Model Choice in Time Series Studies of Air Pollution and Mortality

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Abstract

Multi-city time series studies of particulate matter (PM) and mortality and morbidity have provided evidence that daily variation in air pollution levels is associated with daily variation in mortality counts. These findings served as key epidemiological evidence for the recent review of the United States National Ambient Air Quality Standards (NAAQS) for PM. As a result, methodological issues concerning time series analysis of the relation between air pollution and health have attracted the attention of the scientific community and critics have raised concerns about the adequacy of current model formulations. Time series data on pollution and mortality are generally analyzed using log-linear, Poisson regression models for overdispersed counts with the daily number of deaths as outcome, the (possibly lagged) daily level of pollution as a linear predictor, and smooth functions of weather variables and calendar time used to adjust for time-varying confounders. Investigators around the world have used different approaches to adjust for confounding, making it difficult to compare results across studies. To date, the statistical properties of these different approaches have not been comprehensively compared. To address these issues, we quantify and characterize model uncertainty and model choice in adjusting for seasonal and long-term trends in time series models of air pollution and mortality. First, we conduct a simulation study to compare and describe the properties of statistical methods commonly used for confounding adjustment. We generate data under several confounding scenarios and systematically compare the performance of the different methods with respect to the mean squared error of the estimated air pollution coefficient. We find that the bias in the estimates generally decreases with more aggressive smoothing and that model selection methods which optimize prediction may not be suitable for obtaining an estimate with small bias. Second, we apply and compare the modelling approaches to the National Morbidity, Mortality, and Air Pollution Study (NMMAPS) database which is comprised of daily time series of several pollutants, weather variables, and mortality counts covering the period 1987–2000 for the largest 100 cities in the United States. When applying these approaches to adjusting for seasonal and long-term trends we find that the NMMAPS estimates for the national average effect of PM$_{10}$ at lag 1 on mortality vary over approximately a two-fold range, with 95% posterior intervals always excluding zero risk.

Keywords: Air pollution; Time series; Log-linear regression; Semi-parametric regression; Mortality
1 Introduction

Numerous time series studies have indicated a positive association between short-term variation of particulate matter and daily mortality counts (see e.g. Pope et al., 1995; Dockery and Pope, 1996; Goldberg et al., 2003; Bell et al., 2004, and references therein). Multi-city studies such as the National Morbidity, Mortality, and Air Pollution Study (Samet et al., 2000c,a), the Air Pollution and Health: A European Approach study (Katsouyanni et al., 2001; Samoli et al., 2002), and analyses of Canadian cities (Burnett et al., 1998; Burnett and Goldberg, 2003) have added to the mounting evidence of the adverse health effects of fine particles, even at levels below current regulatory limits. In the United States, these studies have played an important role in setting standards for acceptable levels of ambient particulate matter. In particular, the National Morbidity, Mortality, and Air Pollution Study (NMMAPS) played a central role in the Environmental Protection Agency’s (EPA) development of National Ambient Air Quality Standards (NAAQS) for the six “criteria” pollutants defined by the EPA (Environmental Protection Agency, 1996, 2003).

The critical role of NMMAPS in the development of the NAAQS attracted intense scrutiny from the scientific community and industry groups regarding the statistical models used and the methods employed for adjusting for potential confounding. Confounding occurs when an attribute associated with an outcome is also associated with the exposure of interest but is not a result of the exposure. In time series studies, we are primarily concerned with potential confounding by factors that vary on similar timescales as pollution or mortality. While collectively strengthening the epidemiologic evidence of the adverse health effects of PM, the proliferation of time series studies employing different approaches to modeling and adjusting for confounding highlighted the critical need to assess the statistical properties of these approaches.

The different sources of potential confounding in time series studies of air pollution and mortality can be broadly classified as either measured or unmeasured. Important measured confounders include weather variables such as temperature and dew point temperature. Daily temperature measurements are readily available for metropolitan areas in the United States and numerous studies have demonstrated a relationship between temperature and mortality which is generally positive for warm summer days and negative for cold winter days (e.g. Curriero et al., 2002). One
approach to adjusting for confounding by temperature is to include non-linear functions of current and previous day temperature (and dew point) in the model (Schwartz, 1994a; Kelsall et al., 1997; Samet et al., 1998). Welty and Zeger (2005) developed a rich class of distributed lag models specifically targeted at adjusting for temperature in multi-city time series studies of air pollution and mortality. This class of models includes a variety of predictors such as running means of temperature, non-linear functions of running means, multiple lags of temperature, and interactions between temperature at different lags. They applied their models to the NMMAPS database and found that the national average estimate of the effect of PM$_{10}$ (PM with aerodynamic diameter $< 10 \mu m$) on total non-accidental mortality is robust to a large class of statistical models used to adjust for potential confounding by temperature and dew point temperature. Building on these findings, in this paper we focus on the problem of controlling for unmeasured confounders, that is, seasonal and long term trends.

Unmeasured confounders are factors that influence mortality and vary with time in a manner similar to air pollution. These factors produce seasonal and long-term trends in mortality that can confound the relationship between mortality and air pollution. Influenza and respiratory infections might reasonably be considered among the most important, usually unmeasured or not readily available confounders which produce seasonal patterns in mortality. Typically, epidemic respiratory infections occur from late fall to early spring and influenza epidemics occur in the same interval but with highly variable timing. The net impact of a respiratory virus is to increase mortality overall, explaining much of the higher mortality in winter months. Since air pollution levels also have a strong seasonal pattern, such respiratory virus epidemics are likely to confound the relationship between air pollution and mortality. Daily time series of mortality counts can also be affected by population level trends in survival (including increased/decreased access to improved medical care), changes in population size, and trends in the occurrence of major diseases. These long-term trends could coincide with recent declines in a number of pollution indicators (e.g. TSP and then PM$_{10}$).

A common approach to adjusting for seasonal and long-term trends is to use semiparametric models which incorporate a smooth function of time. The use of nonparametric smoothing in time series models of air pollution and health was suggested in Schwartz (1994a), where generalized
additive Poisson models were used with loess smooths of time, temperature, dew point temperature and PM$_{10}$. This approach can be thought of as regressing residuals from the smoothed dependent variable on residuals from the smoothed regressors. In this setting, the smooth function of time serves as a linear filter on the mortality and pollution series and removes any seasonal or long-term trends in the data. A number of alternatives for representing the smooth functions have been applied including smoothing splines, penalized splines, and parametric (natural) splines (Dominici et al., 2002; Ramsay et al., 2003; Schwartz et al., 2003; Touloumi et al., 2004; Health Effects Institute, 2003). The smooth function of time naturally only accounts for potential confounding by factors which vary smoothly with time. Factors which vary on shorter timescales may also confound the relationship between air pollution and mortality and controlling for them is an important concern.

