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ORIGINAL CONTRIBUTIONS

Estimating Particulate Matter-Mortality Dose-Response Curves and Threshold Levels: An Analysis of Daily Time-Series for the 20 Largest US Cities

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Numerous studies have shown a positive association between daily mortality and particulate air pollution, even at concentrations below regulatory limits. These findings have motivated interest in the shape of the exposure-response relation. The authors have developed flexible modeling strategies for time-series data that include spline and threshold exposure-response models; they apply these models to daily time-series data for the 20 largest US cities for 1987–1994, using the concentration of particulate matter <10 m in aerodynamic diameter (PM_{10}) as the exposure measure. The spline model showed a linear relation without indication of threshold for PM_{10} and relative risk of death for all causes and cardiorespiratory causes; by contrast, for other causes, the risk did not increase until approximately 50 g/m^3 PM_{10}. For all-cause mortality, a linear model without threshold was preferred to the threshold model and to the spline model, using the Akaike information criterion (AIC). The findings were similar for cardiovascular and respiratory deaths combined. By contrast, for causes other than cardiovascular and respiratory, a threshold model was more competitive with a threshold value estimated at 65 g/m^3. These findings indicate that linear models without a threshold are appropriate for assessing the effect of particulate air pollution on daily mortality even at current levels. *Am J Epidemiol* 2000; 152:397–406.

air pollution; models, statistical; mortality

In spite of improvements in air quality in many developed countries, adverse health effects of particulate air pollution remain a regulatory and public health concern. This continued concern is motivated largely by recent epidemiologic studies that have examined both acute and longer-term effects of exposure to particulate air pollution in different cities in the United States and elsewhere in the world (1–5). Many of these studies have shown positive associations between levels of particulate air pollution and daily mortality and morbidity rates, and some of these studies suggest that morbidity and mortality from respiratory and cardiovascular diseases are increased at levels of particulate air pollution below the current US National Ambient Air Quality Standard (150- g/m^3 24-hour average) (6, 7) for particulate matter <10 m in aerodynamic diameter (PM_{10}).

Together, the epidemiologic evidence and the legislative mandate have motivated substantial interest in the shape of the exposure-response relation of PM_{10} with risk for adverse health effects. In this paper we introduce flexible modeling strategies to describe the form of the relation of PM_{10} with mortality and then apply these models to daily time-series data for air pollution and mortality for the largest 20 US cities. We consider and compare three plausible models for the relation between log mortality and PM_{10} concentrations, each having potentially different regulatory implications: model 1, a linear model without a threshold; model 2, a spline dose-response model in which log mortality is a smooth function of

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Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion; CI, confidence interval; PM_{10}, particulate matter <10 m in aerodynamic diameter.

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PM_{10} concentration; and model 3, a threshold model that assumes no relation between PM_{10} and log mortality up to a threshold and a linear relation after the threshold. Under this spectrum of models our goals are the following: 1) to pool information from the 20 cities to more precisely determine the shape of the average dose-response curve; 2) to test the hypothesis that the air pollution-mortality association is approximately linear; and 3) to identify possible threshold pollution concentrations below which an effect of air pollution on daily mortality cannot be detected.

MATERIALS AND METHODS

These analyses use a database developed for a larger project, the National Morbidity, Mortality, and Air Pollution Study. Full details of database development are given elsewhere (8).

Data

The analysis database included mortality, weather, and air pollution data for the 20 largest metropolitan areas in the United States for the 7-year period 1987–1994 (figure 1; table 1) (8). The air pollution data were obtained from the Aerometric Information Retrieval System database maintained by the US Environmental Protection Agency. The Aerometric Information Retrieval System is a computer-based repository of information about air pollution in the United States and various other countries (http://www.epa.gov/airs/airs.html). In some locations, a high percentage of days had missing values for PM_{10} because measurements have been required only every 6 days since 1987 by the Environmental Protection Agency. Daily cause-specific mortality data, aggregated at the level of county, were obtained from the National Center for Health Statistics. After excluding deaths from external causes and in nonresidents of the county, we classified the deaths (9) by age group (<65, 65–74, and ≥75 years) and by cause according to the *International Classification of Diseases*, Ninth Revision: cardiac (codes 390–448); respiratory, including chronic obstructive pulmonary disease and related disorders (codes 490–496), influenza (code 487), and pneumonia (codes 480–486, 507); and other remaining diseases. The hourly temperature and dew point data for each site were obtained from the EarthInfo CD-ROM database (http://www.sni.net/earthinfo). After extensive preliminary analyses that considered various daily summaries of temperature and dew point as predictors, such as daily average, maximum, and 8-hour maximum, we used the 24-hour mean for each day (8, 10, 11). If a city had more than one weather station, we took the average of the measurements from all available stations. The PM_{10} data were also averaged over all monitors in each county. To protect against outliers, a 10 percent trimmed mean was used to average across monitors, after correction for yearly averages for each monitor. This yearly correction is appropriate since long-term trends in mortality are also controlled for in the log-linear regressions. See the reports by Kelsall et al. (12), Dominici et al. (13), and Samet et al. (14) for further details.

Models

In this section, we summarize the log-linear models used to estimate the air pollution/mortality relative rate separately for each location, while accounting for age-specific longer-term trends, weather, and day of the week. The core analysis for each city was a generalized additive model with log link and Poisson error that accounts for smooth fluctuations in mortality that may potentially confound estimates of the pollution effect and/or introduce autocorrelation in mortality series. These models had been developed in earlier work using data from Philadelphia (12) and for the national-level analyses (9, 15).

