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Estimating the acute health effects of coarse particulate matter accounting for exposure measurement error

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SUMMARY

In air pollution epidemiology, there is a growing interest in estimating the health effects of coarse particulate matter (PM) with aerodynamic diameter between 2.5 and 10 μm. Coarse PM concentrations can exhibit considerable spatial heterogeneity because the particles travel shorter distances and do not remain suspended in the atmosphere for an extended period of time. In this paper, we develop a modeling approach for estimating the short-term effects of air pollution in time series analysis when the ambient concentrations vary spatially within the study region. Specifically, our approach quantifies the error in the exposure variable by characterizing, on any given day, the disagreement in ambient concentrations measured across monitoring stations. This is accomplished by viewing monitor-level measurements as error-prone repeated measurements of the unobserved population average exposure. Inference is carried out in a Bayesian framework to fully account for uncertainty in the estimation of model parameters. Finally, by using different exposure indicators, we investigate the sensitivity of the association between coarse PM and daily hospital admissions based on a recent national multisite time series analysis. Among Medicare enrollees from 59 US counties between the period 1999 and 2005, we find a consistent positive association between coarse PM and same-day admission for cardiovascular diseases.

Keywords: Air pollution; Coarse particulate matter; Exposure measurement error; Multisite time series analysis.

1. INTRODUCTION

Ambient particulate matter (PM) is a mixture of solid and liquid particles regulated by the Environmental Protection Agency (EPA) as one of the 6 criteria air pollutants. Under the Clean Air Act, EPA is responsible for establishing national standards for these pollutants to protect public health and the environment

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(Bachmann, 2007). PM can be characterized into the fine and coarse size fractions that represent distinct pollutant mixtures of different sources and properties (Wilson and Suh, 1997). Particle size is an important attribute because it governs the particle's behaviors in the atmosphere and deposition in the respiratory system. Ambient coarse PM is most often released directly as a primary pollutant through mechanical processes such as dust suspension or physical attrition involving grinding and crushing. Mineral residue resulting from combustion burn out (fly ash) also contributes to the coarse fraction. Biogenic compounds including bacterial endotoxin, pollen, and other animal/plant debris may also be present.

Protecting public health from coarse PM has endured considerable controversy in the regulatory context. EPA's current National Ambient Air Quality Standards (NAAQS) use ambient PM_{10} concentration (PM with aerodynamic diameter $\lhd 10$ μm) as the pollutant measure to protect public health from coarse PM. Most studies also routinely use PM_{10} to quantify health risks and have consistently found that increased concentrations of ambient (outdoor) PM_{10} are associated with increased risks of various adverse health outcomes (Pope and Dockery, 2006). However, there exists persistent criticism in interpreting the health effects of coarse PM since PM_{10} contains both the coarse and fine fraction.

Recent studies of coarse PM have increasingly focused on exposure to inhalable coarse particles ($PM_{10-2.5}$) of size between 2.5 and 10 μm aerodynamic diameter. While toxicological evidence supports the potential health effects of coarse PM, current epidemiological evidence is limited and mixed (Brunekreef and Forsberg, 2005). Most time series analysis of ambient $PM_{10-2.5}$ concentrations and short-term mortality showed nonstatistically significant associations except in arid regions such as Mexico City (Castillejos *and others*, 2000) and Phoenix US (Mar *and others*, 2004). Results from both the Harvard Six Cities Study (Dockery *and others*, 1993) and the American Cancer Society cohort (Pope *and others*, 2002) also found no association between long-term exposure to coarse particles and mortality. However, studies have reported statistically significant short-term effects of ambient $PM_{10-2.5}$ on hospital admissions (Peng *and others*, 2008) and mortality (Zanobetti and Schwartz, 2009). Particularly, a multisite time series analysis conducted by Peng *and others* (2008) found that on average across the 108 US counties, ambient $PM_{10-2.5}$ concentration was associated with emergency admissions for cardiovascular diseases, but this association lost statistical significance when adjusted by $PM_{2.5}$.

In a time series design, the health outcome is only available as daily total number of adverse health events in a community, such as a county, a city or a large metropolitan area. Unbiased risk estimates require the exposure measure to coincide with the true average exposure experienced by all at-risk individuals in the community (Zeger *and others*, 2003; Sheppard, 2005). When the ambient pollutant concentration is spatially smooth, current practice of averaging measurements from outdoor monitors provides a reasonable surrogate measure for the population exposure due to outdoor sources. However, coarse PM concentrations often exhibit higher spatial heterogeneity compared to $PM_{2.5}$ and PM_{10}. Therefore, averaging $PM_{10-2.5}$ values from the fixed-location monitors placed in the same community may not capture the true population exposure. Moreover because there is no national monitoring network for $PM_{10-2.5}$, community-level daily $PM_{10-2.5}$ concentrations are calculated based on the limited network of collocated monitor pairs where both PM_{10} and $PM_{2.5}$ are measured at the same location.

One of the main objectives of this paper is to develop a statistical modeling approach and computationally efficient estimation procedures for estimating the health effects of air pollution accounting for exposure measurement error (ME) in multisite time series analyses. We are concerned with the error that results from assigning an incorrect exposure measure to the study population living in an area when (1) pollution concentrations are available from a small number of monitors placed within the community; and (2) the pollution concentrations are highly variable within the community. To incorporate exposure ME in risk estimates, we view monitor-level PM values as error-prone repeated measurements of the true community-level average exposure. Our approach estimates exposure ME by quantifying, on any given day, the disagreement in PM values measured across the monitoring stations located within the same community. Specifically, we develop ME models for a bivariate vector of exposure variables in order

to estimate the effect of $PM_{10-2.5}$ adjusted by $PM_{2.5}$. Joint modeling also addresses the bias where the effect of one pollutant measured with more error is transferred to another pollutant measured with less error (Zidek *and others*, 1996). Finally, we calculate different measures of county-level ambient daily exposure to $PM_{10-2.5}$ and investigate the sensitivity of the national average effect of $PM_{10-2.5}$ on hospital admissions estimated in Peng *and others* (2008).

The exposure ME encountered in the analysis of $PM_{10-2.5}$ is related to the statistical problem known as spatial misalignment (Gotway and Young, 1999). Spatial variation in ambient concentrations and exposure ME caused by spatial misalignment have been addressed in several studies on the long-term health effects of air pollution (Zhu *and others*, 2003; Gyparis *and others*, 2009). However, few have examined its effects specifically in time series analysis. Through simulation studies, Sheppard *and others* (2005) find minor effect attenuation when the ambient concentration varies spatially. Peng and Bell (2010) calculate county-level exposure by first interpolating $PM_{2.5}$ chemical constituents concentration via spatial modeling. The authors show that the resulting county-specific short-term health effects are greater in magnitude and have larger standard errors compared to estimates that do not consider spatial variation in pollution concentration. To our knowledge, no study has investigated the effects of exposure ME in the analysis of $PM_{10-2.5}$ and health.

