}_2 \\ \vdots \\ \mathbf{X}_n \end{pmatrix}$$

Define $\mathbf{M}$, $\mathbf{W}$ and $\mathbf{Y}$ similarly. In the fit of (3), let $\hat{\pi}$ and $\hat{\theta}$ denote the maximum likelihood estimators of π and θ , respectively, and denote the predicted values as $\hat{\mathbf{X}} = \hat{E}(\mathbf{W}|\mathbf{M}) = \mathbf{M}^{\hat{red}} \hat{\mathbf{C}}^{red}$, which are predicted means that do involve random effect estimates. (The hat on $\mathbf{M}^{\hat{red}}$ reflects that it involves $\hat{\pi}$ and $\hat{\theta}$, due to the model reduction that removed linear

dependencies in $\mathbf{M}^{full}$.) Let $\mathbf{V}_{RCIV1} = Var(\mathbf{Y}|\mathbf{M}, \hat{\pi}, \hat{\theta})$ that is estimated when fitting the linear mixed model for $\mathbf{Y}$ as a function of $\mathbf{M}$ and $\mathbf{Z}$ (conditioning on $\mathbf{Z}$ is implied but notation suppressed); denote the associated likelihood function for this model as L_{RCIV1} .

Similarly, let $\mathbf{V}_{RCIV2} = Var(\mathbf{Y}|\hat{\mathbf{X}}, \hat{\pi}, \hat{\theta})$ that is estimated when fitting the linear mixed model for $\mathbf{Y}$ as a function of $\hat{\mathbf{X}}$, and let L_{RCIV2} denote the likelihood function for this model. The estimated covariance matrix $\hat{\mathbf{V}}_{RCIV1}$ is the maximum likelihood estimator of $\mathbf{V}_{RCIV1}$ based on L_{RCIV1} ; similar for RCIV2.

For RCIV1, the maximum likelihood estimator of β , given $(\mathbf{M}, \hat{\pi}, \hat{\theta})$, is

$$\begin{aligned} \hat{\beta}^{RCIV1} &= [\hat{\mathbf{C}}^{red}]^{-1} \hat{\gamma}^{red} \\ &= [\hat{\mathbf{C}}^{red}]^{-1} \left([\hat{\mathbf{M}}^{red}]^t \hat{\mathbf{V}}_{RCIV1}^{-1} \hat{\mathbf{M}}^{red} \right)^{-1} \left([\hat{\mathbf{M}}^{red}]^t \hat{\mathbf{V}}_{RCIV1}^{-1} \mathbf{Y} \right) \end{aligned}$$

For RCIV2, the maximum likelihood estimator of β , given $(\hat{\mathbf{X}}, \hat{\pi}, \hat{\theta})$, is

$$\begin{aligned}
\hat{\beta}^{RCIV2} &= (\hat{\mathbf{X}}^t \hat{\mathbf{V}}_{RCIV2}^{-1} \hat{\mathbf{X}})^{-1} (\hat{\mathbf{X}}^t \hat{\mathbf{V}}_{RCIV2}^{-1} \mathbf{Y}) \\
&= \left([\hat{\mathbf{M}}^{red} \hat{\mathbf{C}}^{red}]^t \hat{\mathbf{V}}_{RCIV2}^{-1} [\hat{\mathbf{M}}^{red} \hat{\mathbf{C}}^{red}] \right)^{-1} \left([\hat{\mathbf{M}}^{red} \hat{\mathbf{C}}^{red}]^t \hat{\mathbf{V}}_{RCIV2}^{-1} \mathbf{Y} \right) \\
&= \left([\hat{\mathbf{C}}^{red}]^t [\hat{\mathbf{M}}^{red}]^t \hat{\mathbf{V}}_{RCIV2}^{-1} \hat{\mathbf{M}}^{red} \hat{\mathbf{C}}^{red} \right)^{-1} (\hat{\mathbf{C}}^{red})^t [\hat{\mathbf{M}}^{red}]^t (\hat{\mathbf{V}}_{RCIV2}^{-1} \mathbf{Y}) \\
&= [\hat{\mathbf{C}}^{red}]^{-1} \left([\hat{\mathbf{M}}^{red}]^t \hat{\mathbf{V}}_{RCIV2}^{-1} \hat{\mathbf{M}}^{red} \right)^{-1} \left((\hat{\mathbf{C}}^{red})^t \right)^{-1} [\hat{\mathbf{C}}^{red}]^t \left([\hat{\mathbf{M}}^{red}]^t \hat{\mathbf{V}}_{RCIV2}^{-1} \mathbf{Y} \right) \\
&= [\hat{\mathbf{C}}^{red}]^{-1} \left([\hat{\mathbf{M}}^{red}]^t \hat{\mathbf{V}}_{RCIV2}^{-1} \hat{\mathbf{M}}^{red} \right)^{-1} \left([\hat{\mathbf{M}}^{red}]^t \hat{\mathbf{V}}_{RCIV2}^{-1} \mathbf{Y} \right)
\end{aligned}$$

Now $\hat{\beta}^{RCIV1} = \hat{\beta}^{RCIV2}$ if $\hat{\mathbf{V}}_{RCIV1} = \hat{\mathbf{V}}_{RCIV2}$. This equality will hold if the same covariance structures are used for $\mathbf{V}_{RCIV1}$ and $\mathbf{V}_{RCIV2}$. To show this, rewrite the likelihoods L_{RCIV1} and L_{RCIV2} as profile likelihoods in terms of covariance parameters (obtained by replacing fixed effect parameters in the respective likelihoods with their maximum likelihood estimators). Then reduce the forms of the profile likelihoods to show that they are equivalent functions when the covariance structures are the same, and hence that the estimators of the covariance parameters must be the same, so that $\hat{\mathbf{V}}_{RCIV1} = \hat{\mathbf{V}}_{RCIV2}$.

