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REVISED ANALYSES OF THE NATIONAL MORBIDITY, MORTALITY, AND AIR POLLUTION STUDY: MORTALITY AMONG RESIDENTS OF 90 CITIES

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This article presents findings from updated analyses of data from 90 U.S. cities assembled for the National Morbidity, Mortality, and Air Pollution Study (NMMAPS). The data were analyzed with a generalized additive model (GAM) using the gam *function in S-Plus (with default convergence criteria previously used and with more stringent criteria) and with a generalized linear model (GLM) with natural cubic splines. With the original method, the estimated effect of PM_{10} (particulate matter 10μm in mass median aerodynamic diameter) on total mortality from nonexternal causes was a 0.41% increase per 10-μg/m^3 increase in PM_{10}; with the more stringent criteria, the estimate was 0.27%; and with GLM, the effect was 0.21%. The effect of PM_{10} on respiratory and cardiovascular mortality combined was greater, but the pattern across models was similar. The findings of the updated analysis with regard to spatial heterogeneity across the 90 cities were unchanged from the original analyses.*

This article describes new analyses, using updated methods, of data assembled on daily air pollution and mortality for the National Morbidity, Mortality and Air Pollution Study (NMMAPS). Findings of this multiyear project were previously reported, both as reports of the Health Effects Institute (Samet et al., 2000b, 2000c) and in the peer-reviewed literature (Daniels et al., 2000; Dominici et al., 2000a, 2000b; Samet et al., 2000a; Zeger et al., 2000). After these original publications became available, researchers discovered that the

This article is reprinted with permission from the Health Institute. The article was originally published in HEI Special Report *Revised Analyses of Time-Series Studies of Air Pollution and Health*, which also includes mother report on NMMAPS II data, 21 short communication reports, two HEI Commentaries by special panels of the Health Review Committee, and an HEI Statement. Further background and data on this revised analysis are available at www.biostat.jhsph.edu/˜fdominic/HEI/nmmaps.htm. Although this document was produced with partial funding by the U.S. Environmental Protection Agency under Assistance Award R82811201 to the Health Effects Institute, it has not been subjected to the agency's peer and administrative review and therefore may not necessarily reflect the views of the agency and no official endorsement by it should be inferred. The contents of this document also have not been reviewed by private party institutions including those that support the Health Institute; therefore, it may not reflect the views or policies of these parties, and no endorsement by them should be inferred.

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results had been affected by use of the *gam* function in the S-Plus software (Insightful Corp., Seattle, WA), which introduced an upward bias in effect estimate of particulate air pollution on mortality.

Bias in the estimates resulted from implementing the generalized additive model (GAM) with the default convergence criteria in the S-Plus *gam* function (version 3.4). The potential for this bias was identified through sensitivity analyses undertaken to better understand unexpected results in analyses peripheral to the NMMAPS focus. Details of how the problem was identified, and of its consequences, are provided elsewhere (Dominici et al., 2002b). Further work is being conducted to explore the basis of this bias and its dependence on details of model specification. Bias from the NMMAPS application of the GAM likely reflects the difficulty of estimating the relatively weak effect of air pollution in data with several temporally correlated variables, including air pollutant levels, temperature, and humidity.

The S-Plus (version 3.4) *gam* function had been used throughout the NMMAPS project to estimate relative rates of mortality attributable to PM_{10} while controlling for time trends, weather variables, and other possible confounders. For the recalculated analyses based on GAMs, we used markedly more stringent convergence criteria (Dominici et al., 2002b).

Other possible problems with using GAMs in time-series analyses of air pollution data have been recently identified. In the presence of concurvity (that is, residual nonlinear correlation in the data), the standard error of the air pollution effect is likely to be underestimated because of the approximate method used for its calculation. Ramsay et al. (2003) further investigated the implications of this standard error approximation in time-series studies of air pollution and mortality. Dominici et al. (2003a) recently released a new *gam* function that calculates the asymptotically exact standard error of the air pollution effect.

We are continuing with methodologic investigations on the adequacy of GAMs for analyses of time-series data in air pollution and health and with comparisons of a GAM with fully parametric alternatives (Dominici et al., 2003a). We have completed reanalyses of the data leading to the most central findings of prior NMMAPS reports and other publications. We have carried out these analyses using (1) the *gam* function with substantially more stringent convergence criteria and (2) a GLM with natural cubic splines, a fully parametric alternative. Additional reanalyses of the NMMAPS data are summarized elsewhere (Dominici et al., 2002a, 2002b, 2003a).

METHODS

The methods of NMMAPS have been fully described in previous reports of the Health Effects Institute (Samet et al., 2000b, 2000c). The NMMAPS project was implemented to describe the effect of particles and other air pollutants on daily mortality across the United States. The methods were intended to provide a picture of regional variation in the effect of particles and to provide a national effect estimate, if appropriate (Dominici et al., 2002a). A uniform approach taken for the within-city models was based on extensive sensitivity analyses of data for Philadelphia (Kelsall et al., 1997); that is, the same variables and smoothing functions were used in each city to control for possible confounding (Table 1).

To evaluate the impact of default *gam* settings on published analyses and to provide updated results, we reanalyzed the NMMAPS data with three methods: model 1, GAM with S-Plus default convergence parameters (the original analyses); model 2, GAM with greatly more stringent convergence parameters than the defaults (Dominici et al., 2002b); and model 3, Poisson regression model with parametric nonlinear adjustments for confounding factors (specifically, generalized linear model [GLM] with natural cubic splines).

Model 1 corresponds to the GAM used in prior analyses (Dominici et al., 2000a, 2002a; Samet et al., 2000a). Model 2 is also the GAM used in previous analyses but with stricter convergence criteria and a substantially larger number of maximum iterations in the local-scoring and backfitting algorithms (Dominici et al., 2003b). Comparison of estimates from models 1 and 2 provides an indication of sensitivity of findings to the convergence criteria. Model 3 (GLM) is a fully parametric analog of model 2, estimated by an iteratively reweighted least squares (IRWLS) algorithm. In model 3, we replaced smoothing splines with natural cubic splines having the same degree of freedom in the smooth functions of time, temperature, dewpoint, and interactions between age group indicators and the smooth functions of time. In model 3 with natural cubic splines and a fixed number of degrees of freedom, the knots were equally spaced at quantiles of the distribution of each covariate. A comparison of estimates from models 2 and 3 indicated the sensitivity of findings to the statistical method selected.