Our ME approach estimates daily county-level $PM_{10-2.5}$ exposure accounting for spatial heterogeneity without explicitly characterizing the spatial gradient. While this approach provides computational advantages, a space–time model for PM_{10} and $PM_{2.5}$ offers an alternative approach for obtaining $PM_{10-2.5}$ exposure measure. However, this increases model complexity significantly when considering daily $PM_{10-2.5}$ concentrations nationally over a long study period. The ability to characterize $PM_{10-2.5}$ spatial variation is also limited by the sparse network of collocated PM_{10} and $PM_{2.5}$ monitors.

The remainder of this paper is organized as follows. Section 2 describes the data sets, the modeling framework and the estimation procedures. In Section 3, we calculate different measures of daily county-level ambient exposure to $PM_{10-2.5}$ and investigate the sensitivity of the national average effect of $PM_{10-2.5}$ on hospital admissions. Section 4 describes a simulation study that examines the impact of $PM_{10-2.5}$ exposure ME and the performance of our proposed method. Finally, discussion and future work appear in Section 5.

2. Methods

2.1 *Data*

Daily average concentrations of $PM_{10-2.5}$ and $PM_{2.5}$ data for the period 1999–2005 were obtained from the EPA's National Air Pollution Monitoring Network in the air quality system (AQS). Without a national monitoring network for $PM_{10-2.5}$, the EPA calculates $PM_{10-2.5}$ values indirectly by subtracting $PM_{2.5}$ from PM_{10} measurements at monitors that are physically located at the same place (collocated monitor pairs). We considered $PM_{2.5}$ measurements from all AQS monitors and $PM_{10-2.5}$ measurements from collocated $PM_{2.5}$ and PM_{10} monitor pairs. We restricted our analysis to the 59 US counties with (1) a population greater than 200 000 based on the 2000 census; (2) at least 2 pairs of collocated PM_{10} and $PM_{2.5}$ monitors; and (3) at least 210 daily $PM_{10-2.5}$ measurements over the study period. Locations of the counties in our study are shown in Figure 1.

Time series of daily emergency hospital admissions for cardiovascular and respiratory diseases were assembled for Medicare enrollees aged 65 years or above within each county (Peng *and others*, 2008). Records were extracted from the National Claim History Files for the period between 1999 and 2005. Based on the International Classification of Diseases, Ninth Revision disease classification, we considered primary diagnosis of admissions due to 2 aggregated causes: (1) cardiovascular disease admissions and (2) respiratory disease admissions.

Fig. 1. 59 US counties with population greater than 200 000, at least 2 pairs of collocated PM_{10} and $PM_{2.5}$ monitors, and at least 210 daily $PM_{10-2.5}$ measurements over the period 1999–2005 (Honolulu, HI and Anchorage, AL not shown).

2.2 *Trimmed mean exposure indicator*

For county c on day t, let W^c_{1tj} and W^c_{2tj} denote the $PM_{10-2.5}$ and $PM_{2.5}$ levels at monitor j, where $j = 1, \ldots, J^c$ and J^t is the total number of $PM_{2.5}$ monitors in county c. For some $PM_{2.5}$ monitors, a collocated PM_{10} monitor is present and both W^c_{1tj} and W^c_{2tj} are observed. Otherwise, only W^c_{2tj} is observed, and we treat W^c_{1tj} as missing. In our study, there were 220 collocated $PM_{2.5}$ and PM_{10} monitor pairs and an additional 173 $PM_{2.5}$ monitors that did not have collocated PM_{10} monitors.

Under the assumption that $PM_{10-2.5}$ and $PM_{2.5}$ concentrations are spatially homogeneous across each county, the standard daily county-level $PM_{10-2.5}$ exposure (X^c_{1t}) and $PM_{2.5}$ exposure (X^c_{2t}) measures are obtained by averaging all available measurements across monitors on a particular day (Samet *and others*, 2000). Specifically, the 10% trimmed mean (TM) is used to exclude extreme monitor-level values that may be invalid. In this algorithm, no PM measurements are excluded in computing the mean on days with less than 3 monitor-level PM measurements and only the maximum and minimum measurements are excluded on days between 3 and 9 PM measurements.

2.3 *ME model*

To illustrate the impact of a spatially heterogeneous pollutant in time series studies of air pollution and health and the importance of defining appropriate population exposure indicators, first consider the following example adopted from Zeger *and others* (2003) and Sheppard (2005). Denote by X_{it} the exposure to a pollutant due to outdoor sources for an individual i on day t. For each individual in the study, we assume that the binary health outcome follows a Bernoulli distribution with probability $\lambda_0 \exp(\beta X_{it})$, where λ_0 represents a baseline risk common across individuals and $\exp(\beta)$ represents the multiplicative change in risk associated with a unit increase in X_{it}.

Let N_t denote the number of at-risk individuals in a community on day t, and let Y_t denote the number of hospital admissions on day t in the population that resides in the community. If the occurrence of outcome is independent across individuals, the community-level outcome count has mean equal to

$$\mu_t = \lambda_0 \sum_{i=1}^{N_t} \exp(\beta X_{it}). \tag{2.1}$$

Since the short-term relative risk of air pollution is typically very small, following Zeger *and others* (2003), a linear approximation to the exponential term in (2.1) gives

$$\log(\mu_t) \simeq \log(\lambda_0 N_t) + \beta\left(\left[\sum_{i=1}^{N_t}(X_{it} - X_t)\right]/N_t\right) + \beta X_t = \log(\lambda_0\, N_t) + \beta\, X_t,$$

where X_t is the average exposure of all at-risk individuals. Under these assumptions, the relative risk obtained by regressing aggregated outcome Y_t on aggregated exposure X_t via log-linear regression is equivalent to the personal risk β. Therefore, X_t represents the "desired but unobserved" exposure indicator in time series analysis.

Let X_t^* be a surrogate exposure indicator calculated, for example, by averaging measurements from some fixed-location monitoring sites within the community. We can rewrite (2.1) as

$$\mu_t = \lambda_0 \sum_{i=1}^{N_t} \exp(\beta(X_{it} - X_t) + \beta(X_t - X_t^*) + \beta X_t^*). \tag{2.2}$$

Applying a similar linear approximation gives

$$\log(\mu_t) \simeq \log(\lambda_0 N_t) + \beta(X_t - X_t^*) + \beta X_t^*. \tag{2.3}$$

Hence, we wish to have the exposure indicator calculated from monitoring data to coincide with the true average exposure ($X_t = X_t^*$).