In many situations it is not clear that the two covariance structures should be the same. Considering the data application, the logical error structure for $\mathbf{V}_{RCIV2}$ includes the random intercept plus AR(1) errors, which is the same covariance structure as for (1); this structure is intuitive for RCIV2 because the estimators are derived from the fit of (1) after simply replacing unknown $\mathbf{X}$ with their predicted values. However, the use of the random intercept and AR(1) error structure for $\mathbf{V}_{RCIV1}$ is clearly only an approximation; the true covariance structure for RCIV1 presented in Section 2.4 was much more complex. However, in many cases, use of different covariance structures may not yield appreciable differences between RCIV methods. For analyses presented in this manuscript that yield estimates of $\hat{\beta}$, we do in fact use the same covariance structures for RCIV1 and RCIV2. Hence, we drop the subscript identifying the algorithm used.

3. Application: The air pollution and asthma data

Using the data obtained from the NJH study, linear mixed models were fit and regression calibration was carried out in order to estimate effects of exposure to ambient PM_{2.5} and SHS exposure, plus their interaction, on LTE₄, a biomarker of inflammation. Data were obtained from 4 separate study years (between 2002 and 2006). Data were collected during the school year, approximately October through April. A fixed-effect class variable for study year was included as a covariate in the health model (for LTE₄, or Y) to account for general year-to-year differences. The SE's for $\hat{\beta}$ were calculated using the model-based approach only. This is because empirical SE's can only be calculated when the same records are used to fit the different mixed models, and data from personal monitors were not available in the last 2 years of the study.

The instrumental variable for SHS exposure, cotinine (M_1), could differ between subjects on a given day, while morning maximum PM_{2.5} measured from a fixed outdoor monitor (M_2)

was subject-invariant within each day. Measured-with-error pollutant exposure variables were personal SHS (W_1) and personal ambient $PM_{2.5}$ (W_2) (assumed to be unbiased for X_1 and X_2 , respectively), both obtained from personal sampling monitors placed in backpacks that children wore on certain days [17-19,22]. The variables M_1 and M_2 were much easier to obtain than W_1 and W_2 , and this is why the instrumental variable approach was used. In the analysis, M_1 , M_2 , W_1 and W_2 were all analyzed on the natural log scale (1 was added before transformation for W_1 and W_2), as their distributions were right skewed. Thus, the same transformation applies when considering the coefficients of X_1 , X_2 and X_1X_2 (i.e., β). The health outcome Y was also analyzed on the natural log scale. Table 1 shows descriptive statistics for variables involved in the analysis. The variables W_1 and W_2 were only available in the first 2 study years and for a subset of days; all others were available in all 4 years. Study subjects typically were involved in more than one study year but very few in all four years. Most variables were collected sporadically but systematically within a study year. For a given child, the variables Y , M_1 , W_1 and W_2 were collected on Monday through Thursday at school for 2 consecutive weeks, and then again for another 2 consecutive weeks a few months later. But due to certain conflicts (e.g., absent student, instrument malfunction, records restricted to days when subjects did not have upper respiratory infections), data were not always obtained on all of these days. The variable M_2 had more data available since it was based on a fixed outdoor monitor. Due to the intermittent data both within and between years, the spatial power structure was used to account for serial correlation in all mixed model fits.

Table 2 demonstrates the fits of the linear mixed models associated with RCIV1 for the data application. As expected, the most significant estimates were $\hat{\theta}_1$ (the ability of cotinine to predict personal SHS exposure) and $\hat{\pi}_2$ (the ability of concentrations from the fixed outdoor monitor to predict personal ambient $PM_{2.5}$ exposure). The random subject variance for the SHS model was much higher than for the personal ambient $PM_{2.5}$ model since exposure to SHS depends largely on whether someone in the household smokes or not, while exposure to ambient $PM_{2.5}$ is relatively similar across subjects due to the spatially homogeneous nature of ambient $PM_{2.5}$. The coefficients for M_1 , M_2 and M^* in the health model were all statistically significant ($p < 0.05$) based on t-tests. Estimates for fixed effects were similar when allowing for an addition parameter for measurement error in the pollutant models (see Section 2.4).

Using the fitted regression models, estimates of $\hat{\beta}$ in (1) were obtained using the RCIV1 methods previously described, and shown in Table 3; toxicity comparisons based on linear combinations of parameter estimates are also presented. The parameter β_1 represents the increase in log LTE_4 per unit increase in $[\log(\text{SHS}+1)]$ when there is no ambient $PM_{2.5}$ pollution; β_2 is the increase in log LTE_4 per unit increase in $[\log(\text{ambient } PM_{2.5}+1)]$ in the absence of SHS; β_3 is the interaction term – the significance of its estimate demonstrates that the relationship between one pollutant and log LTE_4 depends on the level of the other pollutant; the negative sign shows that increased exposure to one pollutant diminishes the additional effect of the other pollutant. Although effects of SHS exposure generally appeared a bit stronger for the sample than for ambient $PM_{2.5}$ exposure, additional tests in the primary model did not indicate significant differences in their toxicity. Specifically, $p =$

0.58 for the increase in LTE_4 per unit increase in SHS at the mean exposure level of ambient $PM_{2.5}$ versus the increase in LTE_4 per unit increase of ambient $PM_{2.5}$ at the mean exposure level of SHS (considering logged variables). Since mean exposure was greater for ambient $PM_{2.5}$ than SHS, one could argue that a better test for toxicity would be like the first, but using the same fixed concentration for the other pollutant rather than the mean. In other words, replace ‘the mean exposure level’ in the previous statement with ‘exposure level c ’. (Recall that although the instrumental variables are not measured in the same units, the pollutant exposure variables are.) This test was also not significant ($p = 0.15$ for any level ‘ c ’ that is the same for both pollutants), but showed a stronger trend for SHS than ambient $PM_{2.5}$.