We estimated the 90 city-specific relative rates of mortality from nonexternal causes associated with a 10-$\mu g/m^3$ increase in PM_{10} under models 1, 2, and 3. The 90-city specific relative rates were pooled across cities using a two-stage hierarchical model and a three-stage regional model with noninformative priors

TABLE 1. Potential Confounders or Predictors in Estimation of City-Specific Relative Rates Associated With Particulate Air Pollution Levels, and Rationale for Their Inclusion in the Model

Modeling of predictors	Primary reasons for inclusion
Indicator variables for the three age groups	To allow for different baseline mortality rates within each age group
Indicator variables for the day of the week	To allow for different baseline mortality rates within each day of the week
Smooth functions of time with 7 df/yr	To adjust for long-term trends and seasonality
Smooth functions of temperature with 6 df	To control for the known effects of weather on mortality
Smooth functions of dew point with 3 df	To control for the known effects of humidity on mortality
Separate smooth functions of time (2 df/yr) for each age group contrast	To separately adjust for longer term time trends within each age group

on the variance components (Dominici et al., 2000a, 2002a). In Appendix A, we provide an assessment of the sensitivity of findings to details of the approach used for combining estimates across cities; these analyses show that the results are robust to these choices. Markov-chain Monte Carlo analyses were performed to estimate posterior distributions of all parameters of interest with the Bayesian inference using Gibbs sampling (BUGS) program (Thomas et al., 1992). For comparison, city-specific estimates were also pooled using fixed-effect models and random-effect models with moment estimator of the between-city variance (DerSimonian & Laird, 1986).

Within each city, multipollutant models provide relative rate estimates of mortality associated with exposure to each of the pollutants included in the model. These relative rates can be pooled in a univariate or multivariate fashion. In a univariate fashion, the city-specific coefficients for each pollutant are pooled separately using fixed effects, random effects, or Bayesian methods. However, univariate pooling ignores the within-city statistical correlations among relative rate estimates for the pollutants jointly included in the model. Because of this limitation, the method of multivariate pooling, which takes these correlations into account, was chosen for all multipollutant analyses. Multivariate pooling was performed by using a Bayesian two-stage multivariate normal model (Lindley & Smith, 1972) implemented by the software TLNISE (Everson & Morris, 2000), which allows specification of noninformative priors on the heterogeneity covariance matrix. Sensitivity analyses of the pooled effects to the specification of the prior distribution on the covariance matrix are reported in Appendix A.

RESULTS

The reanalyses presented in this report focus on the 90 cities included in the complete NMMAPS database. Results were obtained using Bayesian methods that provide posterior means and posterior intervals of the parameters of interest. These are the Bayesian analogs of point estimates and confidence intervals, respectively. The sensitivity of findings with respect to non-Bayesian alternatives has been systematically explored in all NMMAPS analyses. We report estimates of the following quantities of interest:

- National average air pollution effect (posterior mean) and its statistical uncertainty (95% posterior interval).
- Heterogeneity of the air pollution effects across the 90 cities and its statistical uncertainty. The heterogeneity is quantified by the between-city standard deviation of true city-specific air pollution effects.

NATIONAL AVERAGES

The national average estimates varied among models 1, 2, and 3. When we imposed stricter convergence criteria on the *gam* function of S-Plus, the national average estimate across the 90 cities at lag 1 changed from a 0.41% increase in total mortality per 10-μg/m^3 increase in PM_{10} (under model 1) to a 0.27% increase (under model 2). When GLM with natural cubic splines was used (model 3), the national average estimate was 0.21% per 10-μg/m^3 increase in PM_{10}.

Figure 1 plots the original calculations (obtained under model 1) against the updated city-specific effect estimates (obtained under model 3) for total mortality as the outcome and PM_{10} at lag 1. Note the upward bias in the original estimates and the generally close correlation between the pairs of effect estimates from model 1 and model 3. The black square is plotted at the original versus the updated national average estimate across the 90 cities. Its width and height correspond to two standard errors of the national average estimates. With the original approach, the national average estimate was 0.41% per 10-μg/m^3 increase in PM_{10} (posterior SE equal to 0.06); the updated national average estimate was 0.21% per 10-μg/m^3 increase in PM_{10} (posterior SE equal to 0.06).

Figure 2 provides the marginal posterior distributions of the national average estimates, original and updated, for total mortality at lags 0, 1, and 2. The national average estimates for the change in total mortality at lags 0, 1, and 2 were 0.07% (posterior SE equal to 0.06), 0.21% (posterior SE equal to 0.06), and 0.10% (posterior SE equal to 0.06). The upward bias in the original national average estimates is evident. In the updated analyses, the effect remained greatest at lag 1, and the posterior probabilities for a national average effect greater than zero were all close to one. The corresponding point estimates and 95% posterior intervals are given in Figure 3.

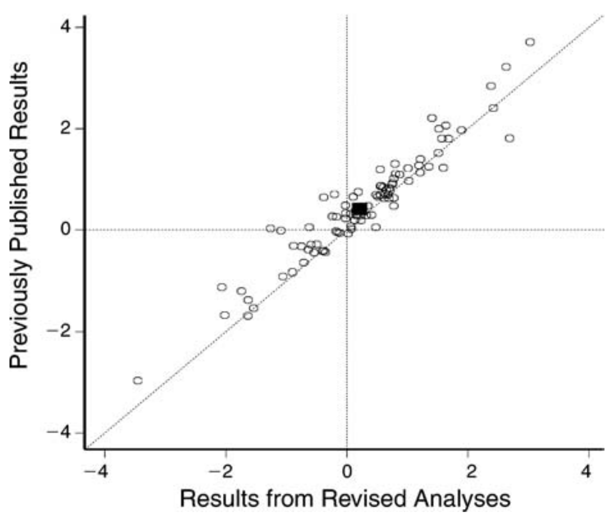

FIGURE 1. Percentage of change in total mortality from nonexternal causes per 10-μg/m^3 incease in PM_{10} at lag 1: previously published versus revised estimates, 90 U.S. cities (1987–1994).

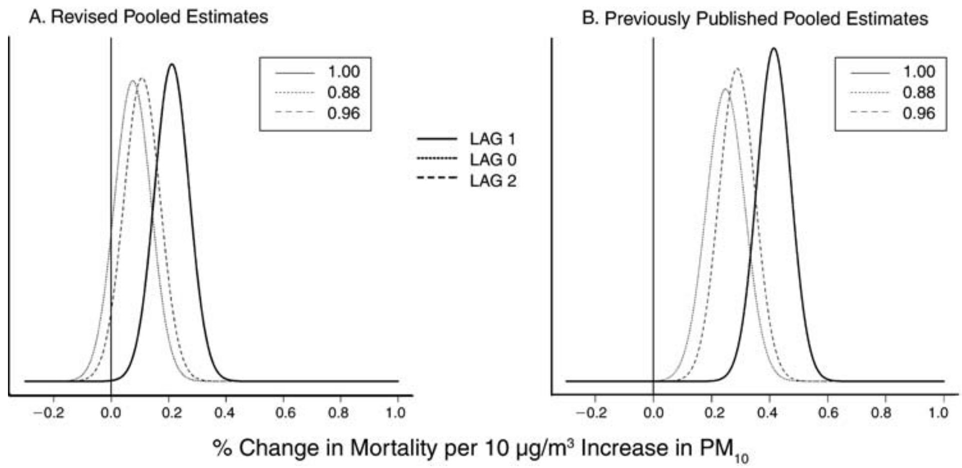

FIGURE 2. Marginal posterior distributions for the national average effect of PM_{10} on total mortality from nonexternal causes at lags 0, 1, and 2 for the 90 U.S. cities.