For coarse PM, ME can occur when the sparse $PM_{10-2.5}$ monitoring network does not fully capture the spatial variation in $PM_{10-2.5}$ concentrations. Here, it is also important to account for the spatial distribution of the at-risk population since individuals can be exposed to different levels of ambient $PM_{10-2.5}$. The standard approach of defining community-level exposure by averaging monitor measurements can over- or underestimate the true average exposure. This bias can also vary temporally because the set of $PM_{10-2.5}$ measurements used to calculate average exposure often varies between days due to missing data or different monitoring schedules.

In the ME modeling approach, we view PM measurements from different monitors on the same day within the same county as error-prone repeated measurements of the unobserved population exposure. Let $\boldsymbol{X}_t^c = (X_{1t}^c, X_{2t}^c)$ denote the unobserved county-level exposure to ambient $PM_{10-2.5}$ and $PM_{2.5}$ experienced by the at-risk population. Under the classical additive ME model (Fuller, 1987), we assume for $j = 1, \ldots, J^c$,

$$\boldsymbol{W}_{tj}^c = \begin{bmatrix} W_{1tj}^c \\ W_{2tj}^c \end{bmatrix} \sim \text{Normal}\left(\begin{bmatrix} X_{1t}^c \\ X_{2t}^c \end{bmatrix}, \Sigma_w^c = \begin{bmatrix} \sigma_1^{2,c} & \rho^c\sigma_1^c\sigma_2^c \\ \rho^c\sigma_1^c\sigma_2^c & \sigma_2^{2,c} \end{bmatrix}\right), \tag{2.4}$$

where the 2 ME variances ($\sigma_1^{2,c}$ and $\sigma_2^{2,c}$) capture same-day between-monitor variability for $PM_{10-2.5}$ and $PM_{2.5}$. Parameter ρ^c captures the correlation between MEs, which is assumed to be constant across days and monitors within the same county. A positive ρ^c indicates that daily monitor-level $PM_{10-2.5}$ and $PM_{2.5}$ measurement pairs tend to deviate from the true exposures in the same direction. Note that at some monitoring locations and on some days, only W_{2tj}^c is observed and W_{1tj}^c is treated as missing. Through Bayesian inference described in Section 2.5, we simultaneously address the ME problem and the imputation of missing monitor-level $PM_{10-2.5}$ measurements.

Additionally, we assume

$$\log \boldsymbol{X}_t^c = [\log X_{1t}^c, \log X_{2t}^c]' \sim \text{Normal}(\ [\boldsymbol{Z}_t^c\eta_1^c, \boldsymbol{Z}_t^c\eta_2^c]', \Sigma_x^c\ ), \tag{2.5}$$

where $\boldsymbol{Z}_t^c$ denotes a covariate vector that includes indicators for month, indicators for day of the week, and calendar dates. Parameters η_1^c and η_2^c denote the corresponding vectors of regression coefficients. The logarithmic transformation accounts for the strictly positive and right-skewed PM concentration measurements. The diagonal elements of Σ_x^c represent the residual variance for log-PM exposure and its off-diagonal element captures the correlation between daily county-level $PM_{10-2.5}$ and $PM_{2.5}$ exposure for county c. Note that we choose to model $\boldsymbol{W}_{tj}^c$ in (2.4) without the log-transformation to allow for negative values of observed $PM_{10-2.5}$ concentrations. Also, $\boldsymbol{X}_t^c$ is then interpreted as an average of the observed monitoring data. Alternatively, $\boldsymbol{W}_{tj}^c$ can be modeled on the log-scale where a multiplicative ME is assumed.

However, the error specification in (2.4) assumes that errors between the observed monitor-level $PM_{10-2.5}$ concentrations and the true county-level exposure are distributed identically with the same error variance across monitors. For a spatially heterogeneous PM, true county-level exposure represents a population-weighted average exposure. Hence, measurements taken at monitors located in less populated areas, relative to the total population of the county, may tend to deviate more from the true average exposure experienced by everyone in the county.

We also consider a ME model with heteroskedastic errors between monitors where the ME variance is weighted inversely to the population living around the monitor. Let P_k^c denote the population of city k in county c. Following notations from (2.4), we now assume

$$[W_{1tj}^c, W_{2tj}^c]' \sim \text{Normal}\left([X_{1t}^c X_{12}^c]', \frac{1}{\alpha_j^c}\Sigma_w^c\right), \tag{2.6}$$

where $\alpha_j^c = P_{k^*}^c / \sum_k P_k^c$ if monitor j is in city k^*. For counties where PM is measured in multiple cities, α_j^c approximates the proportion of at-risk population in county c that are exposed to the PM concentration measured at monitor j. City population data were retrieved from the Site Descriptive Data database of EPA's AQS. Under this ME model, monitors in less populated areas contribute less to the estimation of county-level exposure. We refer to the above model as the population-weighted WME approach.

Finally, we assign the following priors for the model parameters: (1) η_1^c and η_2^c each follows a multivariate Normal distribution with dispersed variances; (2) Σ_w^c follows Inv–Wish$(\upsilon_w \hat{\Sigma}_w^{c,-1}, \upsilon_w)$, where $\upsilon_w = 3$ and $\hat{\Sigma}_w^c$ is the estimated covariance of $\boldsymbol{W}_{tj}^c - \overline{\boldsymbol{W}}_t^c$; and (3) Σ_x^c follows Inv–Wish$(\upsilon_x \hat{\Sigma}_x^{c,-1}, \upsilon_x)$, where $\upsilon_x = 3$ and $\hat{\Sigma}_x^c$ is the estimated residual covariance from regressing $\log \boldsymbol{X}_t^c$ on $\boldsymbol{Z}_t^c$. Following Gelman (2006), we also consider assigning a Uniform[0, 100] on the standard deviations (SDs) and a Uniform[−1,1] on the correlation for either Σ_w^c or Σ_x^c, or both. The differences in posterior inference for selected counties with small numbers of days or monitors were negligible.

2.4 *Health model*

We model the expected number of admissions $E(Y_t^c)$ using Poisson regression:

$$\log E(Y_t^c) = \log N_t^c + \beta_0^c + \beta_1^c X_{1t}^c + \beta_2^c X_{2t}^c + \boldsymbol{\psi}^c \boldsymbol{C}_t^c, \tag{2.7}$$

where N_t^c is the size of the population at risk. Following Dominici *and others* (2006), confounders ($\boldsymbol{C}_t^c$) include seasonal trends, weather effects, and age-group effects that are modeled via natural cubic splines with degrees of freedom d. Specifically, we include: (1) calendar time ($d = 8$ per year), (2) current-day temperature ($d = 6$) and average temperature for the previous 3 days ($d = 6$); (3) current-day dew-point temperature ($d = 3$) and average dew-point temperature for the previous 3 days ($d = 3$); (4) age-group intercept (64–74 vs. 75 and above) and its interaction with a smooth function of calendar time ($d = 1$ per year); and (5) day of the week.