Figure 1 demonstrates the relationship between pollutants and LTE_4 after back-transforming estimates. This figure shows that the effect of one pollutant is stronger when the second pollutant is at lower levels, and also that the strongest effect within a pollutant tends to be at lower concentrations of that pollutant, as indicated by the concave down curves (except when the second pollutant is high). At very high levels of the second pollutant, the relationship between the first pollutant and LTE_4 is actually negative. This may be due to limitations of modeling and sparsity of data at extreme levels of covariates, since it is not expected that such a negative relationship would actually occur.

Since the previous analysis indicated that θ_2 and π_1 may be small or negligible, another analysis was performed after removing the associated terms in (3) and refitting all models.

The estimates followed the same basic pattern as before [$\hat{\beta}_3^{simp} = 1.21$ ($SE = 1.46, p = 0.41$); $\hat{\beta}_1^{simp} = 1.97$ ($SE = 0.96, p = 0.04$); $\hat{\beta}_2^{simp} = 1.45$ ($SE = 0.75, p = 0.05$); $\hat{\beta}_3^{simp} = -0.90$ ($SE = 0.49, p = 0.07$);], but with greater significance for the pollutant toxicity comparisons, particularly when comparing at ‘fixed level c ’ of the second pollutant [$\hat{\beta}_1^{simp} - \hat{\beta}_2^{simp} = 0.52, p = 0.05$], while the test comparing at mean of second pollutant yielded $p = 0.31$. One benefit of this simplified model is that in fits of (3), more records were available for analysis due to missing data patterns for predictors removed from the model [458 records in model for W_1 , up from 451; 560 records in model for W_2 , up from 350]. Generally, the importance of θ_2 and π_1 will depend on the data application, and so the analyst may want to perform fits with and without the associated terms.

4. Simulations

The primary goals of the simulations were to verify whether $\hat{\beta}$ obtained using RCIV1 and RCIV2 are unbiased, and to determine accuracy of standard errors (model-based and empirical) and associated confidence intervals for RCIV1. Secondary goals included determining accuracy of CI’s for RCIV2 that employ naive standard errors, and quantifying accuracy of estimators through mean squared error.

Unless mentioned otherwise, conditions used in the simulations were similar to those found from the data application, denoted as ‘standard settings.’ Conditions that were of primary interest included sample size, level of correlation in errors (for all models) and distribution

type. Other simulations were run to test the robustness of the methods in more extreme conditions. Most simulations used responses for consecutive days rather than intermittent days as were observed in the data application, although a handful of simulations were also run using gaps between responses (results not shown). For each condition, results for both RCIV1 and RCIV2 were obtained, and for each of these, statistics were determined using both empirical and model-based standard error estimates.

Regression coefficients used in the simulations (β , θ , π) were the same as respective estimates from the mixed model fits in the data application to 2 significant digits. (The estimates were essentially the same, whether or not a measurement error variance parameter was added to the covariance structure in the pollution models; see Section 2.4.)

Covariance parameter values were selected after examining model fits with and without the measurement error variance term, as well as using previous knowledge of distributions of pollutants. Errors for (3) were generated using the ‘AR(1) plus ME variance’ covariance structure since it was perceived as a realistic structure for many applications, including the one presented here. However, the single AR(1) structure (excluding the measurement error variance parameter) was used in actual fits for two reasons: (i) fits with the application data using the AR(1) plus ME variance error structure resulted in correlation parameters that appeared to be overestimated, around 0.8 or 0.9, which are highly unlikely for these data; (ii) estimates and standard errors of parameters of primary interest did not change much when adding the extra parameter. (One reason for uncertainty in estimation of correlation was due to intermittency in data collection on subjects over days in the study; no subject had more than 5 consecutive days with observed LTE_4 or cotinine.) Standard settings of covariance parameters were as follows: $\sigma_{\omega_1}^2=0.18$, $\sigma_{\omega_2}^2=0.135$, $\sigma_{u_1}^2=0.05$, $\sigma_{u_2}^2=0.045$, $\sigma_{\varepsilon}^2=0.12$, $\sigma_{b_{x_1}}^2=0.15$, $\sigma_{b_{x_2}}^2=0.01$, $\sigma_{b_Y}^2=0.12$, $\phi_{W_1}=0.6$, $\phi_{W_1}=0.3$, $\phi_Y=0.4$. Note that since approximate covariance structures were used to fit the data that differed from the structures used to generate the data, covariance parameter estimates are not expected to be the same as these parameter settings. In particular, the estimated correlation parameter values in the approximated structure are typically smaller than those listed above. The parameter values were chosen so that the estimates in the approximated structure were similar to those in the data application.

Several statistics were used to judge performance of the regression calibration methods, including confidence interval coverage rate, square root of mean squared error (RMSE), absolute bias (Bias), standard deviation (sim SD: the standard deviation of β estimates across simulation replicates), square root of mean variance (root-mean-variance: square root of the mean of estimated variance of $\text{Var}(\hat{\beta})$ estimates across simulation replicates). The sim SD is an approximation of the true standard error of $\hat{\beta}$, while the root-mean-variance is an estimate of the SE of $\hat{\beta}$ obtained by steps described in the Methods section (asymptotic approach for RCIV1; naive approach for RCIV2). Thus, values of (root-mean-variance)/(sim SD) near 1 indicate that the estimation of the SE is accurate, while values substantially below/above 1 indicate that the method under-/overestimates the SE. For simplicity, we call

this quantity the ‘SE ratio’. For each set of conditions, 1000 simulation replicates were performed.

Table 4 summarizes some key results from the simulations. In all cases, estimates for RCIV1 and RCIV2 were the same, and hence RMSE and Bias were the same. The estimation procedures appear to be relatively unbiased in the range of parameters we investigated. The lower SE ratio for RCIV2 using model-based variance estimators was likely due to the fact that measurement error was not accounted for in the predicted values, leading to underestimated SE’s and slight under-coverage of the confidence intervals. Although use of these naive confidence intervals for RCIV2 would not be recommended, it is noteworthy that under-coverage was within 1% in many cases and not more than about 3% under conditions shown in Table 4.