To specify the approach, let y_{at} be the observed mortality for each age group a = (<65, 65–74, and ≥75 years), PM_{10t} be the level of PM_{10} at day t, and $u_{at} = E(Y_{at})$ be the expected number of deaths at day t. We consider a log-linear model of the form $\log(u_{at}) = \beta PM_{10t}$ + confounders, where β represents the log-relative rate of mortality associated with a unit increase in PM_{10}, and PM_{10t} is the mean of the current day and the previous day's concentration of PM_{10}. If the previous (current) day's concentration of PM_{10} is missing, then we use only the current (previous) day's concentration of PM_{10}. As there were missing values for some variables on some days, we restricted analysis to days with no missing values for all covariates. To assess the sensibility of findings, we also fit the models using the current day's pollution data and also the 1-day lag data.

To control for potential confounding of the pollution relative rates β by longer-term trends due, for example, to changes in health status, seasonality, or influenza epidemics, and to account for any additional temporal correlation in the count time-series, we estimated the pollution effect using only shorter-term variations in mortality and air pollution. To do so, we partialled out the smooth fluctuations in mortality over time by including smooth functions of calendar time $S(time,df)$ for each city. Here, df is a smoothness parameter that we prespecified, on the basis of epidemiologic knowledge of the time scale of the major possible confounders. Taking into account the literature review and our prior work, we selected 7 df per year so that little information from time scales longer than approximately 2 months is included when estimating β. This choice largely eliminates confounding from seasonal influenza epidemics and from longer-term trends possibly due to changing medical practices and health behaviors while retaining as much unconfounded information as possible on the time scale of interest. We also controlled for age-specific longer-term and seasonal variations in mortality, adding a separate smooth function of time with a total of 8 df over all years for each age group. To control for weather, we also fit smooth functions of the same day's temperature ($temp_0$), average temperature for the 3 previous days ($temp_{1-3}$), each with 6 df, and the analogous functions for dew point (dew_0, dew_{1-3}), each with 3 df.

In summary, we fit the following log-linear generalized additive model (16) to obtain the estimated pollution log-relative rate $\hat{\beta}$ and the sample variance $V(\hat{\beta})$ at each