2.5 *Risk estimation*

For the standard time series analysis without ME modeling, county-level exposures ($\boldsymbol{X}_t^c$) are obtained using the 10% TM algorithm described in Section 2.2. Relative risks estimates are obtained by fitting the health model via maximum quasi-likelihood separately for each county.

Due to the complex health model and the large data set, we describe a 2-stage approach that involves 2 separate Markov chain Monte Carlo (MCMC) implementations to estimate relative risks with ME modeling. In the first stage, posterior samples of $PM_{10-2.5}$ and $PM_{2.5}$ time series ($\boldsymbol{X}^c$) given the observed monitor-level data ($\boldsymbol{W}^c$) are obtained by sampling from the following posterior predictive distribution:

$$\text{Stage 1: } [\boldsymbol{X}^c|\boldsymbol{W}^c, \boldsymbol{Z}^c] \propto \int [\boldsymbol{W}^c|\boldsymbol{X}^c, \boldsymbol{\theta}_1^c][\boldsymbol{X}^c|\boldsymbol{Z}^c, \boldsymbol{\theta}_2^c]\pi(\boldsymbol{\theta}_1^c, \boldsymbol{\theta}_2^c)\mathrm{d}\boldsymbol{\theta}_1^c\,\mathrm{d}\boldsymbol{\theta}_2^c, \tag{2.8}$$

where $[\boldsymbol{W}^c|\boldsymbol{X}^c, \boldsymbol{\theta}_1^c]$ represents the "measurement model" given by (2.4) with parameters $\boldsymbol{\theta}_1^c = (\Sigma_w^c)$ and $[\boldsymbol{X}^c|\boldsymbol{Z}^c, \boldsymbol{\theta}_2^c]$ represents the "exposure model" given by (2.5) with parameters $\boldsymbol{\theta}_2 = (\eta_1^c, \eta_2^c, \Sigma_x^c)$. Here, the posterior distribution of $\boldsymbol{X}^c$ does not depend on the health model. Stage 1 computation is carried out by using JAGS version 1.0.3 (Plummer, 2003).

At the second stage, we obtain posterior samples of $[\boldsymbol{X}^c, \boldsymbol{\beta}^c|\boldsymbol{W}^c, \boldsymbol{Z}^c, \boldsymbol{Y}^c]$ by using $[\boldsymbol{X}^c|\boldsymbol{W}^c, \boldsymbol{Z}^c]$ from Stage 1 as the prior distribution of $\boldsymbol{X}^c$. Given health data $\boldsymbol{Y}^c$ for county c, we assume

$$\text{Stage 2: } [\boldsymbol{X}^c, \boldsymbol{\beta}^c|\boldsymbol{W}^c, \boldsymbol{Z}^c, \boldsymbol{Y}^c] \propto [\boldsymbol{Y}^c|\boldsymbol{X}^c, \boldsymbol{\beta}^c, \boldsymbol{\psi}^c][\boldsymbol{X}^c|\boldsymbol{W}^c, \boldsymbol{Z}^c]\pi(\boldsymbol{\beta}^c, \boldsymbol{\psi}^c)d\boldsymbol{\psi}^c, \tag{2.9}$$

where $[\boldsymbol{Y}^c|\boldsymbol{X}^c, \boldsymbol{\beta}^c, \boldsymbol{\psi}^c]$ corresponds to the "health model" from (2.7). To decrease computational burden, we treat $\boldsymbol{\psi}^c$ as nuisance parameters and carry out a profile sampler approach described in Lee *and others* (2005). Specifically, we carry out block Metroplis–Hastings updates between $\boldsymbol{\beta}^c$ and $\boldsymbol{X}^c$, where the acceptance probabilities are calculated using the profile likelihood. Since both $\boldsymbol{X}^c$ and $\boldsymbol{\beta}^c$ are updated by the health data $\boldsymbol{Y}^c$, we refer to this estimation approach as the "Bayesian" approach. This approach also provides samples of $[\boldsymbol{X}^c|\boldsymbol{W}^c, \boldsymbol{Z}^c, \boldsymbol{Y}^c]$, the posterior distribution of the average PM exposure incorporating the health information. Details of the estimation procedure and an example of validating the 2-stage Bayesian approach are provided in Section 1 of the supplementary material available at *Biostatistics* online.

We also estimate the county-specific relative risks $\boldsymbol{\beta}^c$, where we replace $\boldsymbol{X}^c$ in the health model by the marginal posterior mean $E[\boldsymbol{X}^c|\boldsymbol{W}^c, \boldsymbol{Z}^c]$ from stage 1. This plug-in method resembles a regression calibration where the unobservable exposure is replaced by its best linear prediction conditional on the covariates measured without error ($\boldsymbol{Z}_t^c$) and the observed error-prone measurements (Carroll *and others*, 2006). While this method is computationally simple, it does not fully reflect the uncertainty in the exposure measure when estimating $\boldsymbol{\beta}^c$. Also, unlike the Bayesian approach, there is no feedback between the health observations and the exposure estimates. However, since the acute health effects of PM are typically small (relative risk of less than 2% per 10 $\mu g/m^3$ increase in PM), the information in the health model is possibly negligible in determining the posterior distribution of the true county-level PM exposure.

We pool county-specific relative risks $\boldsymbol{\beta}^c = (\beta_1^c, \beta_2^c)$ defined in (2.7) by assuming $\boldsymbol{\beta}^c \sim N(\boldsymbol{\mu}, \Sigma_\beta)$. Here, the parameter of interest, $\boldsymbol{\mu}$, is interpreted as the pooled (national) $PM_{10-2.5}$ and $PM_{2.5}$ effects and Σ_β captures the heterogeneity in relative risks between counties. Denote the estimated county-specific relative risks by $\hat{\boldsymbol{\beta}}^c$ and the corresponding covariance matrix by $\hat{V}^c$ estimated either with or without exposure ME modeling as described in Section 2.5. For the Bayesian approach with ME modeling, we define $\hat{\boldsymbol{\beta}}^c$ and $\hat{V}^c$ as the posterior mean and posterior covariance from the second-stage MCMC. Assuming $\hat{\boldsymbol{\beta}}^c \sim N(\boldsymbol{\beta}^c, \hat{V}^c)$, $\boldsymbol{\mu}$ and Σ_β are estimated using the 2-level Normal independent sampling estimation algorithm of Everson and Morris (2000).

3. RESULTS

Across counties, the median number of $PM_{2.5}$ monitors in a county was 5; the first quartile (Q_1, 25th percentile) was 4; and the third quantile (Q_3, 75th percentile) was 8. Similarly, the median number of $PM_{2.5}$ and PM_{10} collocated monitor pairs was 3 ($Q_1 = 2$ and $Q_3 = 5$). Therefore, by restricting our analysis to collocated monitor pairs, the standard TM exposure for $PM_{10-2.5}$ was calculated based on a considerably smaller number of monitors compared to $PM_{2.5}$. In Figure 2, correlation of daily PM measurements at any pair of monitors in the same county is plotted versus the distance between the monitors. There was considerable larger spatial variability in $PM_{10-2.5}$ measurements compared to $PM_{2.5}$.