Coverage rates for RCIV1 were generally near nominal rate except for slight over-coverage of confidence intervals for model-based estimates for smaller sample sizes. Using the empirical variance estimate, the CI coverage was near nominal rate for RCIV1, even for heavier-tailed (t-distribution with 3 d.f., or t_3) errors or more extreme correlation values. Generally, these results suggest that using a empirical variance estimate may better maintain nominal coverage. However, for even smaller sample sizes ($n = 20$, results not shown), over-coverage of CI’s observed for RCIV1 was more pronounced (CI coverages 97 to 98% for model-based variances; 96 to 97% for empirical); use of these methods is not recommended for such small sample sizes. For RCIV2, model-based CIs demonstrated undercoverage that was most pronounced when the correlations were as high as 0.8. However using empirical variance, even the naive approach with RCIV2 was generally accurate, except for slight undercoverage with smaller sample sizes.

Elements of $\hat{\beta}$ were approximately normally distributed for different conditions we considered, even with the t_3 errors (albeit with occasional outliers), indicating that the use of the delta method for asymptotic variances in such cases is acceptable. The data in our application was not heavy-tailed or skewed (after log transformation), and thus we expect use of the delta method to be appropriate here as well.

Further simulations were run to examine adequacy of the RCIV estimation methods and associated CI coverage rates in other conditions, including changing the correlation parameters for some models but not others, creating gaps between observation times, and increasing variances in the random subject intercept (results not shown). Estimators were still relatively unbiased and CI coverage rates continued to be near nominal rates. However, these methods did produce heavy-tailed distributions with large outliers for $\hat{\beta}$ elements if the surrogate variables for the true predictors of interest had very high variance. In order to assess how the covariance approximations performed relative to ignoring the correlated data completely, some simulations were run using ordinary least squares for model fits rather than linear mixed models. In these cases, the SEs were wildly overestimated (mean[SE]/SD approximately 1.7 to 1.85). This is expected, since effects of interest are largely based on within-subject changes over time, and taking into account the positive correlation between responses within subjects will appropriately reduce associated standard errors.

Overall, for the conditions studied, the model-based SEs for RCIV1 performed relatively well despite the fact that the covariance structures used were simplifications of the true structures; these misspecifications did not appear to affect accuracy greatly. However, when possible, it is recommended that the empirical SEs be used, since they are less hampered by the approximations to covariance structures and independence assumptions.

5. Discussion

Measurement error models and associated estimators are inherently complicated, and become even more complex in longitudinal models involving interaction terms with measured-with-error predictors. We have derived and evaluated explicit forms of estimators for this more difficult situation. Due to the complexity of the true covariance structure, we fit models using approximate forms and found that this generally did not adversely affect bias or confidence interval coverage rates, especially when using empirical variance estimators for the latter. Use of approximations is not uncommon in measurement error and regression calibration methods due to the complexity of the theory. The simulations demonstrated not only the adequacy of asymptotic confidence intervals when using the RCIV1 method for a variety of conditions, but even that the confidence intervals using the naive CI's with RCIV2 were often adequate. Generally, results utilizing empirical SE's were slightly better than those using model-based SE's.

Although use of approximate covariance structures in the methods generally appeared to yield adequate results, simulations suggested that in more extreme situations (e.g., very small sample size or models with very large variance terms), estimator performance may start to suffer. More accurately specifying the covariance structure might improve the performance of the method under a wider range of circumstances. At this point, we have only explored models with two continuous predictors and their interaction, with data for one instrumental variable and one unbiased surrogate variable available in place of each predictor of interest. Our preliminary investigations suggest that this methodology could be extended to models with more covariates and surrogate variables, although the complexity of the matrix operations increases markedly and would likely require even greater approximations to covariance structures to be of any practical use.

In the air pollution and health study, the LTE_4 health outcome was found to increase more rapidly per increase in one pollutant when the 2nd pollutant was lower. The same conclusions were reached in the analysis that involved simply regressing LTE_4 on the instrumental variables [1]. Performing regression calibration allowed us to verify a significant interactive pattern when considering actual pollutant exposures and also provided (for the first time that we know of) an estimate of the effect from personal exposures to co-pollutants, so that direct estimates of effect and more meaningful comparisons between the pollutants could be made; the true exposure concentrations are measured in the same units, while the instrumental variables are not. To determine relative toxicity, we compared slope estimates of pollutants at comparable fixed levels of the other pollutant. The slope of SHS was found to be greater than that of ambient $PM_{2.5}$ (test for $\beta_1 - \beta_2$) with borderline significance ($p = 0.05$) in the model that used only primary instrumental variables (i.e., the simplified model).

The observation of a significant interaction between two co-pollutant exposures, fine particulate matter and secondhand smoke, on health of children with asthma is novel. It was first reported using instrumental variables by Rabinovitch et al. [1], and estimated for actual exposure levels here. The results suggest some type of homeostatic mechanism which generally limits overall effects of a pollutant when a co-pollutant is higher. This mechanism also appears to limit the dose-response effect of one pollutant at higher concentrations, as demonstrated by model fits that improved when the pollutant variables were log-transformed.

The observed decreases in LTE_4 for one pollutant at higher levels of the second pollutant were not anticipated and might be partially due to limitations of the parametric modeling. We are currently exploring longitudinal nonparametric modeling with these data to obtain a more precise understanding of the pollutant-health relationships. Also, an analysis that addresses a more complete set of potential confounders may lead to more precise estimates and toxicity comparisons.

Future methodological research might involve development of inference for the RCIV2 method, which could then be compared with that of the RCIV1 method. One possibility is to use resampling techniques (e.g., bootstrap methods). Such methods would probably include block resampling for longitudinal data. Carroll et al. [3] summarize other regression calibration methods for instrumental variables; these methods could be extended to account for models involving interaction terms and longitudinal data as well.