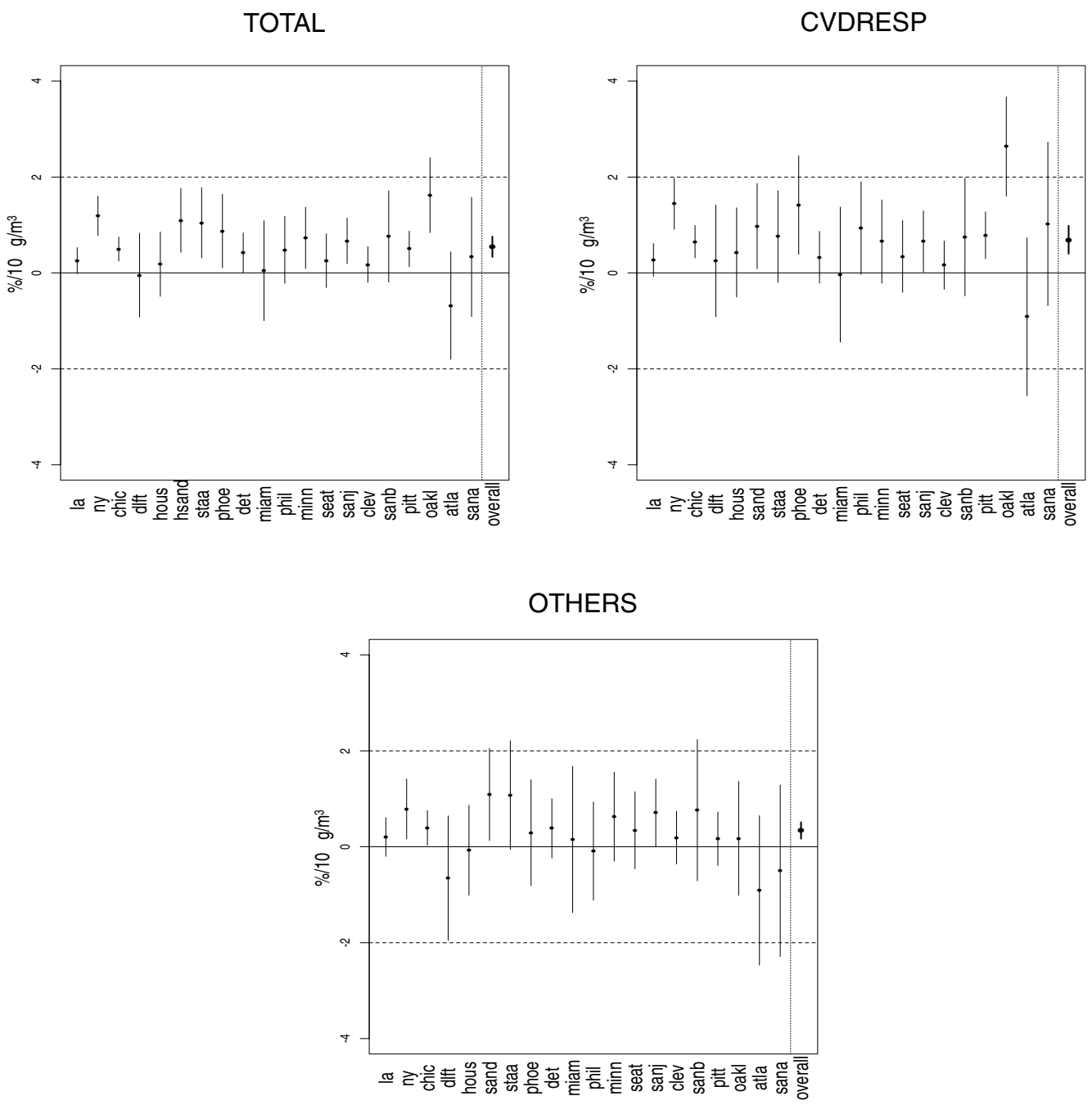

FIGURE 1. Maximum likelihood estimates and 95% confidence intervals of the city-specific mean lag particulate matter <10 m in aerodynamic diameter (PM_{10}) effects on total mortality (TOTAL), cardiovascular and respiratory mortality (CVDRESP), and other-causes mortality (OTHERS), 20 largest US cities, 1987–1994. At the far right are plotted posterior means and 95% credible regions of the overall effect. la, Los Angeles; ny, New York; chic, Chicago; dlft, Dallas-Ft. Worth; hous, Houston; sand, San Diego; staa, Santa Ana-Anaheim; phoe, Phoenix; det, Detroit; miam, Miami; phil, Philadelphia; minn, Minneapolis; seat, Seattle; sanj, San Jose; clev, Cleveland; sanb, San Bernadino; pitt, Pittsburgh; oakl, Oakland; atla, Atlanta; and sana, San Antonio.

location:

$$\log \quad_{at} = \beta \mathrm{PM}_{10t} + \gamma\, DOW + S_1(\text{time, 7/year}) + S_2(\text{temp}_0, 6) + S_3(\text{temp}_{1-3}, 6) + S_4(\text{dew}_0, 3) + S_5(\text{dew}_{1-3}, 3)$$
$$+ \text{intercept for age group } a + \text{separate smooth functions of time (8 df) for age group } a$$
$$= \beta \mathrm{PM}_{10t} + \text{confounders} \qquad (1)$$

TABLE 1. Selected counties, populations, average total deaths, average cardiorespiratory deaths, average other deaths, number of days recording PM_{10}* (D_{PM10}), and PM_{10} daily mean with 10th and 90th percentiles, 20 largest US cities, 1987–1994

City	County(ies)	Population (no.)	Total deaths (no.)	Cardio-respiratory deaths (no.)	Other deaths (no.)	D_{PM10}	PM_{10} (g/m³)
Los Angeles	Los Angeles	8,863,164	148	87	61.15	580	46.0 (21.5, 73.11)†
New York	Bronx, Kings, New York, Richmond, Queens, and Westchester	7,510,646	190.9	108.3	82.61	489	28.8 (16.1, 44.81)
Chicago	Cook	5,105,067	113.9	62	51.89	2,683	35.6 (15.7, 60.28)
Dallas-Ft. Worth	Collin, Dallas, Rockwall, and Tarrant	3,312,553	47.9	26	21.90	624	23.8 (11.4, 39.78)
Houston	Harris	2,818,199	39.9	20	19.83	793	30.0 (13.5, 48.57)
San Diego	San Diego	2,498,016	41.6	22.6	19.04	521	3.6 (18.1, 52.1)
Santa Ana-Anaheim	Orange	2,410,556	32.4	18.7	13.62	480	37.4 (18.4, 59.2)
Phoenix	Maricopa	2,122,101	38.4	20.9	17.45	436	39.7 (21.4, 58.4)
Detroit	Wayne	2,111,687	46.9	26.5	20.41	1,348	40.9 (16.4, 71.1)
Miami	Dade	1,937,094	43.8	23.6	20.16	484	25.7 (16.0, 36.6)
Philadelphia	Philadelphia	1,585,577	42.3	21.5	20.83	495	35.4 (19.0, 56.0)
Minneapolis	Hennepin and Ramsey	1,518,195	26.3	13.9	12.42	2,764	26.9 (10.9, 45.2)
Seattle	King	1,507,319	25.6	13.4	12.24	2,205	25.3 (10.2, 44.8)
San Jose	Santa Clara	1,497,577	19.7	10.7	9.00	945	30.4 (9.3, 61.6)
Cleveland	Cuyahoga	1,412,141	36.5	20.1	16.44	1,298	45.1 (19.7, 78.7)
San Bernadino	San Bernadino	1,412,140	20.6	12.1	8.50	538	37.0 (16.1, 56.2)
Pittsburgh	Allegheny	1,336,449	37.6	21.0	16.89	2,899	31.6 (8.9, 61.2)
Oakland	Alameda	1,279,182	22.2	12.2	9.98	508	26.3 (9.3, 47.8)
Atlanta	Fulton and De Kalb	1,194,788	17.5	8.8	8.71	482	34.4 (15.8, 56.4)
San Antonio	Bexar	1,185,394	20.1	10.5	9.59	670	23.8 (12.3, 36.3)

* PM_{10}, particulate matter <10 m in aerodynamic diameter.
† Numbers in parentheses, 10th and 90th percentiles of PM_{10} daily mean.

where *DOW* are indicator variables for day of week. Samet et al. (14, 17), Kelsall et al. (12), and more recently Dominici et al. (15) give additional details about the rationale for the functions used to control for longer-term trends and weather.