Our study included approximately 5 million Medicare enrollees between the period 1999 and 2005. There were about 2.6 million admissions for cardiovascular diseases and 1.0 million admissions for respiratory diseases. Across counties, the median daily admission for cardiovascular diseases was 18.7 per 100 000 people ($Q_1 = 15.8$ and $Q_3 = 21.4$) and the median for respiratory diseases was 7.4 per 100 000 people ($Q_1 = 6.3$ and $Q_3 = 8.8$).

We considered 5 exposure measures of daily county-average $PM_{10-2.5}$ level. For example, Figure 3 shows the marginal posterior distributions of $PM_{10-2.5}$ exposure on July 17, 2000 in Harris County, TX. The 4 posterior distributions were obtained under different ME modeling and estimation approaches: (1) constant ME variances across monitors without using the health data (ME, $[\boldsymbol{X}|\boldsymbol{W}, \boldsymbol{Z}]$); (2) constant ME variances across monitors using the health data (ME, $[\boldsymbol{X}|\boldsymbol{W}, \boldsymbol{Z}, \boldsymbol{Y}]$); (3) population-WME variances across monitors without using the health data (WME, $[\boldsymbol{X}|\boldsymbol{W}, \boldsymbol{Z}]$); and (4) population-WME variances across monitors using the health data (WME, $[\boldsymbol{X}|\boldsymbol{W}, \boldsymbol{Z}, \boldsymbol{Y}]$). For (2) and (4), the relative risks associated with cardiovascular admissions were simultaneously estimated with $PM_{10-2.5}$ exposure. Also, a vertical line is placed at the 10% TM estimate. The differences in exposure estimates reflect which monitor-level observations were used. On this particular day, there were 4 observations of $PM_{10-2.5}$ concentration: 3 observations 18, 61, and 20 were from Houston and one observation 12 was from Deer Park. The TM $PM_{10-2.5}$ measure excluded 12 and 61 in computing the average; the ME measure considered all values

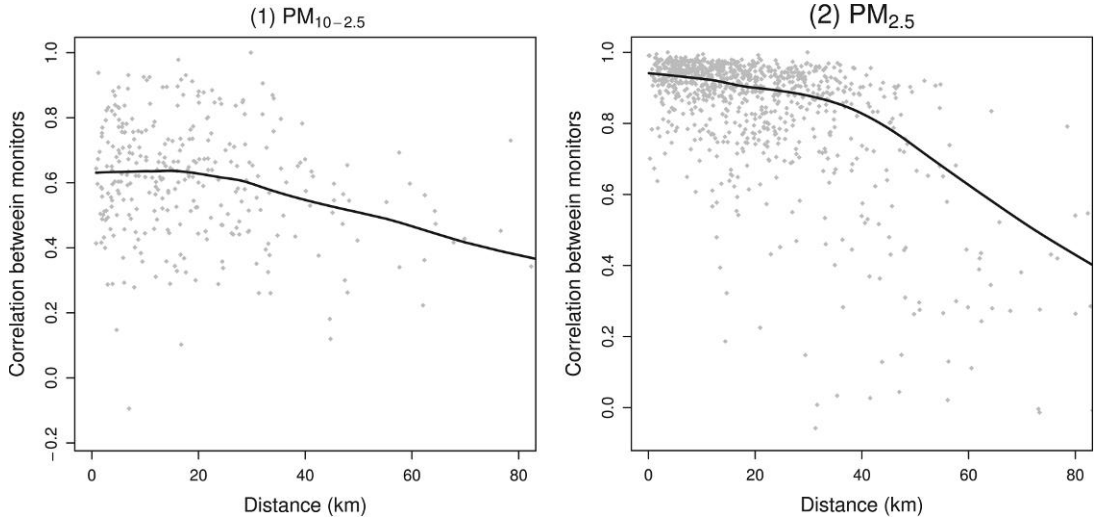

Fig. 2. Correlations of monitor-level daily PM time series calculated between pairs of $PM_{2.5}$ or $PM_{10-2.5}$ monitoring locations in the same county and plotted versus the distance between monitor pair. For $PM_{2.5}$, we used all available monitors without restricting to those with a collocated PM_{10} monitor.

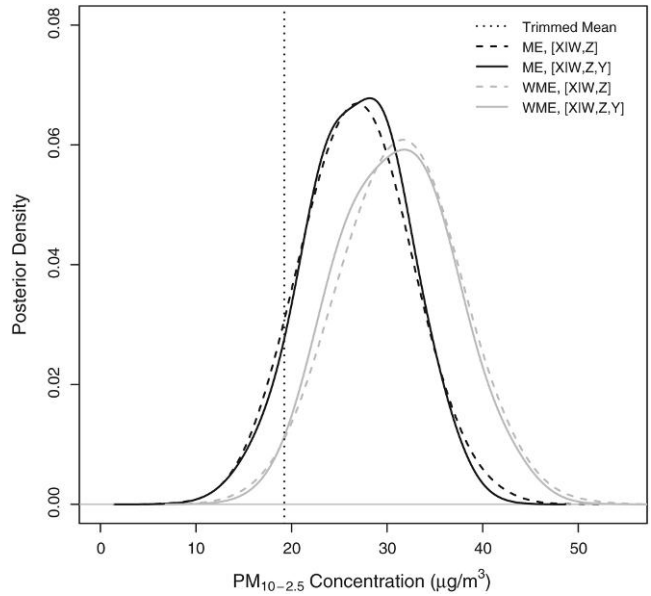

Fig. 3. Posterior distributions of the average exposure to outdoor $PM_{10-2.5}$ concentration on July 17, 2000 in Harris County, TX. The vertical line is placed at the 10% TM estimate. The solid and dotted lines represent 4 different $PM_{10-2.5}$ posterior distributions obtained from ME modeling.

Table 1. *Quantiles of county-specific SD of $PM_{2.5}$ and $PM_{10-2.5}$ time series using either TM, ME modeling with constant error variance (ME), or monitor-specific weighted error variance (WME). The median (*25*th quantile and* 75*th quantile) of the SD across* 59 *counties are given*

	TM	ME	WME
$PM_{2.5}$ (μ g/ m^3)	7.6 (6.1, 9.0)	7.1 (5.8, 8.7)	7.3 (5.9, 8.6)
$PM_{10-2.5}$ (μ g/ m^3)	7.9 (6.2, 12.2)	6.0 (4.4, 10.3)	7.0 (4.8, 11.7)

equally; and the WME measure down weighted the measurement from Deer Park which has a considerably smaller population than Houston.