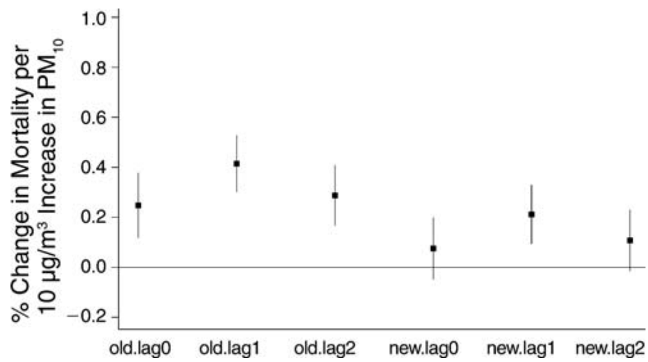

FIGURE 3. Posterior means and 95% posterior intervals of the national average estimates of PM_{10} effects on mortality from nonexternal causes for the previously published (old) and the revised (new) estimates at lag 0, 1, and 2 for the 90 U.S. cities.

Figure 4 shows that the general pattern for cause-specific mortality is unchanged with the greatest effect for cardiovascular and respiratory mortality (0.31% per 10-μg/m^3 increase in PM_{10} at lag 1, posterior SE equal to 0.09). The national average estimates for changes in cardiovascular and respiratory mortality at lags 0 and 2 were 0.13% (posterior SE equal to 0.09) and 0.20% (posterior SE equal to 0.09). The general insensitivity of the PM_{10} effect on total mortality at lag 1 to inclusion of other pollutants in the model is shown in Figure 5. The posterior mean of the national average effect of PM_{10} on total mortality was essentially unchanged with the inclusion of either ozone (O_3) alone or of O_3 with additional pollutants. We also performed sensitivity analyses

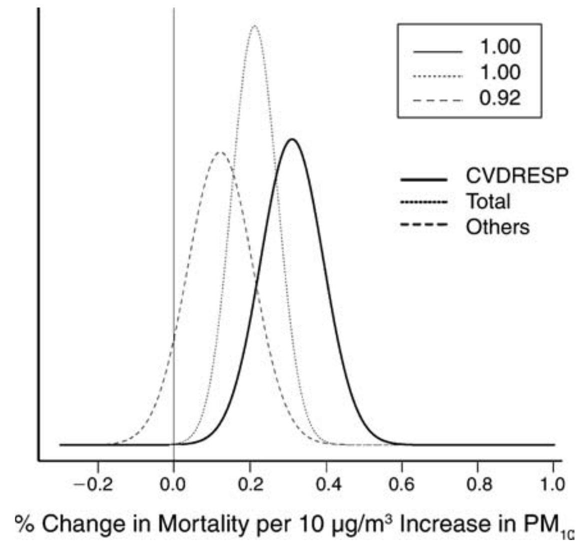

FIGURE 4. Marginal posterior distributions for revised national average effects of PM_{10} at lag 1 for total mortality, cardiovascular-respiratory mortality, and other causes mortality for the 90 U.S. cities.

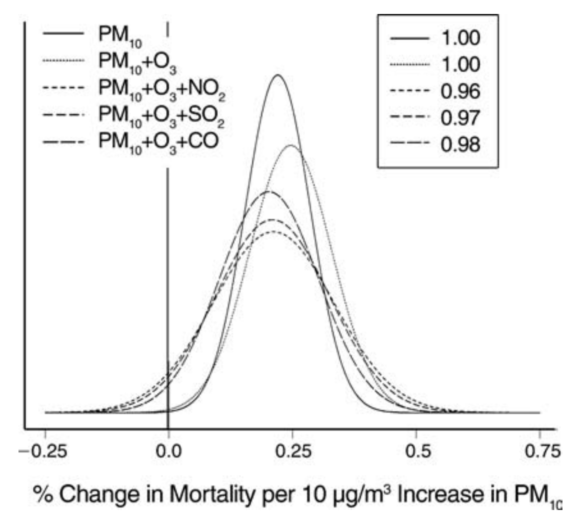

FIGURE 5. Marginal posterior distributions for the revised national average estimates of PM_{10} on total mortality from nonexternal causes at lag 1 with and without control for other pollutants for the 90 U.S. cities.

of the multivariate pooling methods with respect to prior distributions on the between-city covariance matrix. Results are summarized in Table A.1. The national average effect of PM_{10} adjusted for other pollutants was also robust to the choice of priors when pooling was performed in a multivariate fashion.

REGIONAL AVERAGES

The average estimates for total mortality are mapped in Figure 6, and the individual city estimates are plotted by region in Figure 7. The general patterns were unchanged, and the northeast continued to have the highest regional mean. Sensitivity of regional average estimates to lag specification is presented in Figure 8. Values tend to be highest within most regions at lag 1, as found with the national average estimate (Figure 2). Similar analyses were also carried out for cardiovascular and respiratory mortality (Figure 9). For this cause-of-death grouping, the pattern of regional variation was comparable to that for all nonexternal causes of death (Figure 6). The effect of PM_{10} was greatest in the northeast region. Posterior means and 95% posterior intervals of the regional average effects for total mortality and for cardiovascular and respiratory mortality are summarized in Table A.2.

HETEROGENEITY

We first tested the hypothesis of no heterogeneity by performing a standard χ^2 test (Hedges & Olkin, 1985), and we accepted the null hypothesis. This result is likely due to the large statistical uncertainty of the city-specific relative risk estimates. We then repeated the test by gradually reducing the statistical variances and found that a reduction of at least 30% in the statistical variances would be necessary to reject the null hypothesis of no heterogeneity. We then implemented a Bayesian analysis with a two-stage hierarchical model and estimated marginal posterior distribution of the heterogeneity parameter. Table 2 summarizes posterior means and posterior intervals of the between-city standard deviations for total mortality and PM_{10} at lag 1 under models 1, 2, and 3. With the updated method, we estimated slightly less heterogeneity of the air pollution effects among cities. Under the same model for the pooling (a two-stage normal–normal model), the posterior mean of the between-city standard deviation moved from 0.112 in model 1 to 0.088 in model 2. When GLM with natural cubic splines was used (model 3), the posterior mean of the between-city SD was 0.075. The overlap between the three posterior distributions was substantial, suggesting little sensitivity of the pattern of heterogeneity among cities to the analytic approach.

SENSITIVITY ANALYSES

We performed sensitivity analyses of the national average air pollution effects with respect to several key modeling assumptions:

- Adjustment for confounding factors (Figure 10).
- Choice of the prior distributions on the heterogeneity variance (e.g., the between-city standard deviation squared) (Figure 11).