To critically examine the log-linear assumption for particulate levels in model 1, we allowed for greater flexibility in the air pollution/mortality association by assuming that the logarithm of the expected value of the mortality counts is a smooth function of air pollution, specifically, a spline dose-response model; we modeled mortality as a smooth function of $S(PM_{10},\lambda)$, with λ denoting the degrees of freedom for the smoothness of the dose-response curve. A straightforward and flexible approach is to restrict the choice of the smooth functions to the natural cubic splines with a fixed number of knots. These are cubic polynomials within each pair of knots with smooth connections between adjoining segments (continuous first and second derivatives). Our spline dose-response model assumed that:

$$\log \quad_{at} = S(PM_{10t}, \text{knots} = c(30, 60)) + \text{confounders} \qquad (2)$$

We used a natural cubic spline with knots at 30 and 60 g/m³, which is sufficiently flexible to capture the PM_{10}-mortality association in the range of our air pollution data. We located the two knots at 30 and 60 g/m³ because these values are approximately the 25 percent and 75 percent quantiles of the PM_{10} distributions for many of the 20 cities.

To examine the question of whether the mortality effects of particulate pollution are negligible below some level, we also fit a threshold model that we compare with the linear and spline models detailed above.

In the threshold model, we replaced the PM_{10t} term in model 1 with a term of the form $(PM_{10t} - h)^+$, where ($x^+ = x$ if $x \geq 0$ and $x^+ = 0$ if $x < 0$) and h is an unknown change point that is estimated from the data. We then assumed:

$$\log \quad_{at} = \theta(PM_{10t} - h)^+ + \text{confounders} \qquad (3)$$

Note that the parameters β in model 1 and θ in model 3 have different interpretations; β measures the percentage increase in mortality per 10- g/m^3 increase in PM_{10} at any level of the pollutant; θ measures the percentage increase in mortality per 10- g/m^3 increase in PM_{10} when PM_{10t} is higher than h. For PM_{10t} values smaller than h, the log-relative rate of mortality is set to zero.

Estimation

Using the *gam()* function in Splus (MathSoft, Inc., Cambridge, Massachusetts), we fit the generalized additive linear and spline models 1 and 2, respectively, within each city to obtain city-specific estimates and standard errors of the linear effect and of the parameter vector corresponding to the splines. Let ϕ_c denote the city-specific parameters measuring linear and nonlinear effects of PM_{10} on mortality for models 1–2 for city c: $c = 1, \ldots, 20$. For the linear model, $\phi_c = \beta_c$, and for the dose-response model, ϕ_c equals the vector of coefficients corresponding to the splines. To combine the coefficients across cities, we first test for heterogeneity using a generalization of the statistic proposed by DerSimonian and Laird (18) in the context of meta-analysis:

$$X^2 = \sum_C (\hat{\phi}_C - \bar{\phi})^T V_C^{-1} (\hat{\phi}_C - \bar{\phi}) \quad (1)$$

where $\bar{\phi} = (\Sigma_c V_c^{-1})^{-1} \Sigma_c V_c^{-1} \hat{\phi}_c$. Under the null hypothesis of no heterogeneity, X^2 follows a chi-squared distribution with $20x\ dim(\phi_c) - dim(\phi_c)$ degrees of freedom. When we fail to reject the null, we combine the city-specific estimates using a fixed-effects model with weights $W_c = V_c^{-1}$ and an estimator of the form $\bar{\phi} = (\Sigma_c W_c)^{-1} \Sigma_c W_c \hat{\phi}_c$ with variance, $V(\bar{\phi}) = (\Sigma_c W_c)^{-1}$.

If we reject the null, we fit a two-level Bayesian normal hierarchical model (see, e.g., Daniels and Kass (19)),

$$\hat{\phi}_C \sim N(\phi_C, V_C) \quad (2)$$

$$\hat{\phi}_C \sim N(\phi, D) \quad (3)$$

with flat priors on ϕ, the overall coefficient vector, and D, the between-city covariance matrix (i.e., $p(\phi) \propto 1$ and $p(D) \propto 1$). This model is fit using the Gibbs sampler and gives similar results to random effects models (18) with weights of the form $W_c = (D + V_c)^{-1}$ for some estimate of the between-city covariance matrix D.

Because the threshold model 3 assumes that the threshold h is unknown, we implemented the following procedure to jointly estimate θ and h within each city. First, we created a grid of possible thresholds, extending from 5 g/m^3 to 200 g/m^3 with a spacing of 5 g/m^3. Then, conditional on each possible threshold in the grid, we fit model 3 in each city using the *gam* function, thus obtaining a set of coefficients $\{\hat{\theta}(h), h = 5, 10, ..., 200\}$ of maximum likelihood estimates of θ, conditional on h. For each of the 20 cities, we then found the maximum likelihood estimate of h by searching over the grid for the point $\hat{h}$ that maximizes the likelihood $l(\hat{\theta}(h), h)$, and we set $\hat{\theta} = \hat{\theta}(\hat{h})$. This method is equivalent to choosing the pair $(\theta(h),h)$ that maximizes the joint log likelihood, $l(\theta,h)$. We do not pool the coefficients $\hat{\theta}_c$ across cities for the threshold model because coefficients have different interpretations for different h.