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APPENDIX

Using the delta method, we can derive $Var(\hat{\beta}) = \Delta \Sigma \Delta^t$. The form of Σ is as follows.

$$\Sigma = \begin{pmatrix} \Sigma_{\theta} & \Sigma_{\theta\pi} & \Sigma_{\theta\gamma} \\ \Sigma_{\pi\theta} & \Sigma_{\pi} & \Sigma_{\pi\gamma} \\ \Sigma_{\gamma\theta} & \Sigma_{\gamma\pi} & \Sigma_{\gamma} \end{pmatrix} \quad (5)$$

where

$$\begin{aligned}
\Sigma_{\theta\pi} &= \Sigma_{\pi\theta}^t \\
\Sigma_{\theta\gamma} &= \Sigma_{\gamma\theta}^t \\
\Sigma_{\pi\gamma} &= \Sigma_{\gamma\pi}^t \\
\Sigma_{\theta} &= \left(\sum_{i=1}^n \mathbf{M}_i^t \mathbf{V}_{\mathbf{w}_{1i}|\mathbf{M}_i}^{-1} \mathbf{M}_i \right)^{-1} \left(\sum_{i=1}^n \mathbf{M}_i^t \mathbf{V}_{\mathbf{w}_{1i}|\mathbf{M}_i}^{-1} \text{Var}(\mathbf{W}_{1i}|\mathbf{M}_i) \mathbf{V}_{\mathbf{w}_{1i}|\mathbf{M}_i}^{-1} \mathbf{M}_i \right) \left(\sum_{i=1}^n \mathbf{M}_i^t \mathbf{V}_{\mathbf{w}_{1i}|\mathbf{M}_i}^{-1} \mathbf{M}_i \right)^{-1} \\
\Sigma_{\pi} &= \left(\sum_{i=1}^n \mathbf{M}_i^t \mathbf{V}_{\mathbf{w}_{2i}|\mathbf{M}_i}^{-1} \mathbf{M}_i \right)^{-1} \left(\sum_{i=1}^n \mathbf{M}_i^t \mathbf{V}_{\mathbf{w}_{2i}|\mathbf{M}_i}^{-1} \text{Var}(\mathbf{W}_{2i}|\mathbf{M}_i) \mathbf{V}_{\mathbf{w}_{2i}|\mathbf{M}_i}^{-1} \mathbf{M}_i \right) \left(\sum_{i=1}^n \mathbf{M}_i^t \mathbf{V}_{\mathbf{w}_{2i}|\mathbf{M}_i}^{-1} \mathbf{M}_i \right)^{-1} \\
\Sigma_{\gamma} &= \left(\sum_{i=1}^n (\mathbf{M}_i^{\text{red}})^t \mathbf{V}_{\mathbf{Y}_i|\mathbf{M}_i}^{-1} \mathbf{M}_i^{\text{red}} \right)^{-1} \left(\sum_{i=1}^n (\mathbf{M}_i^{\text{red}})^t \mathbf{V}_{\mathbf{Y}_i|\mathbf{M}_i}^{-1} \text{Var}(\mathbf{Y}_i|\mathbf{M}_i) \mathbf{V}_{\mathbf{Y}_i|\mathbf{M}_i}^{-1} \mathbf{M}_i^{\text{red}} \right) \left(\sum_{i=1}^n (\mathbf{M}_i^{\text{red}})^t \mathbf{V}_{\mathbf{Y}_i|\mathbf{M}_i}^{-1} \mathbf{M}_i^{\text{red}} \right)^{-1} \\
\Sigma_{\theta\pi} &= \left(\sum_{i=1}^n \mathbf{M}_i^t \mathbf{V}_{\mathbf{w}_{1i}|\mathbf{M}_i}^{-1} \mathbf{M}_i \right)^{-1} \left(\sum_{i=1}^n \mathbf{M}_i^t \mathbf{V}_{\mathbf{w}_{1i}|\mathbf{M}_i}^{-1} \text{Cov}(\mathbf{W}_{1i}|\mathbf{M}_i, \mathbf{W}_{2i}|\mathbf{M}_i) \mathbf{V}_{\mathbf{w}_{2i}|\mathbf{M}_i}^{-1} \mathbf{M}_i \right) \left(\sum_{i=1}^n \mathbf{M}_i^t \mathbf{V}_{\mathbf{w}_{2i}|\mathbf{M}_i}^{-1} \mathbf{M}_i \right)^{-1} \\
\Sigma_{\theta\gamma} &= \left(\sum_{i=1}^n \mathbf{M}_i^t \mathbf{V}_{\mathbf{w}_{1i}|\mathbf{M}_i}^{-1} \mathbf{M}_i \right)^{-1} \left(\sum_{i=1}^n \mathbf{M}_i^t \mathbf{V}_{\mathbf{w}_{1i}|\mathbf{M}_i}^{-1} \text{Cov}(\mathbf{W}_{1i}|\mathbf{M}_i, \mathbf{Y}_i|\mathbf{M}_i) \mathbf{V}_{\mathbf{Y}_i|\mathbf{M}_i}^{-1} \mathbf{M}_i^{\text{red}} \right) \left(\sum_{i=1}^n (\mathbf{M}_i^{\text{red}})^t \mathbf{V}_{\mathbf{Y}_i|\mathbf{M}_i}^{-1} \mathbf{M}_i^{\text{red}} \right)^{-1} \\
\Sigma_{\pi\gamma} &= \left(\sum_{i=1}^n \mathbf{M}_i^t \mathbf{V}_{\mathbf{w}_{2i}|\mathbf{M}_i}^{-1} \mathbf{M}_i \right)^{-1} \left(\sum_{i=1}^n \mathbf{M}_i^t \mathbf{V}_{\mathbf{w}_{2i}|\mathbf{M}_i}^{-1} \text{Cov}(\mathbf{W}_{2i}|\mathbf{M}_i, \mathbf{Y}_i|\mathbf{M}_i) \mathbf{V}_{\mathbf{Y}_i|\mathbf{M}_i}^{-1} \mathbf{M}_i^{\text{red}} \right) \left(\sum_{i=1}^n (\mathbf{M}_i^{\text{red}})^t \mathbf{V}_{\mathbf{Y}_i|\mathbf{M}_i}^{-1} \mathbf{M}_i^{\text{red}} \right)^{-1}
\end{aligned}$$