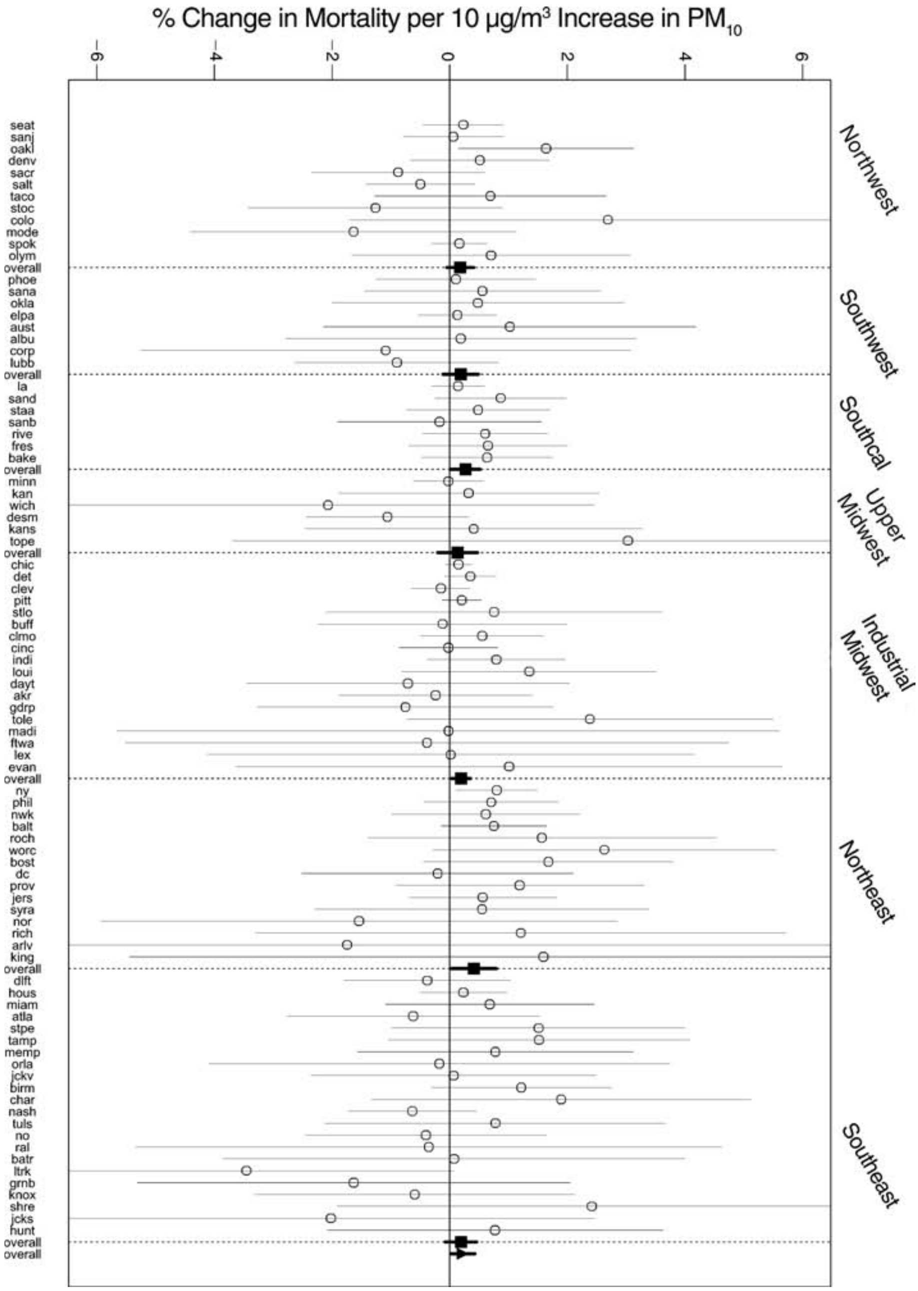

FIGURE 6. Posterior means divided by posterior standard deviations (t ratios) of regional effects of PM_{10} at lag 1 for total mortality from nonexternal causes.

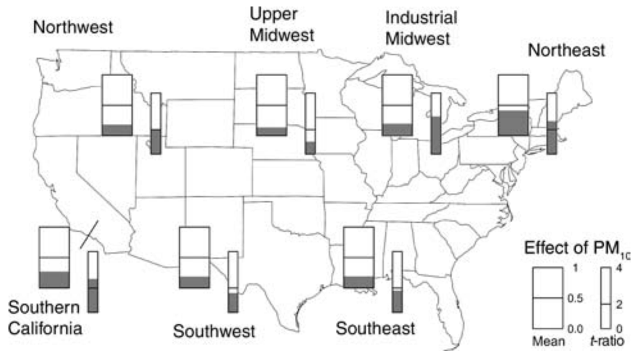

FIGURE 7. Maximum likelihood estimates and 95% confidence intervals of the percentage increase in total mortality from nonexternal causes per 10-μg/m^3 increase in PM_{10} for each location.

- Statistical models for heterogeneity: two-stage hierarchical model, three-stage regional model, and spatial correlation model (Figure A.1).

Figure 10 gives posterior means and 95% posterior intervals of the national average effects of PM_{10} for total mortality from nonexternal causes at lag 1 under 9 alternative scenarios of adjustment for confounding factors. Across the nine scenarios, we varied the degree of freedom for each of the three temporal confounders: time, temperature, and dewpoint. National average effects were not very sensitive to the specification of the degree of freedom in the smooth functions of time, temperature, and weather. The increase in total mortality per 10-μg/m^3 increase in PM_{10} of the pooled estimates ranged from 0.17% to 0.32% under the nine scenarios. The evidence of association was strong in every case.

Posterior distributions of the national average effects of PM_{10} for total mortality at lag 1 under differing prior distributions for the heterogeneity variance are plotted in Figure 11. Pooled effects of PM_{10} were only moderately sensitive to the prior distributions for the heterogeneity variance. Further sensitivity analyses of findings to the choice of the prior distributions are detailed in Appendix A. Sensitivity of the national average estimates to choice of statistical models for heterogeneity is also detailed in Appendix A.