The inclusion of a smooth function of time in a regression model introduces important statistical issues. One generally does not know precisely the complexity of the seasonal and long-term trends in the mortality time series or in the pollution time series. Therefore, a controversial issue is determining how much smoothness one should allow for the smooth function of time. This decision is critical because it determines the amount of residual temporal variation in mortality available to estimate the air pollution effect. Over-smoothing the series (thereby under-smoothing the residuals) can leave temporal cycles in the residuals that can produce confounding bias; under-smoothing the series (thereby over-smoothing the residuals) can remove too much temporal variability and potentially attenuate a true pollution effect. Current approaches to choosing the amount of smoothness include automatic, data-driven methods which choose the degree of smoothness by minimizing a goodness-of-fit criterion and methods based on prior knowledge of the timescales where confounding is more likely to occur.

In this paper we provide a comprehensive characterization of model choice and model uncertainty in time series studies of air pollution and mortality, focusing on confounding adjustment for seasonal and long-term trends. We first identify analytical approaches used commonly in air pollution epidemiology for modelling the smooth function of time and for selecting its degrees of freedom. We then introduce a statistical framework that allows us to compare and evaluate critically the statistical properties of each modelling approach by illustrating its theoretical properties.
and by simulation studies. Finally, we apply the different approaches for confounding adjustment to the National Morbidity, Mortality, and Air Pollution Study (NMMAPS) database containing daily mortality, pollution, and weather data for 100 U.S. cities covering the period 1987–2000. Here, we quantify model uncertainty in the most recent national average estimates of the short-term effects of PM on mortality.

2 Methods and Model Choice

Given time series data on pollution levels, mortality counts, and other variables, we make use of the following statistical model:

\[ Y_t \sim \text{Poisson}(\mu_t) \]
\[ \log \mu_t = \beta_0 + \beta x_t + f(t) + q(z_t) + w_t \]

where \( Y_t \) is the mortality count for day \( t \); \( f \) is a smooth function of the time variable \( t \); \( z_t \) represents an observed time-varying variable such as temperature and \( q \) is a (smooth) function of that variable; \( w_t \) is some other linear term such as a day of the week or holiday indicator. Our goal is to estimate the parameter \( \beta \), the association between air pollution \( (x_t) \) and mortality \( (Y_t) \), in the presence of unobserved, time-varying confounding factors. We assume that these factors potentially influence \( \mu_t \) (\( \mathbb{E}[Y_t] \)) via the smooth function \( f \) and, to produce confounding, are associated with \( x_t \) through another smooth function \( g \), via

\[ x_t = g(t) + \xi_t, \]

where \( \xi_t \sim \mathcal{N}(0, \sigma^2) \) and \( \sigma^2 > 0 \). If \( f \) and \( g \) are correlated at similar timescales, confounding bias can occur because mortality and pollution vary with time in a similar manner. Correlation between \( f \) and \( g \) in a nonparametric setting is sometimes referred to as concurvity, essentially collinearity between non-linear transformations of predictors and is the nonparametric analogue of collinearity in standard multiple regression analysis (Buja et al., 1989; Donnell et al., 1994). The strength of the concurvity between \( f \) and \( g \) is determined by the parameter \( \sigma^2 \), which we assume is strictly greater than zero. If \( \sigma^2 = 0 \), then \( f \) and \( g \) are perfectly correlated and the problem of estimating \( \beta \) is not identifiable. Our statistical and epidemiological target is to determine the degree of smoothness of
that maximally reduces the confounding bias in $\hat{\beta}$, the estimate of the pollution coefficient $\beta$, for $\sigma^2 > 0$.

With a model setup such as (1), in order to estimate $\beta$, one must choose how to represent the smooth function $f$ and then decide on the amount of smoothness allowed for $f$. In practice $f$ is typically represented by a series of basis functions and the smoothness is controlled by the number of basis functions or more generally, a notion of “degrees of freedom.”

2.1 Representing $f$

Common choices for representing the smooth function $f$ in (1) include natural splines, penalized splines, and smoothing splines. (Other less common choices are loess smoothers or harmonic functions.) The first is fully parametric, while the latter two may be considered more flexible.

With natural splines, one constructs a spline basis with knots at fixed locations throughout the range of the data and the choice of knot locations can have a substantial impact on the resulting smooth. Smoothing splines and penalized splines circumvent the problem of choosing the knot locations by constructing a very large spline basis and then penalizing the spline coefficients to reduce the effective number of degrees of freedom. Smoothing splines place knots at every (unique) data point and are sometimes referred to as full-rank smoothers because the size of the spline basis is equal to the number of observations. Penalized splines, sometimes called low-rank smoothers, are more general in their definition in that both the size of the spline basis and the location of the knots can be specified. Low-rank smoothers can often afford significant computational benefits when applied to larger datasets such as those used here. Appendix A provides an overview of the different methods used here; a comprehensive treatment can be found in Ruppert et al. (2003).

We employ three commonly used software implementations to fit models using the different spline bases.

- GLM-NS: The glm function in R (R Development Core Team, 2003) is used with natural cubic splines to represent $f$. The number of degrees of freedom for the spline basis is specified via the df argument of the ns function (in the splines package).
- GAM-R: The gam function in R (from the mgcv package) is used with penalized cubic re-
gression splines to represent $f$. This function allows the user to specify the dimension of the basis (before penalization) as well as a penalty parameter. In our simulations and data analysis we use a basis dimension equal to 40 times the number of years of data. The number 40 per year of data was chosen because it was considered far more degrees of freedom than would be necessary to remove seasonal and long-term variation in pollution and hence, some penalization would be required. The implementation of \texttt{gam} in R uses a form of iteratively reweighted least squares to fit the model and standard errors for the regression coefficients can be obtained in a straightforward manner. The methods and software are described in Wood (2000) and Wood (2001).

- \textbf{GAM-S}: The \texttt{gam} function in S-PLUS is used with smoothing splines to represent $f$. This function is not the same as the \texttt{gam} function in R. Here, the user specifies the target number of degrees of freedom desired. The size of the basis does not need to be specified since it is determined by the number of unique data points. The S-PLUS implementation of \texttt{gam} uses backfitting to estimate the smooth terms and we use the strict convergence criteria suggested in Dominici \textit{et al.} (2002). Standard errors are obtained using the \texttt{gam.exact} software of Dominici \textit{et al.} (2004).

Because of the close relationship between penalized splines and smoothing splines (see Appendix A) we only compare the GLM-NS and GAM-R methods in the simulation study. Furthermore, preliminary comparisons of the penalized spline and smoothing spline methods indicated that they performed similarly. For the analysis of the NMMAPS data in Section 4 we compare all three methods.