and where $\mathbf{V}_{\mathbf{Y}_i|\mathbf{M}_i} = \text{Var}(\mathbf{Y}_i|\mathbf{M}_i)$ and $\mathbf{V}_{\mathbf{W}_{pi}|\mathbf{M}_i} = \text{Var}(\mathbf{W}_{pi}|\mathbf{M}_i)$, for $p = 1, 2$, based on models (1)-(3) and other terms are as previously defined. Empirical forms can be obtained by employing residuals to estimate the middle ‘Var’ and ‘Cov’ quantities in equations above. Model-based forms of block diagonal elements reduce to

$$\begin{aligned}
\Sigma_{\theta} &= \left(\sum_{i=1}^n \mathbf{M}_i^t \mathbf{V}_{\mathbf{w}_{1i}|\mathbf{M}_i}^{-1} \mathbf{M}_i \right)^{-1} \\
\Sigma_{\pi} &= \left(\sum_{i=1}^n \mathbf{M}_i^t \mathbf{V}_{\mathbf{w}_{2i}|\mathbf{M}_i}^{-1} \mathbf{M}_i \right)^{-1} \\
\Sigma_{\gamma} &= \left(\sum_{i=1}^n (\mathbf{M}_i^{\text{red}})^t \mathbf{V}_{\mathbf{Y}_i|\mathbf{M}_i}^{-1} \mathbf{M}_i^{\text{red}} \right)^{-1}
\end{aligned}$$

Model-based block off-diagonal elements were set to $\mathbf{0}$ for analysis; see Section 2.5 for more detail. The form of Δ^t is as follows.

$$\Delta^t = \begin{pmatrix} \frac{\partial \beta_0}{\partial \theta_0} & \frac{\partial \beta_1}{\partial \theta_0} & \frac{\partial \beta_2}{\partial \theta_0} & \frac{\partial \beta_3}{\partial \theta_0} \\ \frac{\partial \beta_0}{\partial \theta_1} & \frac{\partial \beta_1}{\partial \theta_1} & \frac{\partial \beta_2}{\partial \theta_1} & \frac{\partial \beta_3}{\partial \theta_1} \\ \frac{\partial \beta_0}{\partial \theta_2} & \frac{\partial \beta_1}{\partial \theta_2} & \frac{\partial \beta_2}{\partial \theta_2} & \frac{\partial \beta_3}{\partial \theta_2} \\ \frac{\partial \beta_0}{\partial \theta_3} & \frac{\partial \beta_1}{\partial \theta_3} & \frac{\partial \beta_2}{\partial \theta_3} & \frac{\partial \beta_3}{\partial \theta_3} \\ \frac{\partial \beta_0}{\partial \pi_0} & \frac{\partial \beta_1}{\partial \pi_0} & \frac{\partial \beta_2}{\partial \pi_0} & \frac{\partial \beta_3}{\partial \pi_0} \\ \frac{\partial \beta_0}{\partial \pi_1} & \frac{\partial \beta_1}{\partial \pi_1} & \frac{\partial \beta_2}{\partial \pi_1} & \frac{\partial \beta_3}{\partial \pi_1} \\ \frac{\partial \beta_0}{\partial \pi_2} & \frac{\partial \beta_1}{\partial \pi_2} & \frac{\partial \beta_2}{\partial \pi_2} & \frac{\partial \beta_3}{\partial \pi_2} \\ \frac{\partial \beta_0}{\partial \gamma_0} & \frac{\partial \beta_1}{\partial \gamma_0} & \frac{\partial \beta_2}{\partial \gamma_0} & \frac{\partial \beta_3}{\partial \gamma_0} \\ \frac{\partial \beta_0}{\partial \gamma_1} & \frac{\partial \beta_1}{\partial \gamma_1} & \frac{\partial \beta_2}{\partial \gamma_1} & \frac{\partial \beta_3}{\partial \gamma_1} \\ \frac{\partial \beta_0}{\partial \gamma_2} & \frac{\partial \beta_1}{\partial \gamma_2} & \frac{\partial \beta_2}{\partial \gamma_2} & \frac{\partial \beta_3}{\partial \gamma_2} \\ \frac{\partial \beta_0}{\partial \gamma_5} & \frac{\partial \beta_1}{\partial \gamma_5} & \frac{\partial \beta_2}{\partial \gamma_5} & \frac{\partial \beta_3}{\partial \gamma_5} \end{pmatrix} = \begin{pmatrix} -\frac{c_5 + \gamma_5 \pi_0}{c_1^2} & 0 & -\frac{\gamma_5}{c_2^2} & 0 \\ -\frac{c_3 c_5}{c_1^2} - \frac{\gamma_5 \pi_0 \pi_2 \theta_0}{c_2^2} & \frac{\gamma_5 \pi_0 \pi_2}{c_2^2} + \frac{c_5 \pi_2}{c_1^2} & \frac{\gamma_5 \pi_2 \theta_0}{c_2^2} - \frac{c_5 \theta_2}{c_1^2} & -\frac{\gamma_5 \pi_2}{c_2^2} \\ \frac{c_4 c_5}{c_1^2} - \frac{\gamma_5 \pi_0 \pi_1 \theta_0}{c_2^2} & \frac{\gamma_5 \pi_0 \pi_1}{c_2^2} - \frac{c_5 \pi_1}{c_1^2} & \frac{\gamma_5 \pi_1 \theta_0}{c_2^2} + \frac{c_5 \theta_1}{c_1^2} & -\frac{\gamma_5 \pi_1}{c_2^2} \\ \frac{c_6 + \gamma_5 \theta_0}{c_1^2} & -\frac{\gamma_5}{c_2^2} & 0 & 0 \\ \frac{c_3 c_6}{c_1^2} - \frac{\gamma_5 \pi_0 \theta_0 \theta_2}{c_2^2} & \frac{\gamma_5 \pi_0 \theta_2}{c_2^2} - \frac{c_6 \pi_2}{c_1^2} & \theta_2 \left(\frac{\gamma_5 \theta_0}{c_2^2} + \frac{c_6}{c_1^2} \right) & -\frac{\gamma_5 \theta_2}{c_2^2} \\ -\frac{c_4 c_6}{c_1^2} - \frac{\gamma_5 \pi_0 \theta_0 \theta_1}{c_2^2} & \frac{\gamma_5 \pi_0 \theta_1}{c_2^2} + \frac{c_6 \pi_1}{c_1^2} & \theta_1 \left(\frac{\gamma_5 \theta_0}{c_2^2} - \frac{c_6}{c_1^2} \right) & -\frac{\gamma_5 \theta_1}{c_2^2} \\ 1 & 0 & 0 & 0 \\ \frac{c_3}{c_1} & -\frac{\pi_2}{c_1} & \frac{\theta_2}{c_1} & 0 \\ -\frac{c_4}{c_1} & \frac{\pi_1}{c_1} & -\frac{\theta_1}{c_1} & 0 \\ \frac{\pi_0 \theta_0}{c_2} & -\frac{\pi_0}{c_2} & -\frac{\theta_0}{c_2} & \frac{1}{c_2} \end{pmatrix}$$