We calculated the SD of county-level $PM_{2.5}$ and $PM_{10-2.5}$ levels across days and Table 1 gives the median, Q_1, and Q_3 across 59 counties for different exposure measures. First, daily variation of county-average $PM_{10-2.5}$ levels derived from ME and WME were lower compared to TM and this decrease was less significant for $PM_{2.5}$. PM daily variation decreases when ME is considered because the model assumes that the observed PM concentrations are more noisy than the true exposure. Specifically, a large decrease in time series SD reflects greater disagreement between same-day monitor-level measurements. Moreover, for both $PM_{10-2.5}$ and $PM_{2.5}$, the decrease in daily variation was more significant for the ME measures compared to the WME measures. If PM levels vary across cities of different population sizes, county-average exposure is determined mainly by measurements in cities with large populations. Since the true exposure represents a population-weighted average exposure, the WME approach can result in smaller ME because disagreement between PM measurements in cities with small populations and the true exposure is down-weighted.

Table 2 gives some pairwise correlations between $PM_{10-2.5}$ and $PM_{2.5}$ exposure measures obtained using either TM or WME across counties. Comparing rows 1 and 2, higher correlations are observed

Table 2. *Quantiles of correlations between different measures of county-level daily $PM_{10-2.5}$ and $PM_{2.5}$ exposures across* 59 *counties. Exposure measures for $PM_{2.5}$ and $PM_{10-2.5}$ are derived using either TM or WME modeling*

	Correlation between	Minimum	25%	50%	75%	Maximum
(1)	$PM_{10-2.5,TM}$, $PM_{10-2.5,WME}$	0.50	0.89	0.92	0.95	1.00
(2)	$PM_{2.5,TM}$, $PM_{2.5,WME}$	0.72	0.94	0.97	0.99	1.00
(3)	$PM_{2.5,TM}$, $PM_{10-2.5,TM}$	−0.20	0.05	0.12	0.23	0.59
(4)	$PM_{2.5,WME}$, $PM_{10-2.5,WME}$	−0.15	0.05	0.18	0.32	0.59

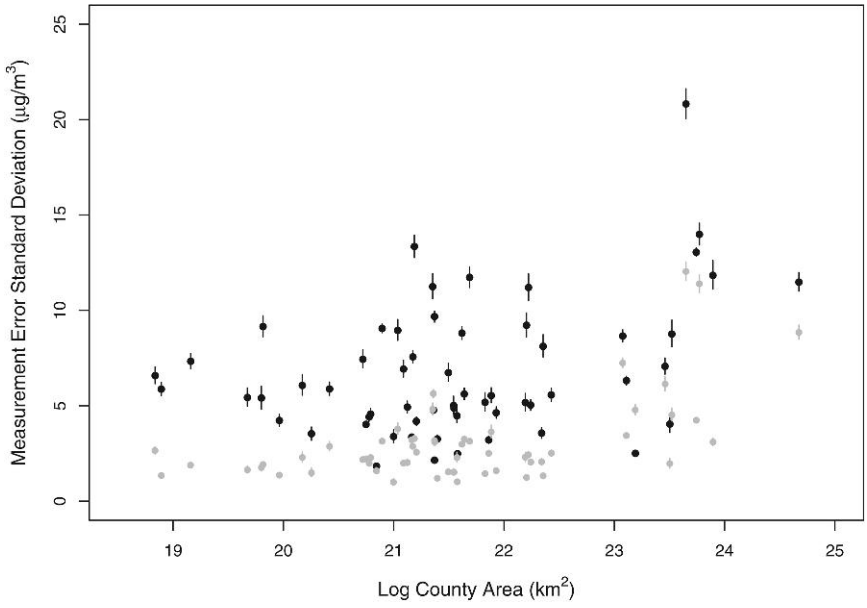

Fig. 4. County-specific ME SD ($\sigma_1^{2,c}$ and $\sigma_2^{2,c}$ in (2.4) for $PM_{10-2.5}$ (black) and $PM_{2.5}$ (gray) plotted versus log county land area (cubic kilometer) for 59 counties. Each bullet denotes the posterior mean and the vertical line indicates the 95% posterior interval.

between different $PM_{2.5}$ measures compared to $PM_{10-2.5}$. This is expected since $PM_{2.5}$ level is less heterogeneous spatially and the ME approach results in less calibration when the between-monitor agreement is strong. Comparing rows 3 and 4, we find that deriving $PM_{10-2.5}$ and $PM_{2.5}$ exposures via ME modeling increases the correlation between the 2 pollutants slightly. We also found very high correlation between the average exposure measures derived from the 2 ME models (ME vs. WME) for $PM_{10-2.5}$ and $PM_{2.5}$, having minimum correlation of 0.82 and 0.87, respectively, in the 59 counties (not shown in table).

The ME variances, $\sigma_1^{2,c}$ and σ_2^{c} in (2.4) quantify the variability across monitors of the PM values. Figure 4 plots the posterior mean and 95% intervals for the ME SD versus log-transformed county land area (square kilometer). We found greater between-monitor variation for $PM_{10-2.5}$ (black) measurements compared to $PM_{2.5}$ (gray) measurements, even though the 2 pollutants had similar average concentration over the study period. The median ME SD across counties for $PM_{10-2.5}$ is 5.6 ($Q_1 = 4.4$ and $Q_3 = 8.8$) and for $PM_{2.5}$ is 2.3 ($Q_1 = 1.7$ and $Q_3 = 3.2$). In Figure 4, it also appears that larger counties were associated with greater between-monitor variation in PM measurements. We also found evidence