\subsection*{2.2 Selecting the Degrees of Freedom for $f$}

Given a particular representation of $f$ described in Section 2.1, one must then choose the amount of smoothness to allow for $f$. We examine model selection approaches that have already been used extensively by investigators in the area of time series modelling of air pollution and health data. A general strategy is to use a data-driven method and select a $df$ which optimizes a particular criterion. For example, one approach is to choose the $df$ which leads to optimal prediction of...
the mortality outcome series (e.g. Burnett and Goldberg, 2003) while another is to select the \( df \) which best predicts the pollution series (Dominici et al., 2004). A third strategy is to minimize the autocorrelation in the residuals (e.g. Schwartz, 2000; Katsouyanni et al., 2001; Samoli et al., 2002, 2003; Touloumi et al., 2004). With each of these approaches, a number of Poisson regression models are fit using a range of \( df \) values (other covariates such as weather variables and the pollutant variable are included). Then, for each fitted model, a model selection criterion is evaluated with the “optimal” \( df \) being that which minimizes the criterion. In multi-city studies, this approach can lead to a different \( df \) selected for each city (using a common criterion across cities), potentially allowing city-specific characteristics of the data to influence the estimated smoothness of \( f \).

Another approach we examine here is to use a fixed degrees of freedom, perhaps based on biological knowledge or previous work. For multi-city studies, this approach generally leads to fitting the same model to data from each city. The original NMMAPS analyses took this approach and used 7 degrees of freedom per year of data (Samet et al., 2000b). One can explore the sensitivity of \( \hat{\beta} \) by varying the \( df \) used in the model(s) and examining the associated changes in \( \hat{\beta} \).

In summary, we explore the following strategies for deciding on an appropriate degrees of freedom (\( df \)) for \( f \).

1. **Fixed Degrees of Freedom**: Choose a fixed \( df \) based on biological knowledge or previous work and include a sensitivity analysis to explore the variability of \( \hat{\beta} \) with respect to \( df \). For the sensitivity analysis we estimate \( \beta \) for 1, 2, \ldots, 20 \( df \) per year of data.

2. **AIC**: Choose the \( df \) that minimizes the Akaike Information Criterion (Akaike, 1973). AIC is commonly used for selecting particular covariates and has been applied to the smooth function of time. For a model with \( df \) degrees of freedom, AIC is defined as

\[
AIC(df) = -2 \times (\text{max log-likelihood}) + 2df.
\]

3. **BIC**: Choose the \( df \) that minimizes the criterion of Schwarz (1978). This criterion is often referred to as the Bayesian Information Criterion (BIC) and is sometimes used as an approximation to the posterior model weight, for example, in Bayesian model averaging (e.g. Daniels
et al., 2000; Clyde, 2000). BIC can be written as

$$\text{BIC}(df) = -2 \times (\text{max log-likelihood}) + (\log n) \, df$$

where $n$ is the number of observations.

4. **Minimum residual autocorrelation (PACF):** Choose the $df$ that minimizes the autocorrelation in the residuals. In practice we can minimize the sum of the absolute value of the partial autocorrelation function (PACF) of the residuals for a fixed number of lags. An alternative is choosing the $df$ using a test for white noise in the residuals (e.g. Goldberg et al., 2001, and others). While this approach is used in the literature, we do not explore it here because common tests for white noise (such as the portmanteau test) are either functions of the autocorrelation function coefficients or are closely related (Brockwell and Davis, 2002). Hence, the $df$ which minimizes the sum of the absolute value of the PACF coefficients should correspond closely with the $df$ that leads a test for white noise to fail to reject the null hypothesis.

5. **GCV-PM**$_{10}$: Choose the $df$ that best predicts the pollution series, as measured by generalized cross-validation (Gu, 2002). This approach is a simplified version of the mean squared error minimization procedure described in Dominici et al. (2004).

### 3 Simulation Study

In this section we describe a simulation study designed to assess the bias and mean squared error of $\hat{\beta}$ under different basis representations for $f$ and the five approaches to selecting $df$ described in Section 2. Our goal is to generate data from confounding scenarios comparable to situations found in real data and evaluate the estimation procedures in each of these scenarios. The definition of the scenarios relies upon the timescales at which confounding occurs and the strength of the concurrence between the pollutant series and the seasonal trend. All of the simulations were conducted in R using the `glm` and `ns` functions to fit natural spline models and the `gam` function in the `mgcv` package to fit penalized spline models.
Our statistical framework for the simulations is:

\[ Y_t \sim \text{Poisson}(\mu_t) \]
\[ \log \mu_t = \beta_0 + \beta \text{PM}_t + f(t) + q(\text{temp}_t) \]  \hspace{1cm} (3)
\[ \text{PM}_t = g(t) + r(\text{temp}_t) + \xi_t \hspace{1cm} \xi_t \sim \mathcal{N}(0, \sigma^2). \]

where \( \text{PM}_t \) and \( \text{temp}_t \) are the PM\(_{10}\) and temperature time series, respectively. We assume that \( f \) and \( g \) have the following natural spline representations:

\[ f(t) = \sum_{j=1}^{m_1} a_j B_j(t) \]  \hspace{1cm} (4)
\[ g(t) = \sum_{j=1}^{m_2} b_j H_j(t), \]

where the \( B_j \) and \( H_j \) are known basis functions and \( m_1 \) and \( m_2 \) are the degrees of freedom for \( f \) and \( g \), respectively. The functions \( q \) and \( r \) also have natural spline representations with \( n_1 \) and \( n_2 \) degrees of freedom.

In order to simulate mortality and pollution data, we first specify values \( m_1, m_2, n_1, \) and \( n_2 \). Then, we fit a log-linear Poisson regression model to the Minneapolis/St. Paul total non-accidental mortality data to obtain estimates of the spline coefficients \( a_1, \ldots, a_{m_1} \) and a standard linear regression model to the PM\(_{10}\) data to obtain estimates of the spline coefficients \( b_1, \ldots, b_{m_2} \). Data from Minneapolis/St. Paul for the years 1987–1994 were used because the city has daily measurements of PM\(_{10}\) and a sufficient number of deaths to produce a stable estimated effect of PM\(_{10}\) on mortality. We also estimate the residual variance from the PM\(_{10}\) regression model for the Minneapolis/St. Paul data and call it \( \sigma_0^2 \). The parameter \( \sigma_0^2 \) is used later to control how much concavity will exist in the simulated data.