where

$$\begin{aligned}
 c_1 &= \pi_1\theta_2 - \pi_2\theta_1 \\
 c_2 &= \pi_1\theta_2 + \pi_2\theta_1 \\
 c_3 &= \pi_2\theta_0 - \pi_0\theta_2 \\
 c_4 &= \pi_1\theta_0 - \pi_0\theta_1 \\
 c_5 &= \gamma_2\pi_1 - \gamma_1\pi_2 \\
 c_6 &= \gamma_2\theta_1 - \gamma_1\theta_2
 \end{aligned}$$

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Figure 1.

Relationships between LTE_4 and exposure to one pollutant, modified by exposure to a second pollutant. Solid lines show estimated mean LTE_4 as a function of secondhand smoke (SHS), by quartiles of fine particulate matter (ambient $PM_{2.5}$). Dashed lines show estimated mean LTE_4 as a function of ambient $PM_{2.5}$, by quartiles of SHS. Quartile symbols are

Q1=25th percentile, Q2=50th percentile, Q3=75th percentile. Predicted mean values $\left[e^{x\hat{\beta}} \right]$ were obtained using RCIV1 methods; $\hat{\beta}$ values are as shown in Table 3. (RCIV2 yields the same point estimates when the same covariance structure is used.) The graph illustrates that increases in LTE_4 per unit increase in one pollutant are steepest when the second pollutant is lower. Both outcome and predictors were analyzed on the natural log scale but inverted back for presentation, resulting in curves.

Table 1

Descriptive statistics of variables involved in the analysis. The statistics were computed by first averaging repeated measures within subjects, and then averaging over subjects. All variables were analyzed on the natural log scale; 1 was added before transformation for W_1 and W_2 due to 0 values. Units for pollutant exposure variables and ambient $PM_{2.5}$ measured at the local monitor were $\mu\text{g}/\text{m}^3$; units for LTE_4 were pg per mg of creatinine; units for cotinine were ng per mg of creatinine (all before transformation).

Variable	Average subject mean	Average subject SD	Average number of responses per subject [†]	Numer of subjects
Log(LTE_4) (Y)	4.49	0.35	24.5	85
Log(SHS exposure+1) (W_1)	1.51	0.42	11.5	64
Log(Ambient $PM_{2.5}$ exposure + 1) (W_2)	1.92	0.41	11.3	50
Log(Cotinine) (M_1)	1.67	0.64	24.6	85
Log(Ambient $PM_{2.5}$) at local monitor (M_2)	2.67	0.62	392.7	90

[†] Less data were available to fit mixed models due to different missing value patterns for variables used in the same model. Subjects in the study but without data for a given variable were not included in number of records or number of subjects.

Table 2

Estimates of parameters in linear mixed models (SE in parentheses) associated with RCIV1. There were 451, 350 and 1160 records for analysis in the regression models for W_1 , W_2 and Y , respectively. Data from the first two study years (2002-03, 2003-04) were available to fit models for W_1 and W_2 ; data from all four study years were available to fit model for Y . Ambient $PM_{2.5}$ was measured at a fixed, outdoor monitor. Correlations are meaningful for responses on consecutive days.

Predictor or covariance quantity	Regression of W_1 (personal SHS exposure) on M_1, M_2	Regression of W_2 (personal ambient $PM_{2.5}$) on M_1, M_2	Regression of Y (LTE ₄) on M_1, M_2, M^*
Intercept	$\hat{\theta}_0 = 1.202 (0.127)$	$\hat{\pi}_0 = 1.184 (0.123)$	$\hat{\gamma}_0 = 4.107 (0.085)$
Cotinine (M_1)	$\hat{\theta}_1 = 0.141 (0.028)$	$\hat{\pi}_1 = 0.025 (0.020)$	$\hat{\gamma}_1 = 0.109 (0.035)$
Ambient $PM_{2.5}$ (M_2)	$\hat{\theta}_2 = 0.009 (0.034)$	$\hat{\pi}_2 = 0.227 (0.038)$	$\hat{\gamma}_2 = 0.070 (0.028)$
M^*			$\hat{\gamma}_5 = -0.023 (0.010)$
Year 1 [†]			$\hat{\tau}_1 = 0.048 (0.0049)$
Year 2 [†]			$\hat{\tau}_2 = 0.204 (0.046)$
Year 3 [†]			$\hat{\tau}_3 = 0.292 (0.044)$
Random subject variance	$\hat{\sigma}_{bX_1}^{*2} = 0.16$	$\hat{\sigma}_{bX_2}^{*2} = 0.01$	$\hat{\sigma}_{bY}^{*2} = 0.12$
Correlation	$\hat{\phi}_{W_1}^* = 0.46$	$\hat{\phi}_{W_2}^* = 0.21$	$\hat{\phi}_Y^* = 0.40$
Residual variance	$\hat{\sigma}_{\omega_1}^{*2} = 0.22$	$\hat{\sigma}_{\omega_2}^{*2} = 0.18$	$\hat{\sigma}_{\epsilon}^{*2} = 0.12$

[†]Relative to Year 4.