MULTIPOLLUTANT ANALYSES

Finally, we updated analyses of the effects of pollutants other than PM_{10} on total mortality (Figures 12 through 16). These analyses include varying sets of the 90 cities, depending on the availability of the various pollutants for the individual cities. Because the data were more limited, the 95% posterior intervals of the national averages were substantially wider for these analyses than for those directed at PM_{10}. For O_3 (Figure 12), the estimates were uniformly positive, both for O_3 alone and with inclusion of other pollutants in the model,

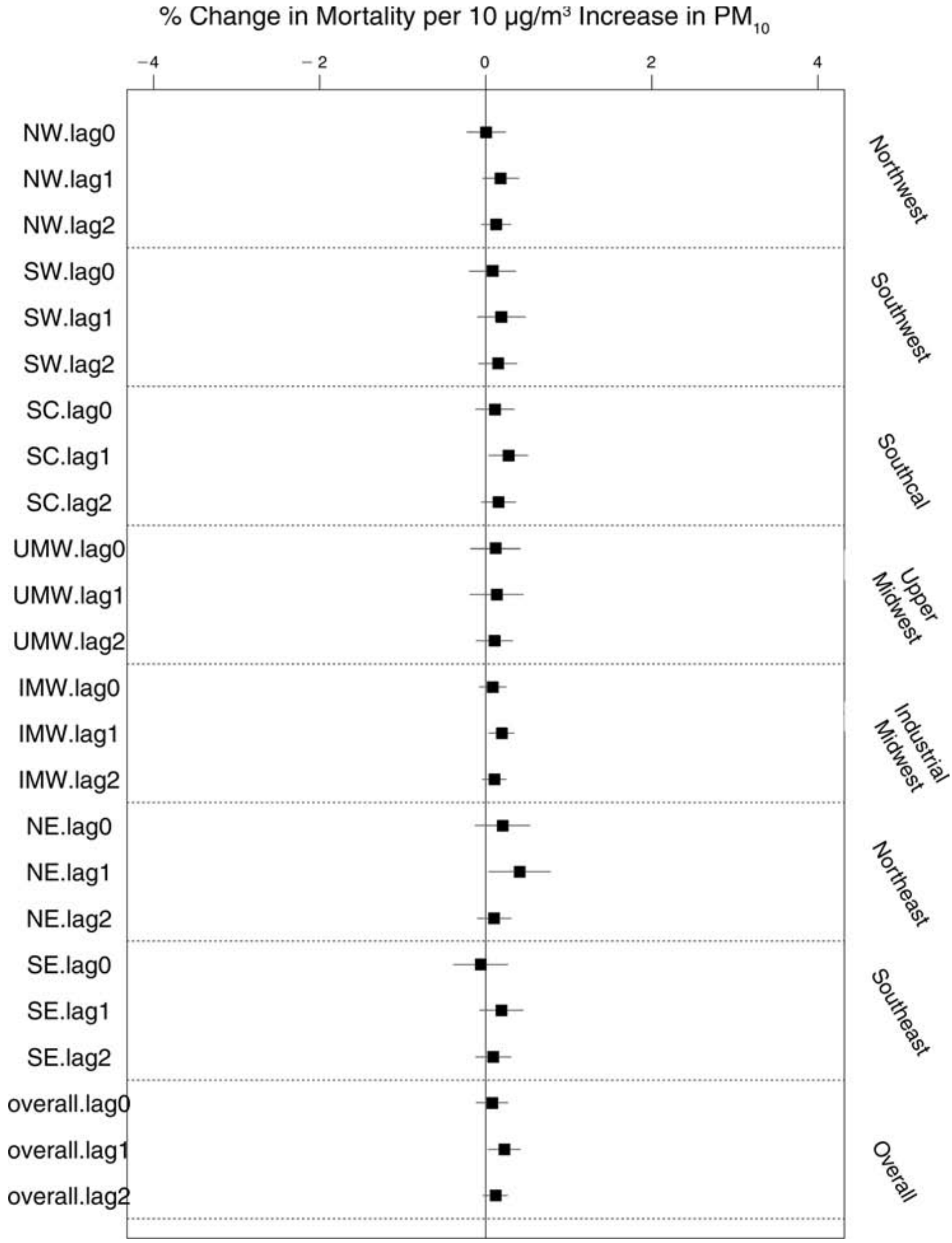

FIGURE 8. Posterior means and 95% posterior intervals of regional effects of PM_{10} on total mortality from nonexternal causes at lags 0, 1, and 2 for the 88 U.S. cities.

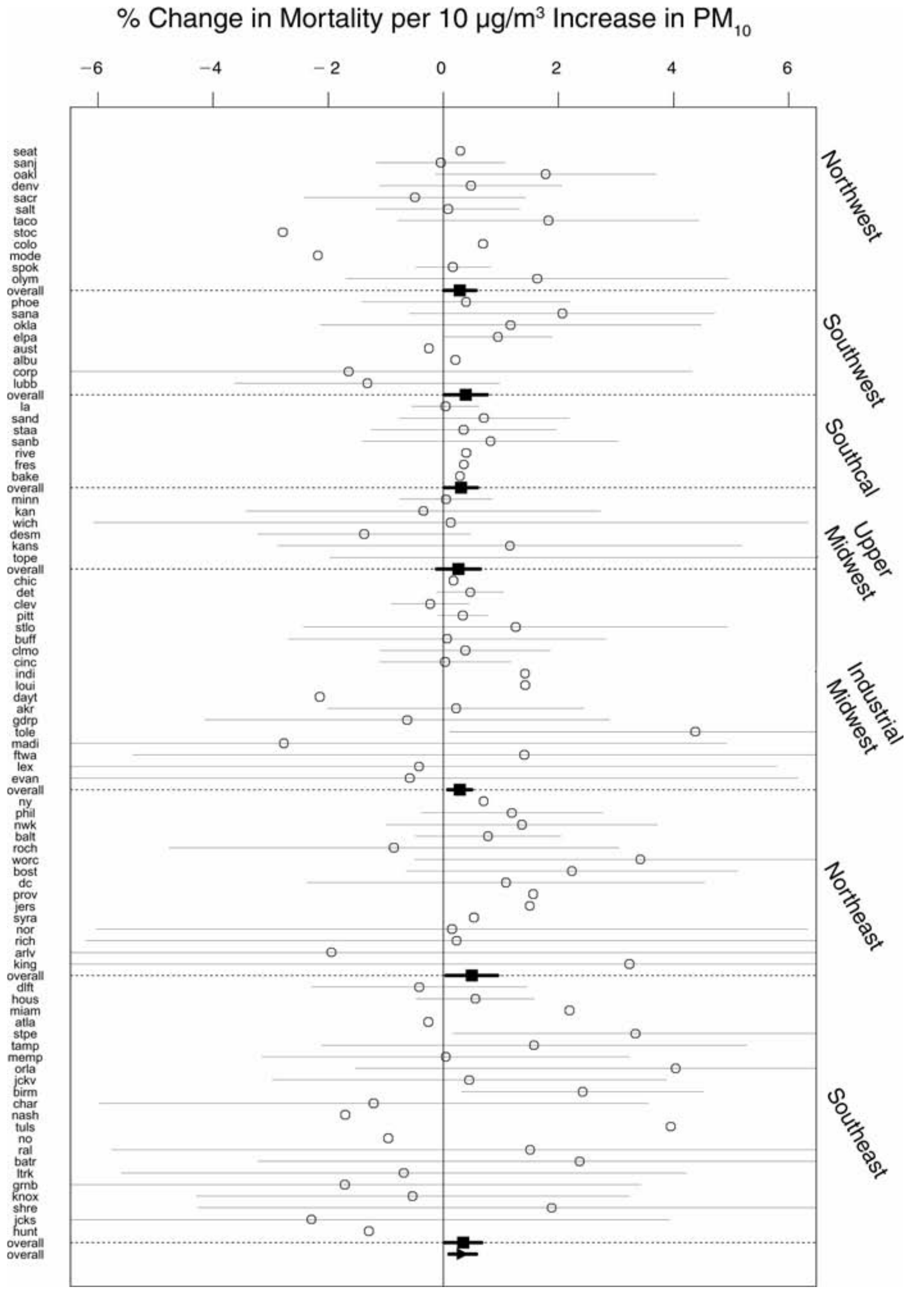

FIGURE 9. Maximum likelihood estimates and 95% confidence intervals of the percentage change in cardiovascular and respiratory mortality per 10-μg/m^3 increase in PM_{10} for each location.