We did not compute the covariance matrix for the coefficients and threshold jointly, or a standard error for the threshold as for most cities, estimation of the threshold was quite unstable and standard information-based approaches failed. Consequently, to find an estimate of the overall threshold, we chose the value, $\hat{h}$, which minimizes the deviance (or equivalently, maximizes the log likelihood):

$$\hat{h} = \arg\min_h Dev\,(h)$$

where $Dev(h) = \Sigma_c Dev_c(h) = -2\Sigma_c l_c(h)$ with $Dev_c(h)$ and $l_c(h)$ are the city-specific deviance and log-likelihood evaluated at h, respectively. We consider h ranging in $\{0, 5, 10, \ldots, 75$ g/m$^3\}$, where 75 g/m^3 is the largest PM_{10} level for which the parameters of the threshold model were identified for all 20 cities. We consider the linear case ($h = 0$) as a special case of the threshold model when estimating the overall h. To find a measure of uncertainty for the threshold, we first calculate the following weights:

$$w_h = \frac{\exp(-0.5 Dev(h))}{\sum_{h \in H} \exp(-0.5 Dev(h))}; \text{ for } h = 0, \ldots, 75,$$

where w_h measures the extent to which the data support the hypothesis that h is the true threshold $H = \{0, 5, \ldots, 75\}$. We then define a 95 percent credible set as $\{(h_L,h_U): \Sigma_{h=h_L}^{h=h_U} w_h \geq 0.95\}$. The approach of computing the credible set for the overall threshold using the weights, w_h, is similar in concept to inverting the likelihood ratio (see, e.g., (20)), and it can be further justified by showing its connection to the Bayesian information criterion (BIC) and posterior mode probabilities. The BIC for a model M corresponding to a threshold h, $BIC(M_h)$, is given by $Dev(h)$ + (number of parameters) × log(sample size). The approximate posterior probability of M_h, when also considering the models with the other thresholds, is

$$P(M_h|\text{data}) = \frac{\exp(-0.5 \times BIC(M_h))}{\Sigma_{j=0}^{15} \exp(-0.5 \times BIC(M_{(5\times j)}))}$$

$$= \frac{\exp(-0.5 \times Dev(h))}{\Sigma_{j=0}^{15} \exp(-0.5 \times Dev(5 * j))}$$

$$= w_h$$

The first equality holds if we assume that each threshold is equally likely a priori. The second equality holds since all models being considered here have the same number of parameters. The weight w_h can then be interpreted as an approximate posterior probability of the model M_h.

In addition to obtaining an overall curve that draws information from all cities, we also compared the models within each city and over all cities to determine which best fits the

data. We used the Akaike information criterion (AIC) for this purpose (21). The AIC for each model is a combination of the deviance and the number of parameters in the model: AIC = deviance + 2(number of parameters). The second term provides a penalty for models with more parameters. The model with a lower value of AIC is preferred. To compare the threshold and the linear models using AIC, we exclude $h = 0$ (linear) when we fit the threshold model. However, to compute our overall estimate, we include $h = 0$ as a possible value.

RESULTS

Figure 1 gives city-specific and overall estimates and 95 percent confidence intervals for the PM_{10} effects under the linear model. The results are reported using the mean of concurrent day (lag 0) and previous day (lag 1) pollution values. For all causes, there was an increase in mortality with increasing level of PM_{10}. Overall, the largest effect was estimated for respiratory and cardiovascular mortality, with an increase in mortality of 0.69 percent (95 percent confidence interval (CI): 0.40, 0.98) for a 10- g/m^3 increase of PM_{10}. The estimates for total and other mortality were 0.54 percent (95 percent CI: 0.33, 0.76) and 0.34 percent (95 percent CI: 0.17, 0.51), respectively. Table 2 reports point estimates and 95 percent credible regions of the overall effects of PM_{10} using concurrent day (lag 0) and previous day (lag 1) pollution levels and mean lag. The overall effects of PM_{10} are robust with respect to lag specification.

Figure 2 shows the spline dose-response curves for all cause, cardiorespiratory, and other cause mortality for the mean lag and lags 0 and 1. For total and cardiorespiratory mortality, the spline curves are roughly linear, consistent with the absence of a threshold. For mortality from other causes, there appears to be little increase in risk until the PM_{10} concentration exceeds 50 g/m^3. Thus, this curve suggests that the threshold model (model 3) may be reasonable for other-cause mortality. The shapes of the dose-response curves do not change substantially for mean lag, lag 0, and lag 1.

The tests for heterogeneity for the dose-response curves across cities indicated heterogeneity for total and cardiovascular and respiratory mortality for mean lag. The heterogeneity of the curves for mean lag and total mortality appears in figure 3, which displays the overall curve and the city-specific curves estimated from the Bayesian hierarchical model. Although there appears to be considerable heterogeneity across cities, the curves have similar shapes and no one or two cities appear to dominate the estimate of the overall curve.