All of the parameters estimated from the Minneapolis/St. Paul data are then treated as the “true” coefficients from which to simulate. The framework in (3) ensures that some concavity will exist between the simulated mortality and pollution data, the strength of which we can control via the specification of \( \sigma^2 \), the variance of \( \xi_t \) in (3). For example, if we set \( \sigma^2 = \sigma_0^2/10 \), this would produce simulated data with high concavity. Note that we do not generate temperature data; it remains fixed in each of the simulations.

We simulate the following four confounding scenarios:
1. \(g(t)\) is smoother than \(f(t)\), moderate concurvity. Confounding bias might occur because longer cycles in the air pollution are correlated with the longer cycles in mortality and the amount of correlation depends on the variance \(\sigma^2\). However, the mortality counts might also be affected by factors that vary at shorter cycles than pollution. Here we set \(m_1 = 7 \times 8 = 56\), \(m_2 = 4 \times 8 = 32\), \(n_1 = 6\), \(n_2 = 3\), and \(\sigma^2 = \sigma_0^2\).

2. \(g(t)\) is smoother than \(f(t)\), high concurvity. Same as in Scenario 1 except that we set \(\sigma^2 = \sigma_0^2/10\). Here the pollution variable \(PM_t\) is very tightly correlated with the smooth function of time \(f\).

3. \(g(t)\) is rougher than \(f(t)\), moderate concurvity. Confounding bias might occur because longer cycles in air pollution are correlated with the longer cycles in the mortality counts. Temporal variation in pollution levels might also be affected by factors that vary at shorter cycles than the mortality counts. Here we set \(m_1 = 32\), \(m_2 = 56\), \(n_1 = 3\), \(n_2 = 6\), and \(\sigma^2 = \sigma_0^2\).

4. \(g(t)\) is rougher than \(f(t)\), high concurvity. Same as in Scenario 3 except that we set \(\sigma^2 = \sigma_0^2/10\).

The four simulation scenarios are summarized in Table 1. Our simulation framework does not address the issue of measurement error in the pollutant variable. Since such error can in some situations attenuate the estimated pollution effect, it may be useful in the future to employ a more elaborate simulation framework to investigate in depth the impact of measurement error.

We generate mortality and pollution data from these scenarios assuming no pollution effect (\(\beta = 0\)). For each scenario listed in Table 1 we simulate \(N = 500\) datasets and fit a Poisson regression model to each using either natural splines or penalized splines for a range of different values of \(df\). That range was 1–20 \(df\) per year of data in the simulated dataset, which in this case was 8 years. Figure 1 shows one of the simulated datasets for the scenario where \(g\) is smoother than \(f\) and there is high concurvity. To each simulated dataset we apply the five \(df\) selection methods described in Section 2 and investigate under which circumstances we would wrongly report a statistically significant air pollution effect.

Figure 2 shows boxplots of the 500 estimates of \(\beta\) obtained by using 1 to 20 \(df\) per year in the
smooth function of time. The left column shows estimates obtained by using natural splines and right column shows the results of using penalized splines to represent $f$. The bottom four plots show the estimates obtained under the high concurvity scenario (“high cc”). In general, while the variance of the estimates tends to increase as the number of degrees of freedom for $f$ is increased, the decrease in bias is far more dramatic. Under moderate concurvity (top four plots) the bias in the estimates is only serious for $df$ between 1 and 4 for natural splines (between 1 and 6 for penalized splines).

The apparent decrease in the bias of $\hat{\beta}$ with increasing $df$ is explained in Dominici et al. (2004) for the natural spline case and explored by Rice (1986) and Speckman (1988) in the nonparametric setting. Dominici et al. (2004) showed that for natural splines, if we select $df$ to be equal to the $df$ necessary to represent the $g$ function in (3), then $\hat{\beta}$ is either unbiased (when $g$ is rougher than $f$) or asymptotically unbiased ($g$ smoother than $f$). For example, with $g$ rougher than $f$, we should see very little bias in $\hat{\beta}$ for $df$ larger than or equal to 7 per year. In the nonparametric setting, Rice and Speckman both showed that in order to obtain an estimate of $\beta$ whose bias converges at the usual parametric rate, one must undersmooth the estimate of $f$ (see Appendix A.1 for more details). An important conclusion here is that when using either natural splines or penalized splines, the amount of smoothing in $f$ required to obtain an estimate of $\beta$ with small bias could be less than the amount of smoothing required to obtain a good estimate of $f$ alone (see also Green and Silverman, 1994, ch. 4).

Under high concurvity, the differences between using natural splines and penalized splines are greater. For natural splines, the bias drops rapidly between 1 and 4 $df$ per year and is stable afterwards. For penalized splines, the bias drops much more slowly and does not appear to level off until 9 or 10 $df$ per year. In general, the estimates of $\beta$ appear to be less sensitive to the relationship between the $g$ and $f$ functions (i.e. $g$ smoother/rougher) than to the amount of concurvity in the data or the basis representation used.

In our comparison of the model selection criteria described in Section 2.2, for each simulated dataset and criterion, we obtain a “best” $df$, call it $\hat{df}$, that is the value of $df$ associated with the fitted model which minimizes the criterion. The estimate of $\beta$ chosen by the model selection
criterion for dataset $i$ is $\beta^{(i)}_{\hat{d}}$. We can then estimate the bias, standard error, and root mean squared error (RMSE) of $\hat{\beta}_{\hat{d}}$ from the simulation output for a particular model selection criterion and basis choice. Clearly, the RMSE for a criterion depends on an effective balance between the bias and variance of the estimates.

The average bias, standard error, and RMSE (all multiplied by 1000) for $\hat{\beta}$ selected by each of the criteria/bases under the different scenarios are shown in Table 2. Along the rows labelled “$df = m_1$”, Table 2 also shows the same results for the estimates of $\beta$ when the $df$ used to generate the data (whose specific values are shown in Table 1) is used as the “best” $df$ rather than minimizing one of the model selection criteria. Under moderate concavity, each of the four data-driven methods perform reasonably well with respect to RMSE with BIC always having the largest RMSE. As expected, all of the methods perform worse under high concavity, with BIC having an RMSE more than twice as large as the other methods in some instances.

Table 2 also shows the contribution of bias and variance to the RMSEs of the estimates of $\beta$ obtained via the model selection criteria. Generally, estimates from all of the criteria incur more bias when using penalized splines for the smooth function of time as opposed to natural splines. GCV-PM$_{10}$ is very nearly unbiased in all of the scenarios. The largest bias (0.159) occurs with penalized splines, under high concavity and when $g$ is smoother than $f$. AIC has a relatively small bias under the moderate concavity scenarios but tends to incur more bias than GCV-PM$_{10}$ under the high concavity scenarios (particularly when penalized splines are used). The price for using GCV-PM$_{10}$ over the other methods appears to be an increase in the standard error of the estimates in some cases.