TABLE 2. Posterior Means and Posterior 95% Intervals of the Between-City Standard Deviations for Total Mortality at Lag 1 Under the Three Models

	Posterior mean	Posterior 95% interval
Model 1[a]	0.112	0.022, 0.298
Model 2[b]	0.088	0.021, 0.240
Model 3[c]	0.075	0.021, 0.198

[a]GAM with default convergence parameters.
[b]GAM with more stringent convergence parameters.
[c]GLM with natural cubic splines.

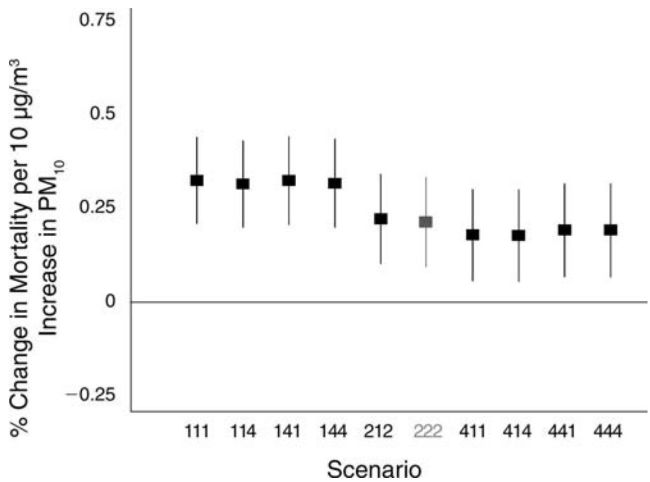

FIGURE 10. Posterior means and 95% posterior intervals of national average estimates of PM_{10} effects on total mortality from nonexternal causes at lag 1 for the 90 U.S. cities, under 9 alternative scenarios for adjustments for confounding factors.

although the 95% posterior intervals were wide. The data for estimating the effect of O_3 were limited to the summer months (Figure 13). For sulfur dioxide (SO_2) (Figure 14), nitrogen dioxide (NO_2) (Figure 15), and carbon monoxide (CO) (Figure 16), the results did not indicate associations of these pollutants with total mortality.

DISCUSSION

The NMMAPS modeling strategy originated with extensive exploration of the sensitivity of findings from the Philadelphia time-series data (Kelsall et al., 1997). That work used GAM as the basic modeling approach and was implemented with the function *gam* in S-Plus. The *gam* default convergence criteria of S-Plus version 3.4 were used. The initial phase of model development (Kelsall

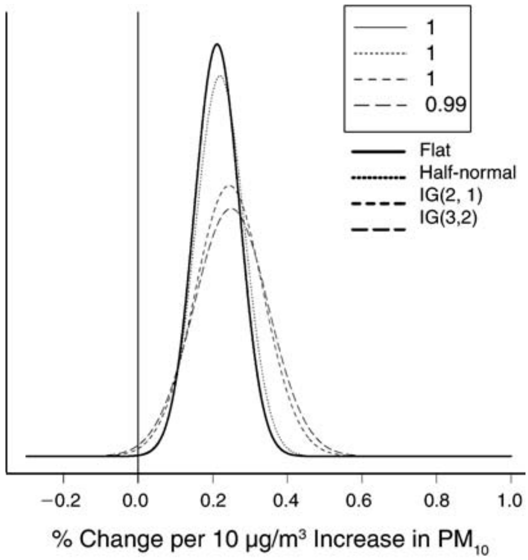

FIGURE 11. Marginal posterior distributions for national average estimates of PM_{10} effects on total mortality from nonexternal causes at lag 1 under 4 prior specifications for heterogeneity variance: (1) flat $1/\sigma^{-2} \sim G(0.001, 0.001)$; (2) half-normal $\sigma^2 \sim N(0,1000)I\sigma_{2>0}$; (3) $\sigma^2 \sim IG(2, 1)$; and (4) $\sigma^2 \sim IG(3, 2)$. *IG* denotes the inverse gamma distribution.

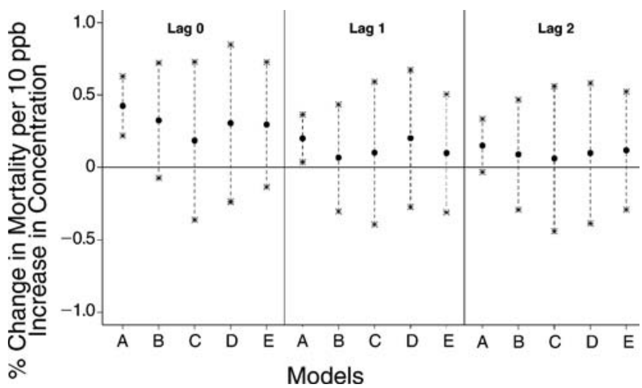

FIGURE 12. Posterior means and 95% posterior intervals of national average estimate of O_3 effect on total mortality from nonexternal causes at lags 0, 1, and 2 within sets of the 90 cities with pollutant data available.

et al., 1997) included detailed sensitivity analyses with respect to model specification for confounder adjustment and exposure variables but not with respect to either the statistical model itself or the software for implementing the model.

We have now identified an unanticipated influence on the quantitative NMMAPS results. As documented in Dominici et al. (2002b), the NMMAPS

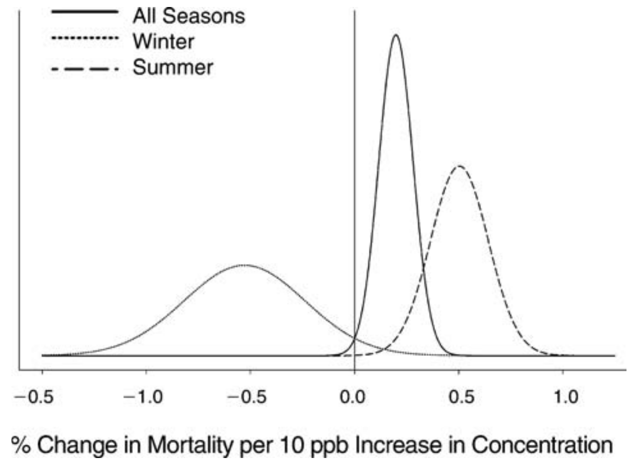

FIGURE 13. Marginal posterior distributions of the national average estimates of O_3 effects on total mortality at lag 0 for all seasons, summer (June, July, August) and winter (December, January, February) for the 90 cities.