Table 3

Estimates of parameters in model (1) based on the RCIV1 estimation method. Tests for linear combinations of parameters, representing toxicity tests, are also shown. Asymptotic standard errors were derived using the delta method as described in Section 2.5, and p-values are based on Wald tests assuming asymptotic normality.

Parameter / Comparison	Estimate	Standard error	P-value (Z approx.)
β_0 (Intercept)	1.88	1.10	0.09
β_1 (SHS slope in absence of ambient PM _{2.5})	1.58	0.71	0.03
β_2 (Ambient PM _{2.5} slope in absence of SHS)	1.14	0.58	0.05
β_3 (Interaction)	-0.72	0.36	0.05
$\beta_1 - \beta_2$ (Toxicity comparison 1 [†])	0.44	0.30	0.15
$\beta_1 - \beta_2 + \beta_3 (\mu_2 - \mu_1)$ (Toxicity comparison 2 [‡])	0.15	0.27	0.58

[†]SHS slope evaluated at level c of ambient PM_{2.5}, versus ambient PM_{2.5} slope at level c of SHS.

[‡]SHS slope evaluated at mean ambient PM_{2.5}, μ_2 , versus ambient PM_{2.5} slope evaluated at mean SHS, μ_1 ; μ_1 and μ_2 were estimated using the averages of W_1 and W_2 , respectively, based on available data.

Table 4

Simulation results for RCIV1 and RCIV2 methods, based on various conditions; 1000 replicates were performed for each condition. Confidence interval coverage is between 93.6% to 96.4%, with 95% confidence, for a method that actually has nominal (95%) coverage; CI coverages outside of this range are bolded. Unless otherwise noted, normal errors (in all models) and covariance parameter settings as given in Section 4 were used. There were 10 repeated measures per subject (consecutive days) for all simulations; n refers to subject sample size.

Conditions [‡]	Parameter	Root MSE	Bias	Model-based variance				Empirical variance			
				SE ratio [†]		CI coverage (%)		SE ratio [†]		CI coverage (%)	
				RCIV1	RCIV2	RCIV1	RCIV2	RCIV1	RCIV2	RCIV1	RCIV2
$n = 50$	β_0	1.89	0.02	1.06	0.94	96.6	93.5	1.03	0.98	95.7	92.8
	β_1	1.30	-0.01	1.04	0.94	97.0	93.7	1.01	0.98	94.7	93.1
	β_2	1.02	-0.01	1.07	0.93	96.9	93.4	1.03	0.97	96.1	92.4
	β_3	0.70	0.01	1.03	0.94	97.0	93.5	1.00	0.97	94.8	92.9
$n = 50, f_3$ errors	β_0	1.70	-0.03	1.05	0.94	97.1	94.4	1.01	1.01	95.3	93.9
	β_1	1.14	0.02	1.04	0.94	96.9	94.4	1.00	1.01	95.1	94.1
	β_2	0.93	0.01	1.05	0.94	97.2	94.9	1.02	1.00	95.8	94.0
	β_3	0.62	-0.01	1.03	0.95	97.5	94.6	1.00	0.99	95.4	93.7
$n = 100$	β_0	1.17	-0.01	1.05	0.95	96.3	94.2	1.00	1.03	95.1	95.0
	β_1	0.77	0.01	1.04	0.95	96.5	94.2	1.00	1.03	95.3	94.8
	β_2	0.62	0.01	1.04	0.95	95.9	93.5	1.00	1.01	95.1	94.4
	β_3	0.40	-0.01	1.02	0.95	95.9	93.7	0.99	1.01	94.6	94.1
$n = 100$ Corr. = 0.2	β_0	1.09	0.02	1.03	0.94	95.6	93.2	1.00	1.01	94.4	94.5
	β_1	0.76	-0.01	1.02	0.95	94.9	93.0	0.99	1.01	94.3	94.0
	β_2	0.58	-0.01	1.03	0.94	95.6	93.2	1.00	1.00	94.9	93.9
	β_3	0.40	0.01	1.01	0.95	94.9	92.9	0.99	1.00	94.4	94.1
$n = 100$ Corr. = 0.8	β_0	1.03	-0.03	1.02	0.88	95.8	92.0	1.01	1.05	95.4	95.2
	β_1	0.69	0.02	1.02	0.89	95.8	91.9	1.01	1.05	95.2	95.2
	β_2	0.54	0.02	1.01	0.89	95.6	91.8	1.02	1.04	95.0	94.6
	β_3	0.36	-0.01	0.99	0.90	95.2	91.8	1.01	1.04	95.1	94.8
$n = 200$	β_0	0.85	-0.02	1.04	0.95	95.9	93.3	1.01	1.05	95.6	95.6

Conditions [‡]	Parameter	Root MSE	Bias	Model-based variance				Empirical variance			
				SE ratio [†]		CI coverage (%)		SE ratio [†]		CI coverage (%)	
				RCIV1	RCIV2	RCIV1	RCIV2	RCIV1	RCIV2	RCIV1	RCIV2
	β_1	0.56	0.01	1.04	0.96	95.8	93.8	1.01	1.05	95.8	95.9
	β_2	0.46	0.01	1.03	0.95	95.8	93.5	1.02	1.03	95.7	95.7
	β_3	0.30	-0.01	1.02	0.96	95.8	93.9	1.01	1.04	95.8	95.7

[†] Square root of the mean of the $Var(\hat{\beta})$ estimates, divided by the standard deviation of β estimates across simulation replicates.

[‡] Stated conditions were used in all models.