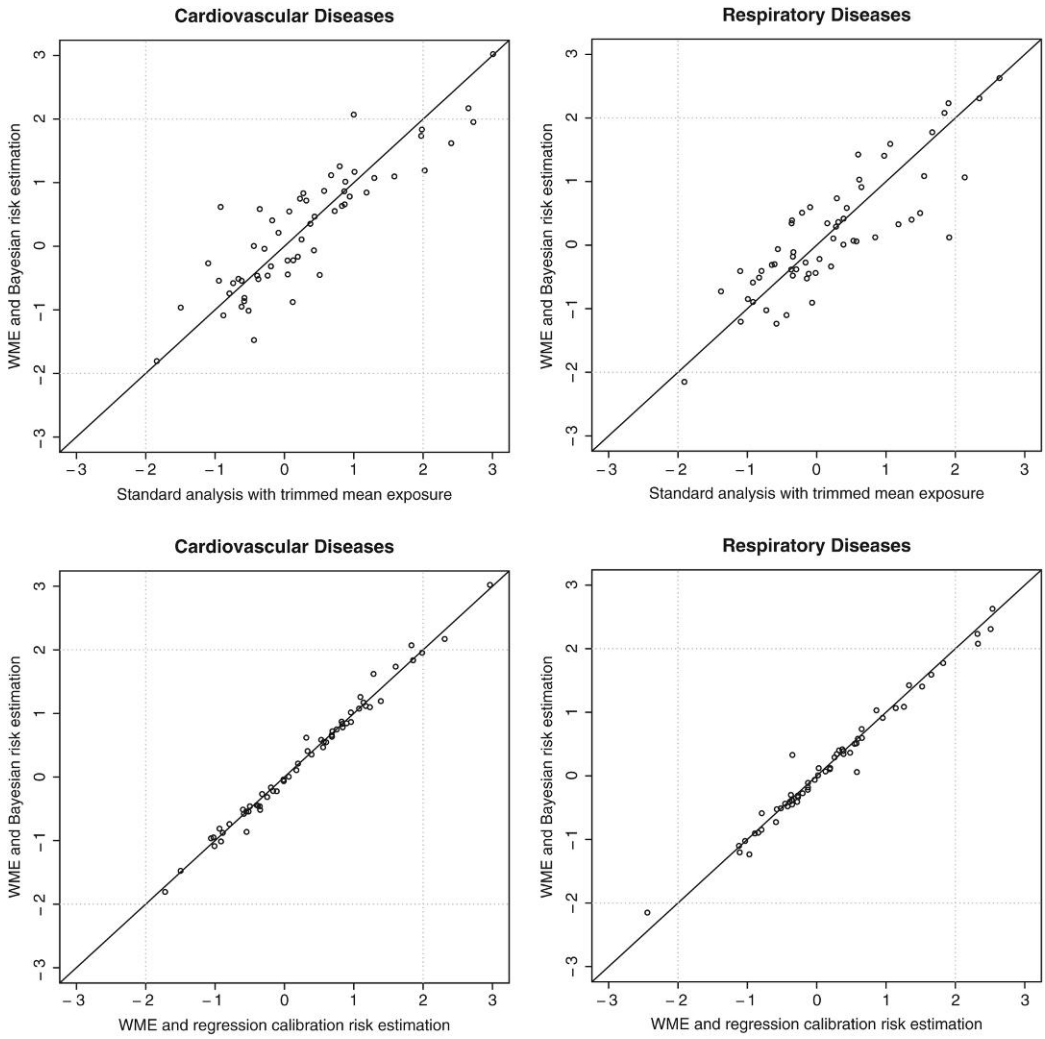

Fig. 5. Upper panels: scatter plot of county-specific standardized health effect estimates for $PM_{10-2.5}$, $\hat{\beta}_1^c/\text{SE}\,(\hat{\beta}_1^c)$, comparing 2 approaches: (1) including ME modeling with monitor-specific weighted error variance (WME) versus (2) using TM as $PM_{10-2.5}$ exposure. Lower panels: scatter plot of county-specific standardized health-effect estimates for $PM_{10-2.5}$, $\hat{\beta}_1^c/\text{SE}\,(\hat{\beta}_1^c)$, using exposure derived from WME comparing Bayesian risk estimation versus regression calibration.

of a weak positive association between $PM_{2.5}$ and $PM_{10-2.5}$ measurement errors at collocated monitors for some counties. The posterior means of ρ^c across 59 counties have a median of 0.10 ($\min = -0.23$, $Q_1 = -0.1$, $Q_3 = 0.4$, $\max = 0.6$) .

The 2 upper panels in Figure 5 plot the county-specific standardized coefficients, $\hat{\beta}_1^c/\text{SE}\,(\hat{\beta}_1^c)$ to examine the strength and direction of the health effect of $PM_{10-2.5}$ on cardiovascular and respiratory admissions estimated using different exposure measures. Comparing estimates derived from standard TM exposure and WME with the Bayesian risk estimation, we did not observe large changes in the health effects' direction. However, there is attenuation for large $\hat{\beta}_1^c/\text{SE}\,(\hat{\beta}_1^c)$ possibly due to increased uncertainty in risk

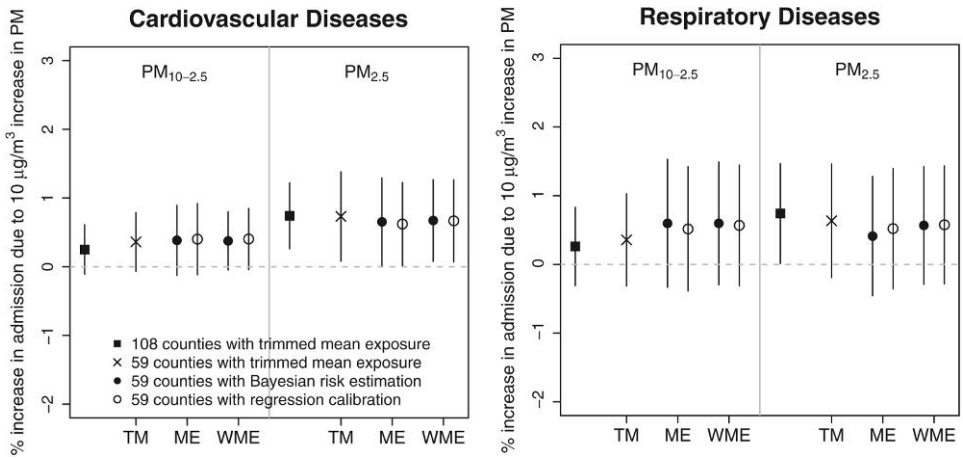

Fig. 6. Percent increase in emergency hospital admissions rates for cardiovascular and respiratory diseases per 10 $\mu g/m^3$ increase in same-day particulate matter concentration. Exposure measures for $PM_{2.5}$ and $PM_{10-2.5}$ are derived using either TM, ME modeling with constant error variance across monitors (ME) or monitor-specific weighted error variance (WME).

estimates when MEs are accounted for. From the 2 bottom panels in Figure 5, we show that in our application, standard error (SE), $\hat{\beta}_1^c/\text{SE}$ ($\hat{\beta}_1^c$) for cardiovascular and respiratory admissions are very similar between those derived from regression calibration and those estimated through the Bayesian approach. For the Poisson health model, regression calibration will result in some bias in the relative risk estimates; however in the analysis of $PM_{10-2.5}$, the uncertainty in exposure appears to dominate.

Figure 6 gives the pooled estimates of percent increase in cardiovascular and respiratory disease admissions per 10 $\mu g/m^3$ increase in same-day particulate matter concentration. Exposure measures for $PM_{2.5}$ and $PM_{10-2.5}$ were derived using either TM, ME, or WME, and we considered both regression calibration and Bayesian risk estimations. The original Peng *and others* (2008) estimates based on 108 counties using TM exposure are also shown. We found consistent positive effects for $PM_{10-2.5}$ and $PM_{2.5}$ with different exposure measures and estimation procedures. For cardiovascular admissions, effects of $PM_{2.5}$ remain statistically significant under different scenarios. The posterior intervals are wider under ME modeling compared to using the standard TM exposure. Also, when ME modeling are used, the confidence intervals are wider for Bayesian risk estimations compared to regression calibration and the bias associated with regression calibration appears negligible.