The PACF criteria performs reasonably well under moderate concavity but has a large bias under high concavity, particularly when using penalized splines. However, the relative increase in bias for the PACF criteria when going from the moderate concavity to the high concavity scenarios is comparable to the other criteria. The BIC criteria performs poorly under all of the scenarios. The larger penalty associated with BIC generally leads to using few degrees of freedom which, from Figure 2, can produce estimates with high bias.
4 NMMAPS Data Analysis

We apply our methods to the National Morbidity, Mortality, and Air Pollution Study (NMMAPS) database which is comprised of daily time series of air pollution levels, weather variables, and mortality counts. The original study examined data from 90 cities for the years 1987–1994 (Samet et al., 2000c,a). The data have since been updated to include 10 more cities and 6 more years of data, extending the coverage until the year 2000. The entire database is available via the NMMAPSdata R package (Peng and Welty, 2004) which can be downloaded from the Internet-based Health and Air Pollution Surveillance System (iHAPSS) website at http://www.ihapss.jhsph.edu/.

The full model used in the analysis for this section is larger than the simpler model described in Section 3. We use an overdispersed Poisson model where, for a single city,

\[
\log E[Y_t] = \text{age specific intercepts} + \text{day of week} + \beta PM_t + f(\text{time, } df) \\
+ s(\text{temp}_t, 6) + s(\text{temp}_{1-3}, 6) + s(\text{dewpoint}_t, 3) + s(\text{dewpoint}_{1-3}, 3).
\]

Here, \( f \) is the smooth function of time represented with different bases and \( s(\cdot, d) \) indicates a smooth function with \( d \) degrees of freedom. In addition to a smooth function of time and the \( PM_{10} \) series, the model includes smooth functions of temperature, dewpoint temperature, and three day running means of each (denoted by the subscript \( 1-3 \)). There is also an indicator variable for the day of the week and a separate intercept for each age category (\(<65, 65-74, \) and \( \geq 75 \) years old).

For each city, we choose each of the three fitting procedures (i.e. representations of the smooth function of time) described in Section 2.1 and fit an overdispersed Poisson model. We then minimize one of the criteria described in Section 2.2 and obtain a best \( df \), call it \( \hat{df} \), with which we obtain an estimate \( \hat{\beta}_{df} \) for that city. This process is then repeated for all 100 cities in the database to obtain \( \hat{\beta}_{df}^{(1)}, \ldots, \hat{\beta}_{df}^{(100)} \) and their standard errors. These city-specific estimates are pooled using a two-level hierarchical normal model (similar to that used in Dominici et al., 2000) with flat priors on the overall estimate and the between-city covariance matrix (Everson and Morris, 2000a,b). The result is a “national average estimate” summarizing the effect of \( PM_{10} \) on mortality for the 100 cities. We run this entire process for each of the three fitting procedures and three model selection criteria: AIC, PACF, and GCV-PM\(_{10}\). For the overdispersed Poisson models we use a modified AIC of the
form (Hastie and Tibshirani, 1990)

\[
\text{AIC} = -2 \times (\text{max log-likelihood}) + 2 \, df \, \hat{\phi},
\]

where \( \hat{\phi} \) is the estimated dispersion parameter.

Table 3 shows the results of applying the model selection criteria and using different representations of the smooth function of time for the NMMAPS data. The estimates presented are the national average estimates of the percent increase in mortality for a 10 \( \mu g/m^3 \) increase in PM\(_{10} \) at lag 1. The results are consistent with what we observed in the simulation studies — AIC and GCV-PM\(_{10} \) produce very similar estimates while the PACF estimates are somewhat larger. The estimates obtained by AIC and GCV-PM\(_{10} \) are comparable to the estimates reported in previous NMMAPS analyses (e.g. Dominici et al., 2002, 2003; Peng et al., 2005), although with smaller 95% posterior intervals due to the additional data used in the current analysis.

A problem arises with the PACF procedure when cities with a regular pattern of missing PM\(_{10} \) data are included (a phenomenon common with U.S. data). In particular, for cities where PM\(_{10} \) is measured only once every six days, one can only estimate the autocorrelation of the residuals at lag 6. The national average estimates in the second column of Table 3 were computed by ignoring the 1 in 6 pattern in the data. Cities with sporadic missing PM\(_{10} \) values do not cause a problem in computing the PACF.

Figure 3 shows a sensitivity analysis of the national average estimate with respect to the number of degrees of freedom per year assigned to the smooth function of time. In this figure, rather than minimize one of the model selection criteria and obtain an optimal \( df \) in each city, we use a fixed number of degrees of freedom per year for all of the cities. The figure shows the change in the national average estimate as the \( df \) is varied. When using natural splines, the estimates appear to stabilize after 9 \( df \) per year at around a 0.15% increase in mortality with a 10 \( \mu g/m^3 \) increase in PM\(_{10} \) at lag 1. The estimates obtained using smoothing splines also appear to stabilize, but at a higher value. The estimates obtained using penalized splines are very close to the smoothing spline estimates up to approximately 12 \( df \) per year, after which the penalized spline estimates decrease slightly.
5 Discussion

We have developed a framework for quantifying and characterizing model uncertainty in multi-city time series studies of air pollution and mortality. The complexity of the time series data require the application of sophisticated statistical models capable of estimating relatively small effects. Furthermore, these effects have important policy implications, making a critical evaluation of the diverse modelling approaches proposed in the literature an important task.

We have conducted a simulation study to compare commonly used approaches to adjusting for seasonal and long-term trends in air pollution epidemiology under a variety of realistic scenarios of confounding. The simulations quantify the average bias and standard error associated with each of the different modelling approaches. In addition to the simulation study we have applied all of the methods to the NMMAPS database, the largest publicly available database containing time series data of air pollution and mortality. Our analysis of the NMMAPS data is important because it demonstrates that the national average estimates of the effect of PM$_{10}$ at lag 1 are robust to different model selection criteria and smoothing methods. The results presented here strengthen recent findings from multi-city time series studies regarding the effects of short-term increases in air pollution on daily mortality.

We have focused on the smooth function of time used to control for seasonal and long-term trends in mortality. The different approaches to representing the smooth function and to specifying its smoothness have varying effects on the bias and variance of the estimates depending on how the methods are combined and on the concavity present in the data. When using data-driven methods to specify the smoothness, higher concavity leads to more biased estimates as does using penalized splines over natural splines, although the impact of concavity is far greater.