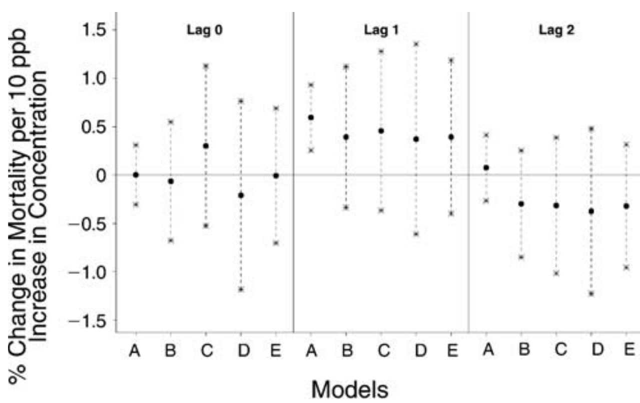

FIGURE 14. Posterior means and 95% posterior intervals of national average estimates of SO_2 effects on total mortality from nonexternal causes at lags 0, 1, and 2 within sets of the 90 cities with pollutant data available.

estimates of national average relative risks depend upon the convergence criteria in S-Plus and on the specific statistical model used. In our particular application, reliance on the default convergence criteria led to an upward bias of 0.14% (0.41–0.27) per 10-μg/m^3 increase in PM_{10}. When a GLM was used instead of a GAM, the estimate became 0.21% per 10-μg/m^3 increase in PM_{10}. In addition, standard errors of the cityspecific estimates were smaller in the GAM than in the GLM by 16% on average, even when more strict convergence parameters in the S-Plus function *gam* were used (Chambers & Hastie, 1992; Ramsay et al., 2003).

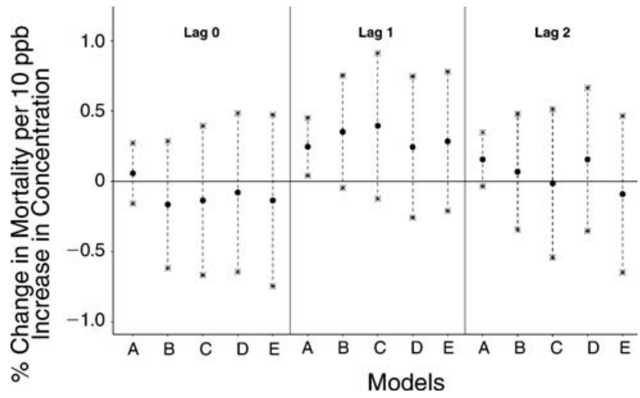

FIGURE 15. Posterior means and 95% posterior intervals of national average estimates for NO_2 effects on total mortality from nonexternal causes at lags 0, 1, and 2 within sets of the 90 cities with pollutant data available.

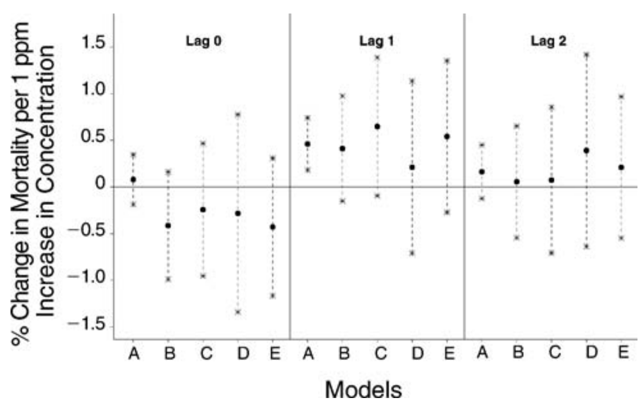

FIGURE 16. Posterior means and 95% posterior intervals of national average estimates for CO effects on total mortality from nonexternal causes at lags 0, 1, and 2 within sets of the 90 cities with pollutant data available.

While the quantitative estimates changed with the tighter convergence criteria in the *gam* function or with switching to a GLM, the major scientific findings of NMMAPS did not. Strong evidence remains of an association between acute exposure to particulate air pollution (PM_{10}) and daily mortality 1 d later (lag 1). This association was strongest for respiratory and cardiovascular causes of death, as anticipated based on concepts of underlying susceptibility. The association of PM_{10} with mortality could not be attributed to any of the other pollutants studied: NO_2, CO, SO_2, or O_3.

In our NMMAPS reanalyses, we compared the original results to updates using a GAM with more stringent convergence criteria and a GLM. For

NMMAPS, our simulation studies showed that the GLM produced less biased estimates of the pollution relative rate than did the GAM. Given our current understanding, we conclude the following.

1. GAMs with nonparametric smoothers (such as smoothing splines or locally weighted smoothers [LOESS]) provide a more flexible approach for adjusting for confounders compared to GLM with regression splines. This approach might also result in a lower prediction error for GAMs than for GLMs.
2. Work is in progress to overcome the problem of underestimating standard errors in GAM (Dominici et al., 2003a); preliminary results point toward an easy and not computationally expensive solution.
3. Multicity analyses are less affected by underestimation by a GAM of the city-specific standard errors than are single-city analyses. In multicity analyses, the statistical uncertainty of the national average air pollution effect is measured by the total variance, defined as the sum of the within-city plus the between-city variance. Under hierarchical approaches for multicity analyses, underestimation of the within-city variances is compensated by overestimation of between-city variance, resulting in an almost unchanged total variance (Daniels et al., 2003).

Further statistical comparisons among alternative modeling approaches for analyses of time-series data in air pollution and health are warranted, as is the development of new methods that avoid these pitfalls. In summary, the analyses reported by Dominici et al. (2002b) indicate some sensitivity of the quantitative, but not qualitative, results of the air pollution time-series analyses to modeling approaches and estimation procedures. Given the weak and nonspecific acute effect of air pollution on daily mortality, sensitivity of estimates to model choice would be anticipated, particularly because of the need to control for other time-correlated factors (such as temperature and season) that affect mortality. National average estimates were roughly equally sensitive to the adjustment for confounding factors under a range of plausible scenarios within model choice.

Particulate matter continued to be associated with mortality in the updated analyses, and the general pattern of spatial variability across the United States was unchanged. Ozone was associated with total mortality in the summer months. In our judgment, the new sources of uncertainty arising from model choice lead to quantitative changes in estimates without qualitative implications. Development of analytic models underlying the NMMAPS results involved multiple points of decision with assumptions: for example, choice of statistical model (e.g., GAM or GLM), adjustment for confounding factors (e.g., specification of temperature, season, and long-term trends in disease), and specification of exposure. Each of the decisions made by the modeler may affect the model results to a degree. While some sensitivity of findings to modeling decisions is inherent in estimating the small acute effects of particles on mortality, overall consistency of results across reasonable modeling choices is needed. We have found such consistency in these updated analyses of the NMMAPS data.