4. SIMULATION STUDY

This section describes a simulation study that examines the impact of $PM_{10-2.5}$ exposure ME and the performance of our proposed method using data from Clark County, NV. Clark County contains 8 $PM_{10-2.5}$ monitoring locations from 5 cities with population ranging from about 200 to half a million. On each day t, we do not observe the complete vector of monitor-level measurements $\boldsymbol{X}_t = (x_{t1}, x_{t2}, \ldots, x_{t8})'$. Across the 1337 days with at least one $PM_{10-2.5}$ measurement, the average number of measurements per day was 4.3.

We generated 100 replicate data sets of the complete monitor-level $PM_{10-2.5}$ values as follows. We assumed $\boldsymbol{X}_t \sim$ Normal $(\hat{\boldsymbol{B}}Z_t, \hat{\Sigma})$, where Z_t is the $p \times 1$ vector of covariates from (2.5). Parameter $\hat{\boldsymbol{B}}$ is an $8 \times p$ matrix of monitor-specific regression coefficients and parameter $\hat{\Sigma}$ is the 8×8 residual

Table 3. *Simulation study results: median bias, average* 95% *confidence interval (C.I.) width, and root mean squared error for $PM_{10-2.5}$ relative risk in Clark County, Nevada. At-risk population is allocated to each monitor either equally (Scenario* 1*) or proportional to the city population that the monitor is in (Scenario* 2*). Exposure measures considered include: TM or ME modeling without (ME) or with (WME) heteroskedastic variances*

	Scenario 1			Scenario 2		
	True	TM	ME	True	TM	WME
Bias ($\times 10^4$)	− 0.02	−0.39	−0.18	−0.01	−0.33	−0.16
C.I. width ($\times 10^4$)	1.62	3.11	3.93	1.94	3.04	3.03

covariance matrix. These parameters were estimated from the observed data and the between-monitor correlation ranges from 0.3 to 0.8. Given the observed $PM_{10-2.5}$ concentrations, missing concentrations were imputed using the corresponding conditional mean and covariance. We used the complete PM data set to generate hospital admissions. However, in constructing the TM exposure measures and in carrying out ME modeling, we followed the observed missing data structure and ignored the imputed $PM_{10-2.5}$ concentrations.

We set the total number of at-risk individuals to be 43 410. We considered 2 exposure scenarios by allocating the population to each monitor either (1) equally or (2) proportional to the city population that the monitor is in. Finally, for each simulated $PM_{10-2.5}$ data set, we generated daily total admission with a baseline risk of 1.8×10^{-4} and a relative risk of 0.5% per 10 unit increase $PM_{10-2.5}$ concentration following the Poisson model in (2.7) without additional confounders. Relative risk for $PM_{10-2.5}$ was then estimated using the TM, ME, or WME exposure measures. Here, we only considered the estimation approach without using the health data ($[\boldsymbol{X} \mid \boldsymbol{W}, \boldsymbol{Z}]$) due to computational limitation.

Table 3 gives the median bias and average 95% confidence interval length for the relative risk estimates. With the TM exposure measures, we found that attenuation occurs in both scenarios and our ME approaches (ME and WME) reduce this bias. ME modeling increases the confidence interval width when the same number of individuals are exposed to different concentrations (scenario 1). In this case, our method effectively propagates the uncertainty in population exposure when between-monitor disagreement is present. However, when the number of at-risk individuals varies across $PM_{10-2.5}$ concentrations (scenario 2), the WME exposures does not result in wider confidence intervals. This is likely due to recovering some exposure variability that is oversmoothed by simply averaging monitor-level concentrations.

5. Discussion

EPA does not regulate $PM_{10-2.5}$ directly but continues to use PM_{10} as a surrogate to protect public health. In the most recent 2006 NAAQS revision for particulate matter, a 24-h $PM_{10-2.5}$ standard was proposed but ultimately not accepted due to insufficient evidence linking short-term $PM_{10-2.5}$ exposure and adverse health outcomes (Environmental Protection Agency, 2006). Time series analysis plays an important role in providing epidemiological evidence for the acute health effects of PM and in establishing regulatory standards (Greenbaum *and others*, 2001). Its popularity is due to the ability to utilize public databases to estimate the relatively small acute effects with large study populations. However, recent interest in quantifying the health effects of $PM_{10-2.5}$ raises statistical questions regarding the time series design when the pollutant concentration varies spatially.

In this paper, we address the challenge of exposure ME due to spatial misalignment through ME modeling. The goal is to obtain risk estimates that reflect the uncertainty in $PM_{10-2.5}$ exposure in a time series study. This differs from the past work that has focused predominantly on errors due to either (1)

the discrepancy between ambient levels measured outdoors versus total personal exposure (Dominici *and others*, 2000) or (2) the ecological bias that results from using aggregated outcome and exposure to infer individual-level risk (Sheppard, 2005; Sheppard *and others*, 2005).

Computing average community-level exposure with monitor-specific weights is a common practice in time series analysis. The TM approach represents a simple way to remove extreme values observed on a particularly day; however, this may oversmooth a spatially varying exposure when the number of measurements per day is small. A similar approach taken by Zanobetti and Schwartz (2009) first removes monitors that are not well correlated with others in the same region to avoid measurements that are due to local pollution sources not reflective of the overall population exposure. However, this approach does not address the scenario when all monitors are poorly correlated with each other. In contrast, our ME method is a parametric approach that provides average exposure estimates and accounts for the same-day between-monitor variability using all available data. Moreover, by allowing error variances to be inversely proportional to the population living around each monitor, we automatically specify monitor-specific weights in computing average exposure.

While this paper is motivated by the analysis of $PM_{10-2.5}$ and health, we note that the analysis of $PM_{2.5}$ chemical constituents shares similar challenges in exposure ME. For example, the metal constituents in $PM_{2.5}$ can exhibit high spatial heterogeneity and the minor components are often measured with high instrumental ME. One limitation of the proposed approach is that we need to restrict our analysis to counties with at least 2 pairs of collocated monitors. Future work will borrow information across counties by building regression models for the ME variances to predict the extent of exposure ME for counties that only have a single $PM_{10-2.5}$ measurement each day. Our model also assumes the MEs to be independent between days and does not model the temporal correlation between pollutant concentrations. This is because $PM_{10-2.5}$ measurements are typically only available every sixth day. But at some locations where daily measurements of $PM_{10-2.5}$ are available, additional modeling of these temporal trends should be explored.

SUPPLEMENTARY MATERIAL

Supplementary material is available at http://biostatistics.oxfordjournals.org.

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