Our results show that both fully parametric and nonparametric methods perform well, with neither preferred. Sensitivity analysis from the simulation study indicates that neither the natural spline nor the penalized spline approach produces any systematic bias in the estimates of the log relative rate $\beta$. However, that is not to say that the two approaches are equivalent; the data analysis must be tuned to the specific approach. The results of Rice (1986) and Speckman (1988) suggest that with a nonparametric approach (such as penalized splines), one must use a $df$ that is
not optimal for predicting mortality in order to obtain an estimate of $\beta$ with an acceptable rate of convergence for the bias. The simulation study in Section 3 confirms this notion in that one needs to use a larger $df$ to achieve the same average bias as the corresponding estimate obtained via natural splines (see e.g. Figure 2). Therefore, the automatic use of criteria such as GCV or AIC for selecting the $df$ could be potentially misleading (particularly with high concurvity) since they are designed to choose the $df$ that will lead to optimal prediction of the mortality series, not necessarily to accurate estimation of $\beta$.

For parametric models (with natural splines), Dominici et al. (2004) showed that one must use a $df$ at least as large as that needed to best predict the pollution series. They suggested using a procedure such as GCV to estimate this $df$ and then use the bootstrap to minimize an estimate of the mean squared error for $\hat{\beta}$. Our simplified version (GCV-PM$_{10}$) of their approach performs very well in the simulations and produces estimates of $\beta$ that are nearly unbiased under all of the scenarios, even under high concurvity.

The failure of BIC to produce competitive estimates of $\beta$, while dramatic, is not of concern in assessing the relation between air pollution and health because it has generally not been applied. Although it is sometimes used to provide an approximate Bayes posterior (relative) probability for each $df$, our modelling setup is far from that considered by Schwarz (1978). That is, as $n \to \infty$, we also have that the dimension of the model $\to \infty$, which can lead BIC to choose the wrong model (Stone, 1979; Berger et al., 2003; Hansen and Yu, 2003). The use of BIC in this setting, for example, in conjunction with Bayesian model averaging, requires further exploration.

Under moderate concurvity, AIC produces estimates of $\beta$ with relatively small bias. Shibata (1976) demonstrated for autoregressive time series models that AIC has the potential to select larger and larger models as the sample size increases (see also Ripley, 1996), a feature that is perhaps desirable here. Stone (1979) also showed that in certain situations where the dimension of the model $\to \infty$, AIC can choose the right model as $n \to \infty$. However, it is important to note that using AIC to select the $df$ that best predicts mortality still may not lead to the best estimate of $\beta$ in this setting. For example, in Table 2, we see that when $g$ is rougher than $f$, the estimates selected by AIC are much more biased than when $g$ is smoother than $f$.
Selecting the degrees of freedom for the smooth function of time by minimizing autocorrelation in the residuals is an heuristic approach that is widely used in the air pollution and health literature. Schwartz (1994b) suggested that the presence of residual autocorrelation may lead to underestimation of standard errors and as a result, biased hypothesis tests of the pollutant variable coefficient; minimizing such autocorrelation would seem a natural goal. Although underestimation of standard errors can lead to possibly incorrect inferences about the city-specific coefficients, Daniels et al. (2004) showed that in a multi-city context, the underestimation of the city-specific standard errors would have to be severe (or the the number of cities very small) in order to result in a substantial change in the national average (pooled) estimate.

Our simulation study indicates that inducing some residual (negative) autocorrelation may be necessary to reduce the bias in estimates of the pollution coefficient \( \hat{\beta} \). Figure 2 shows that increasing the \( df \) tends to decrease the bias in the pollution coefficient estimates while slightly increasing the variability of these estimates. Table 2 indicates that with penalized splines, using the true \( df \) may not be sufficient to reduce the bias in \( \hat{\beta} \). Generally, undersmoothing the data (i.e. increasing the \( df \) for the smooth function of time) induces residual autocorrelation at a number of lags.

The conclusion that residual autocorrelation may be necessary to control for confounding bias emphasizes the importance of distinguishing between model uncertainty and adjustment uncertainty. When addressing model uncertainty, we select the covariates that best explain the variability in the response which, in our setting, would require selecting the \( df \) to obtain white noise in the residuals. With adjustment uncertainty, we select the covariates that minimize confounding bias in the exposure effect estimate. Previous contributions in semi-parametric regression (Speckman, 1988; Dominici et al., 2004) have shown that, if the goal of inference is confounding adjustment, the model should include all the covariates needed to explain variation in the exposure of interest, not the outcome. Therefore, in our setting, we need to select enough degrees of freedom for the smooth function of time to explain the variation in air pollution. This selected \( df \) might be smaller or larger than the optimal one needed to explain variation in the response, thus leaving autocorrelation in the residuals.
Also of concern is the application of the minimum PACF procedure to datasets with regular patterns of missing data. Although the NMMAPS analysis in Section 4 indicates that the effects of the missing data are not profound, it nevertheless seems inappropriate to apply this procedure for those data.

All of our conclusions from the simulation study are based on assuming a true $\beta = 0$. While our results would generalize in a standard linear regression framework to situations where $\beta \neq 0$, the use of a non-identity link function here precludes such generalization. The performance of all the estimation methods for $\beta \neq 0$ merits exploration. However, with time series models for air pollution and mortality an important concern is distinguishing correctly between a very small, but non-zero effect and a true zero effect. Hence, in this paper we have concentrated on the scenario where the true $\beta$ is zero.

While incorporating a smooth function of time is a widely used method to control for seasonal patterns, it is by no means the only option. Case–crossover analyses (Navidi, 1998) have also been applied to the U.S. data and represent an entirely different approach to controlling for confounding by season (Schwartz et al., 2003; Schwartz, 2004). The results in those studies were qualitatively similar to those obtained here for the effect of PM$_{10}$ at lag 1, although the estimates obtained in Schwartz et al. (2003) were slightly higher. Of course, the case–crossover analyses also face challenging model choice questions such as choosing the “window” for selecting referent cases or controls. Nevertheless, the analyses are relevant because they further reinforce the notion that results from multi-city time series studies are robust to alternative methodologies and data analytic approaches.

6 Acknowledgments

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HEI, nor do they necessarily reflect the views and policies of EPA, nor motor vehicle or engine manufacturers.

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A  Details of Representations for $f$

Natural splines are piecewise cubic polynomials defined on a grid of knot locations spanning the range of the data. The function itself, as well as its second derivative, are continuous on the entire range of the data and the function is restricted to be linear beyond the endpoints. The smoothness of a natural spline fit is controlled by the number of knots used. Fewer knots represent smoother fits while $n$ knots (where $n$ is the sample size) will lead to interpolation of the data. The knot locations are often chosen to be at regressor values associated with equally spaced quantiles but could, in principle, be anywhere.