The histograms in figure 4 show the posterior probabilities (w_h) of the thresholds (h) for each category of cause-specific mortality and for the mean of lag 0 and lag 1 PM_{10}. The posterior distributions of the thresholds are skewed to the right for total mortality and cardiovascular and respiratory mortality and skewed to the left for other causes of mortality. The posterior mode and 95 percent credible regions for the threshold at lag 0 and lag 1 are summarized in table 3. The posterior mode does not change substantially across different lags. Likelihood functions are more informative for the mean lag than for lag 0 and lag 1 and, therefore, lead to more reliable threshold estimates with narrower confidence intervals. The threshold estimates ranged between about 15 and 65 g/m^3 PM_{10}, corresponding approximately to the 10th and 80th interquartile ranges of the PM_{10} distributions for most of the cities. The category of other-cause mortality had the highest, most probable threshold, at 65 g/m^3 (95 percent credible regions: 55, 75). However, for cardiovascular and respiratory mortality, the data give more support to low values of h (as 0, 5, 10 g/m^3) than for total mortality, indicating that the threshold, if any, for cardiovascular and respiratory mortality may be lower than the threshold for total mortality. The posterior modes for the thresholds for cardiovascular and respiratory mortality and for total mortality were, respectively, 15 g/m^3 (95 percent credible region: 0, 20) and 15 g/m^3 (95 percent credible region: 10, 20).

We more formally examined the hypothesis of linearity in the PM_{10}-mortality relation by comparing the AIC values obtained under the linear, threshold, and spline dose-response models. Table 4 shows the difference in the AIC values between the threshold and linear models and between the spline dose-response and linear models for lags 0 and 1 and for the mean lag for total, cardiovascular and respiratory, and other-cause mortality. Positive values of these differences indicate that the linear model is preferred over the threshold and spline models, respectively. To compare the spline and the threshold models, the model with the smaller AIC difference is preferred.

We can see that the spline model is never preferred at any lag or type of mortality. In comparing the linear and threshold models, we find that the linear model is preferred for all cases except for the mean lag in the case of "other" mortality. This preference is consistent with visual assessment of

TABLE 2. Posterior means and 95% credible regions (numbers in parentheses) of the overall effects (percentage increase in mortality per 10-unit increase in PM_{10}*) at mean lag, lag 0, and lag 1 on total, cardiovascular and respiratory, and other-causes mortality, 20 largest US cities, 1987–1994

	Total mortality	Cardiovascular and respiratory mortality	Other-causes mortality
Mean current and previous day PM_{10} measure (mean lag)	0.54 (0.33, 0.76)	0.69 (0.40, 0.98)	0.34 (0.13, 0.55)
Current day (lag 0)	0.41 (0.21, 0.66)	0.48 (0.09, 0.88)	0.31 (0.01, 0.68)
Previous day (lag 1)	0.46 (0.27, 0.69)	0.58 (0.34, 0.87)	0.25 (0.03, 0.48)

* PM_{10}, particulate matter <10 m in aerodynamic diameter.