Penalized splines can provide a more flexible way to model non-linear relationships. They have been presented in the literature in a number of ways and we use the general definition, $\hat{\eta}^T \mathbf{B}(x)$, where

$$\hat{\eta} = \arg\min_{\eta} \sum_{i=1}^{n} \left( y_i - \eta^T \mathbf{B}(x_i) \right)^2 + \alpha \eta^T \mathbf{H} \eta.$$ 

$\mathbf{B}(x)$ is a spline basis matrix (evaluated at the point $x$), $\alpha$ is a penalty (smoothing) parameter, and $\mathbf{H}$ is a penalty matrix.

Versions of penalized splines essentially boil down to different specifications of the spline basis matrix $\mathbf{B}$ and the form of the penalty $\mathbf{H}$. A common approach constructs a natural spline or $B$-spline basis using a large number of knots (far more than generally considered necessary) and then shrinks the coefficients to reduce the effective degrees of freedom and increase smoothness in the overall function estimate (Marx and Eilers, 1998; Wood, 2000). The amount of smoothness in the estimated curve (i.e. shrinking of the coefficients) is controlled by $\alpha$. As $\alpha \downarrow 0$, the amount of smoothing decreases and the estimated curve approaches the full parametric fit. As $\alpha \uparrow \infty$, the amount of smoothing increases and the estimated curve approaches a polynomial function.

The most extreme approach to knot placement in the penalized spline framework is to place the maximum number of knots possible, that is, one knot at every data point. The resulting fit is then called a smoothing spline. Time series data are typically regularly spaced and the smoothing spline scheme leads to $n$ equally spaced knots along the time period of the dataset. Since smoothing splines can be considered a special case of penalized splines (Ruppert et al., 2003), we expect that results obtained using smoothing splines and penalized splines would be very similar, except
perhaps in the case of penalized splines where too few knots are used (see e.g. discussion in Eilers and Marx, 1996).

The complexity of a spline basis representation can be measured by its degrees of freedom. Since the previously mentioned approaches are linear, they can be represented by the \( n \times n \) smoother matrix which maps the observed data to the smooth predicted values. The *effective degrees of freedom* are computed by the trace of the smoother matrix (Buja et al., 1989; Hastie and Tibshirani, 1990). For fully parametric fits such as those using natural splines, this trace equals the number of estimated parameters in the model.

### A.1 Estimation of \( \beta \)

For the purposes of this section, we will take more simplified version of (1), focusing on the estimation of \( \beta \) and the smooth function of time \( f \). Using matrix notation, we can rewrite (1) as

\[
\begin{align*}
Y & \sim \text{Poisson}(\mu) \\
\log \mu & = X\beta + f
\end{align*}
\]  

(5)

where \( Y = y_1, \ldots, y_n \), \( f \) is the function \( f \) evaluated at \( t = 1, \ldots, n \) and \( X \) is the \( n \times 2 \) design matrix containing a column of ones and the pollution time series \( x_1, \ldots, x_n \).

Given one of the spline bases described in Section 2.1, we can rewrite (5) as

\[
\log \mu = X\beta + B\gamma
\]

where \( B \) is the \( n \times d \) matrix of \( d \) basis functions and \( \gamma \) is a \( d \)-vector of coefficients. The number of columns of the basis matrix \( B \) will be different depending on whether natural splines, penalized splines, or smoothing splines are used.

We use iteratively reweighted least squares (IRLS) to fit model (5) using natural splines. Let \( W \) be the \( n \times n \) (diagonal) weight matrix and \( z \) the working response from the last iteration of the IRLS algorithm. Let \( X^* \) be the complete design matrix, i.e. \( X^* = [X \mid B] \). Using a GLM procedure with natural cubic splines, we can estimate \( \beta \) and \( \gamma \) simultaneously as

\[
\begin{bmatrix}
\hat{\beta}_{ns} \\
\hat{\gamma}
\end{bmatrix} = (X^{*T}WX^*)^{-1}X^{*T}Wz.
\]
For penalized splines, we first need to construct the smoother matrix for the nonparametric part of the model. Given a value for the smoothing parameter $\alpha$ and a fixed (symmetric) penalty matrix $H$, the smoother matrix for $f$ is

$$S = B(B^T B + \alpha H)^{-1} B^T$$

and the estimate of $\beta$ is

$$\hat{\beta}_{ps} = (X^T W (I - S) X)^{-1} X^T W (I - S) z.$$

Rice (1986) and Speckman (1988) both showed that while the variance of $\hat{\beta}_{ps}$ converges at the standard parametric rate for $n \to \infty$, the bias converges to zero at the much slower nonparametric rate. The slow convergence of the bias comes from the fact that the smoother matrix $S$ is not a true projection, unlike the hat matrix in parametric regression (Speckman, 1988). The performance of both $\hat{\beta}_{ns}$ and $\hat{\beta}_{ps}$ using various model selection criteria was illustrated in Sections 3 and 4.

Speckman described an alternative estimator for $\beta$ for which the bias and variance both converge at the usual parametric rate. For $S$ symmetric, the modified estimator is

$$\hat{\beta}_{ps}^* = (X^T W (I - S)^2 X)^{-1} X^T W (I - S)^2 z.$$

If we let $\tilde{X} = (I - S) X$ and $\tilde{z} = (I - S) z$, then the modified estimator can be written as

$$\hat{\beta}_{ps}^* = (\tilde{X}^T W \tilde{X})^{-1} \tilde{X}^T W \tilde{z},$$

which is the estimate one might obtain from a regression of $\tilde{z}$ on $\tilde{X}$. Hence, this modified estimator has the form of a regression of partial residuals.

A simple calculation shows that estimating $\beta$ using $\hat{\beta}_{ps}^*$ is equivalent to estimating $\beta$ with $\hat{\beta}_{ps}$ but with the modified smoother matrix

$$\tilde{S} = I - (I - S)^2$$

$$= S(2I - S)$$

Buja et al. showed that $\text{tr}(\tilde{S}) \geq \text{tr}(S)$ and hence, in order to obtain an estimate of $\beta$ for which the bias and variance converge at the parametric rate, one must implicitly use an undersmoothed
estimate of $f$. If $\Lambda$ is the diagonal matrix of eigenvalues $\lambda_1, \ldots, \lambda_n$ for the smoother matrix $S$, a simple calculation reveals that

$$\text{tr}(\tilde{S}) = \text{tr}(S(2I - S))$$

$$= \text{tr}(\Lambda(2I - \Lambda))$$

$$= \sum_{i=1}^{n} 2\lambda_i - \lambda_i^2$$

$$= \text{tr}(S) + \left\{ \sum_{i=1}^{n} \lambda_i(1 - \lambda_i) \right\}. \quad (6)$$

The quantity in brackets can be interpreted as the extra degrees of freedom required for the modified estimate $\tilde{\beta}_{ps}^*$, i.e. the amount of undersmoothing required. It is important to note that the extra degrees of freedom in (6) may be small and furthermore, using $\tilde{\beta}_{ps}^*$ only provides the same rate of convergence for the bias as using $\tilde{\beta}_{ns}$. For a fixed $n$ the two estimates may be quite different.