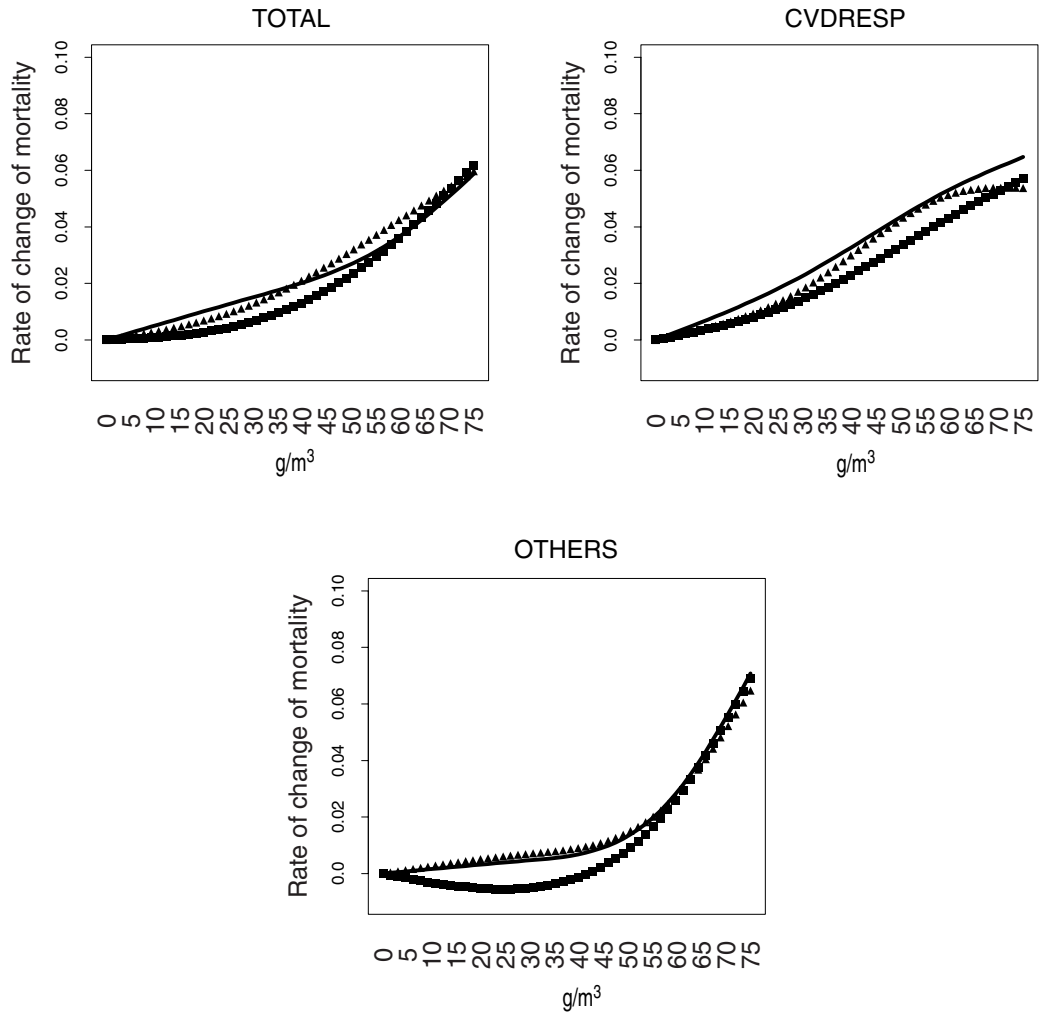

FIGURE 2. Mortality-particulate matter <10 m in aerodynamic diameter (PM_{10}) dose-response curves for total (TOTAL) mortality, cardiovascular and respiratory (CVDRESP) mortality, and other causes (OTHERS) mortality, 20 largest US cities, 1987–1994. The dose-response curves for the mean lag, current day, and previous day PM_{10} are denoted by solid lines, squared points, and triangle points, respectively.

the spline dose-response curves for other causes of mortality.

DISCUSSION

The shape of the exposure-response relation between levels of an environmental agent and risk for adverse effects may have profound implications for developing regulations to protect public health (22–24). Linear models are often assumed on a biologic basis or for computational simplicity, but nonlinear models may have plausibility as well, depending on the agent. For some environmental agents, for example, ionizing radiation, there has been extensive consideration for cancer risk of the shape of the dose-response or exposure-response relation (25, 26).

For air pollution, the shape of the exposure-response relation for various adverse health effects, including mortality, has also long been of interest as researchers have attempted to supply useful evidence for policymakers seeking to minimize risk to public health. For the "criteria air pollutants," regulated under section 109 of the Clean Air Act, the administrator of the Environmental Protection Agency is required to set standards that protect health with an "adequate margin of safety." This language provides a strong rationale for exploring the shape of the exposure-response relation. Approaches for doing so have included the fitting of threshold linear models and various nonlinear models to observational data and the restriction of analyses to lower concentrations. In fact, the continued demonstration of adverse effects of air pollution over recent decades, even as concentrations of pollutants have declined, suggests that exposures have not yet gone below no-effect thresholds, if such exist.

For air pollution and daily mortality, the topic of this report, a number of investigators have explored the shape of the exposure-response relation (27, 28). These analyses have been exclusively carried out within single locations and consequently have limited statistical power to provide evidence in support of a particular model versus alterna-

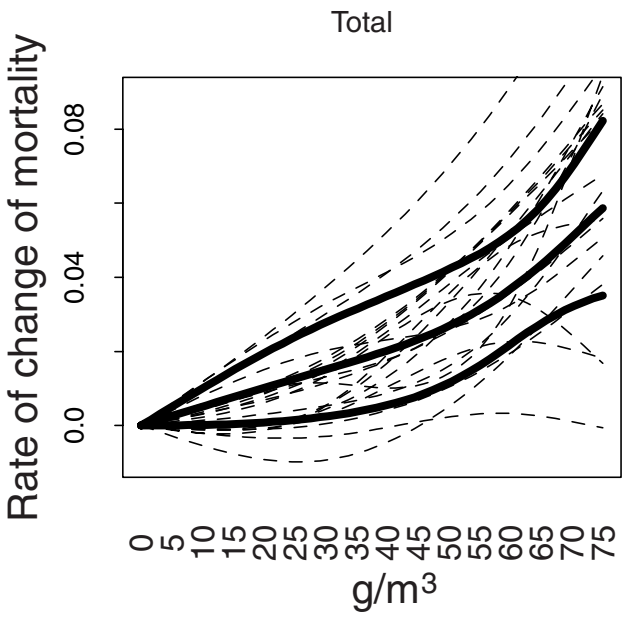

FIGURE 3. Particulate matter <10 m in aerodynamic diameter (PM_{10})-total mortality dose-response curve for the mean lag PM_{10} and 95% credible regions (solid lines), 20 largest US cities, 1987–1994. Dashed lines denote the Bayesian estimates of the city-specific dose-response curves.

tives. Additionally, many of the early studies used methods that would no longer be considered optimal. In this paper, we introduce and apply two statistical models, a spline dose-response model and a threshold model, to daily time-series data for the 20 largest US cities. By use of multiple locations, power is gained and generalizability is enhanced. We also offer a method for characterizing the uncertainty of estimated thresholds. Smith et al. (29) have used piecewise polynomials and cubic splines to estimate nonlinear relations of particulate air pollution with mortality, but their approach was limited to data for single locations.

For total and cardiovascular and respiratory mortality, our findings suggest that there is no threshold, but for other causes of mortality there is evidence for a threshold level below which an effect is small for PM_{10}. As expected, the estimated threshold PM_{10} levels for cardiovascular and respiratory mortality and for total mortality are lower than the threshold PM_{10} level for other-cause mortality (15 g/m^3 and 65 g/m^3, respectively). The model comparisons based on the AIC always choose the log-linear dose-response model except for "other" causes of mortality, with mean lag. The linear model was found to be adequate for total and for respiratory and cardiovascular mortality. Results were not sensitive to the lag specification for PM_{10}.