**B Tables and Figures**

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Concurvity</th>
<th>$\sigma^2$</th>
<th>$m_1$ (df for $f$)</th>
<th>$m_2$ (df for $g$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$g(t)$ smoother than $f(t)$</td>
<td>moderate</td>
<td>$\sigma_0^2$</td>
<td>56</td>
<td>32</td>
</tr>
<tr>
<td>$g(t)$ smoother than $f(t)$</td>
<td>high</td>
<td>$\sigma_0^2 / 10$</td>
<td>56</td>
<td>32</td>
</tr>
<tr>
<td>$g(t)$ rougher than $f(t)$</td>
<td>moderate</td>
<td>$\sigma_0^2$</td>
<td>32</td>
<td>56</td>
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<tr>
<td>$g(t)$ rougher than $f(t)$</td>
<td>high</td>
<td>$\sigma_0^2 / 10$</td>
<td>32</td>
<td>56</td>
</tr>
</tbody>
</table>

Table 1: Simulation scenarios: $\sigma_0^2 = 186.7$ for scenarios where $g(t)$ is smoother than $f(t)$ and $\sigma_0^2 = 182.2$ for scenarios where $g(t)$ is rougher than $f(t)$. 

http://biostats.bepress.com/jhubiostat/paper55
Figure 1: Example of simulated mortality and PM$_{10}$ data. The negative values in the PM$_{10}$ series come from the original data being represented as deviations from an overall mean. In this example, $g$ is smoother than $f$ and there is high concurvity.
| Basis | Natural splines | Penalized splines | | | | | | | | Concurvity | Moderate | High | Moderate | High | | | | | | g(t) | smoother | rougher | sm | r | sm | r | sm | | | df = m1 | | | | | | | | | Bias | AIC | 0.012 | 0.012 | 0.026 | 0.119 | 0.061 | 0.152 | 0.421 | 1.000 | | | PACF | 0.059 | 0.305 | 0.401 | 1.701 | 0.383 | 0.570 | 2.359 | 2.675 | | | BIC | 0.492 | 0.471 | 3.302 | 2.782 | 0.663 | 0.652 | 3.343 | 2.884 | | | GCV-PM10 | 0.021 | 0.002 | 0.014 | 0.034 | 0.121 | 0.041 | 0.159 | -0.030 | | | df = m1 | 0.013 | 0.005 | 0.018 | 0.024 | 0.059 | 0.306 | 0.416 | 1.715 | | | Std. Error | AIC | 0.255 | 0.258 | 0.823 | 0.803 | 0.252 | 0.252 | 0.752 | 0.692 | | | PACF | 0.268 | 0.299 | 1.002 | 0.833 | 0.267 | 0.253 | 0.770 | 0.543 | | | BIC | 0.305 | 0.308 | 0.798 | 0.730 | 0.257 | 0.243 | 0.540 | 0.501 | | | GCV-PM10 | 0.255 | 0.258 | 0.818 | 0.805 | 0.249 | 0.253 | 0.741 | 0.742 | | | df = m1 | 0.256 | 0.253 | 0.819 | 0.695 | 0.250 | 0.243 | 0.712 | 0.541 | | | RMSE | AIC | 0.361 | 0.364 | 1.164 | 1.142 | 0.362 | 0.388 | 1.144 | 1.399 | | | PACF | 0.383 | 0.521 | 1.473 | 2.068 | 0.538 | 0.673 | 2.598 | 2.783 | | | BIC | 0.654 | 0.641 | 3.490 | 2.968 | 0.756 | 0.737 | 3.429 | 2.969 | | | GCV-PM10 | 0.361 | 0.365 | 1.157 | 1.138 | 0.372 | 0.361 | 1.060 | 1.049 | | | df = m1 | 0.361 | 0.357 | 1.158 | 0.982 | 0.359 | 0.460 | 1.089 | 1.878 | | |

Table 2: Average bias, standard error, and root mean squared error (RMSE) of $\hat{\beta}$ (all $\times 1000$) from 250 simulations. Each column represents a scenario determined by the basis used for fitting (natural splines/penalized splines), the concurvity in the simulated data, and the relationship between $g(t)$ and $f(t)$, i.e. $g(t)$ smoother (sm) or rougher (r) than $f(t)$.

<table>
<thead>
<tr>
<th>Model</th>
<th>AIC</th>
<th>PACF</th>
<th>GCV-PM10</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLM-NS (natural splines)</td>
<td>0.20$^{(0.11,0.29)}$</td>
<td>0.25$^{(0.14,0.36)}$</td>
<td>0.20$^{(0.10,0.29)}$</td>
</tr>
<tr>
<td>GAM-R (penalized splines)</td>
<td>0.25$^{(0.16,0.34)}$</td>
<td>0.35$^{(0.24,0.46)}$</td>
<td>0.26$^{(0.16,0.35)}$</td>
</tr>
<tr>
<td>GAM-S (smoothing splines)</td>
<td>0.27$^{(0.18,0.37)}$</td>
<td>0.35$^{(0.24,0.46)}$</td>
<td>0.26$^{(0.16,0.37)}$</td>
</tr>
</tbody>
</table>

Table 3: National average estimates and 95% posterior intervals of the percent increase in mortality with a 10 $\mu g/m^3$ increase in PM$_{10}$ at lag 1 using different model selection criteria and representations of the smooth function of time, $f(t)$.
Figure 2: Sensitivity analysis of $\beta$. The boxplots show the distribution of $\hat{\beta}$ over 250 simulations using 1–20 $df$ per year in the smooth function of time $f$ (the true $\beta = 0$). The methods used were GLM with natural cubic splines (GLM) and GAM with penalized splines (GAM-R).
Figure 3: Sensitivity analysis of the national average estimate of the percent increase in mortality for a 10 $\mu g/m^3$ increase in PM$_{10}$ at lag 1. City-specific estimates were obtained from 100 U.S. cities using data for the years 1987–2000 and the estimates were combined using a hierarchical normal model. The three fitting methods used are GLM with natural cubic splines (GLM-NS), GAM with penalized splines (GAM-R), and GAM with smoothing splines (GAM-S). The shaded region shows 95% posterior intervals for the estimates obtained using GLM-NS.