The findings are consistent with analyses of daily time-series data that have shown significant, positive associations

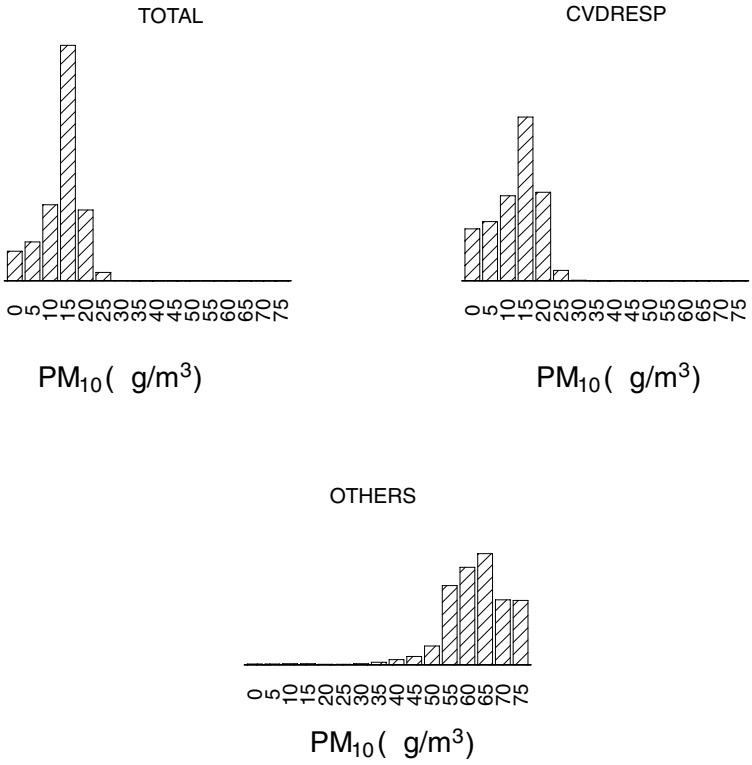

FIGURE 4. Posterior probabilities (w_h) of the thresholds for each cause-specific mortality and for the mean lag particulate matter <10 m in aerodynamic diameter (PM_{10}), 20 largest US cities, 1987–1994. TOTAL, total mortality; CVDRESP, cardiovascular and respiratory mortality; OTHERS, other mortality.

TABLE 3. Posterior mode and 95% credible regions (numbers in parentheses) of the threshold for mean lag 0 and lag 1, lag 0, and lag 1 PM_{10}* values (expressed as g/m³), 20 largest US cities, 1987–1994

	Total mortality	Cardiovascular and respiratory mortality	Other-causes mortality
Mean current and previous day PM_{10} measure (mean lag)	15 (10, 20)	15 (0, 20)	65 (50, 75)
Current day (lag 0)	20 (5, 70)	0 (0, 45)	40 (5, 75)
Previous day (lag 1)	15 (0, 30)	20 (0, 50)	60 (5, 75)

* PM_{10}, particulate matter <10 m in aerodynamic diameter.

TABLE 4. AIC* for the threshold and dose-response models calibrated such that AIC for the linear model is 0, 20 largest US cities, 1987–1994†,‡

	AIC		
	Lag 0	Lag 1	Mean lag
Total mortality			
Threshold	1.6	19.3	1.9
Spline	22.3	24.0	19.1
Cardiovascular and respiratory mortality			
Threshold	1.8	9.8	13.3
Spline	37.8	20.5	21.7
Other-causes mortality			
Threshold	11.9	15.7	–2.0
Spline	25.2	28.0	17.8

* AIC, Akaike's information criterion.
† The threshold model has one more parameter than the linear model; the spline model, two more.
‡ Table 4 considers only thresholds of 5–75.

between particle levels and mortality counts at current concentrations (3, 27). While analytical details of the studies are different, essentially all analyses have modeled log mortality as having a linear relation with particulate matter concentration. The general finding of a positive association implies that any threshold or no-effect level lies at the lower end of the concentration range. In fact, there is evidence of increasing effect at lower concentrations (9, 15, 27). Descriptive analyses have been consistent in showing approximately linear relations as well (30, 31).

We note several limitations of our methodology that are amenable to solution with further development. One limitation of our estimation method for the threshold is that some cities offered only vague information and, therefore, we could not estimate city-specific thresholds very well or evaluate heterogeneity across cities in the threshold values. With regard to the spline dose-response model, the number and locations of the knots were fixed in advance. A small improvement might be to jointly estimate the spline dose-response curves and the number and location of the knots. Methods need to be developed for this purpose. On the other hand, we fixed the knots at reasonable locations in the span of PM_{10} levels and had sufficient flexibility at concentrations of public health concern.

The first limitation might be addressed using a two-level hierarchical model. For example, the following second level might be added to the current model 2:

$$\log(h^C) \sim N(\log(h), \tau^2)$$

where h^c denotes the city-specific threshold, h the overall threshold, and τ^2 the between-location variability of the thresholds. Model fitting could be performed using Monte Carlo Markov chain techniques. If the threshold h^c varies substantially across cities, the 20-city average curve would not have a threshold form but would tend to be smoother. Hence, our analysis, which indicates that the linear dose-response is preferred for total and cardiovascular and respiratory mortality, does not exclude the possibility that thresholds vary across the country. The second problem can be addressed by extending the work in Denison et al. (32) on Bayesian curve fitting and applying it within the context of the two-level model.

The present results give an indication that the risk-free levels of PM_{10} are likely lower than the National Ambient Air Quality Standard for PM_{10}. These findings indicate that linear models without a threshold are appropriate for assessing the effect of particulate air pollution on daily mortality, even at current levels.

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