APPENDIX A. SENSITIVITY ANALYSES

National Average With Respect to Models for Heterogeneity

We have performed sensitivity analyses on the estimate of national average with respect to model assumptions about heterogeneity and spatial correlation (Table A.1). In the first model, known as the three-stage regional model (Daniels et al., 2003), we grouped the 88 counties into 7 geographic regions (Northwest, Upper Midwest, Industrial Midwest, Northeast, Southern California, Southwest, Southeast), following the stratification of the United States used in the *1996 Review of the National Ambient Air Quality Standards for Particulate Matter,*(U.S. Environmental Protection Agency, 1996). We assumed that city-specific estimates belonging to a particular region have a distribution with mean equal to the corresponding regional effect. This assumption implies that regional heterogeneity exists: City-specific estimates of the air pollution effects are shrunk toward their regional means, and regional means are shrunk toward the national mean, respectively. The results of this model are shown in Figures 6 and 9 and in Table A.2.

TABLE A.1. National Average Effects of PM_{10} at Lag 1 on Total Mortality Under Four Multipollutant Models and Four Prior Distributions on Heterogeneity Covariance Matrix

	Posterior means and 95% posterior regions			
	$PM_{10} + O_3$	$PM_{10} + O_3 + NO_2$	$PM_{10} + O_3 + SO_2$	$PM_{10} + O_3 + CO$
Prior 1	0.27 (0.12,0.44)	0.21 (−0.01,0.44)	0.21 (0.02,0.42)	0.24 (0.05,0.43)
Prior 2	0.25 (0.08,0.44)	0.22 (−0.04,0.50)	0.22 (−0.03,0.47)	0.20 (0.00,0.41)
Prior 3	0.28 (0.11,0.46)	0.21 (0.03,0.43)	0.20 (0.00,0.41)	0.24 (0.05,0.45)
Prior 4	0.24 (0.09,0.41)	0.21 (−0.02,0.46)	0.21 (−0.02,0.46)	0.20 (0.00,0.39)

Note. Prior 1 is a uniform prior on the shrinkage covariance matrix, Prior 2 is the reference prior, Prior 3 is the Jeffrey's prior, and Prior 4 is a flat prior on the second stage covariance matrix. See Everson and Morris (2000) for details on the prior distributions.

TABLE A.2. Regional Effects for PM_{10} at Lag 1 on Total Mortality From Nonexternal Causes and on Cardiovascular and Respiratory Mortality

	Posterior means and 95% posterior regions		
Regions	Total (baseline prior)	Total mortality (Prior A)	CVDRESP (baseline prior)
Northwest	0.18 (− 0.04,0.40)	0.21 (− 0.06,0.49)	0.29 (0.01,0.56)
Southwest	0.19 (− 0.10,0.48)	0.22 (− 0.10,0.55)	0.39 (0.02,0.75)
Southcal	0.27 (0.03,0.51)	0.30 (0.00,0.60)	0.31 (0.02,0.59)
Uppermidwest	0.13 (− 0.19,0.46)	0.19 (− 0.18,0.55)	0.26 (− 0.11,0.63)
Industmidwest	0.19 (0.04,0.35)	0.24 (0.00,0.47)	0.29 (0.08,0.49)
Northeast	0.41 (0.04,0.78)	0.38 (0.01,0.76)	0.50 (0.05,0.94)
Southeast	0.19 (− 0.07,0.45)	0.22 (− 0.07,0.51)	0.34 (0.03,0.66)
National	0.22 (0.03,0.42)	0.25 (0.03,0.48)	0.34 (0.10,0.57)

One limitation of this regional modeling approach is that two cities, far apart in terms of their geographical distance but belonging to the same geographical region, are considered more similar than two closer cities that belong to two separate geographical regions. To overcome this limitation, we relaxed the regional model assumption by developing a second model called the spatial correlation model (Dominici et al., 2002a). Here we assumed that each city-specific air pollution effect is shrunk toward the average air pollution effects in the neighboring cities, where the definition of neighboring cities is based on their geographical distance (Diggle et al., 1998).

The national average estimate is robust to these model assumptions. Posterior means and posterior 2.5th and 97.5th percentiles of the national average estimate for total mortality and PM_{10} at lag 1 can be calculated under three models:

1. Two-stage hierarchical model (our baseline approach applied to 90 cities), which assumes independence among the city-specific effects.
2. Three-stage regional model (described previously as applied to 88 cities).
3. Spatial correlation model (described previously as applied to 88 cities).

With these models, the results were 0.21 (0.04, 0.33), 0.22 (0.03, 0.40), and 0.22 (0.10, 0.38), respectively.

Figure A.1A shows the marginal posterior distributions of the overall effects under models 1, 2, and 3. As expected, model 2 shows a slightly larger posterior interval than models 1 and 3 because of the assumption of regional heterogeneity. More specifically, in model 2 the heterogeneity is defined as total variance (i.e., the sum of the variance across cities of the city-specific effects within each region plus the variance across regions of the regional estimates).

Figure A.1B shows the profile likelihood (obtained under a two-stage normal–normal hierarchical model) and the marginal posterior distributions of the standard

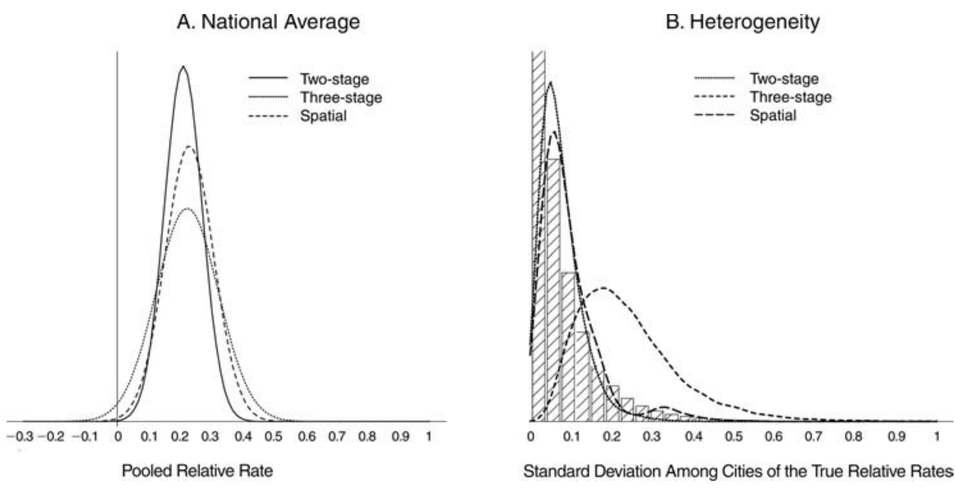

FIGURE A.1. Marginal posterior distributions of national average estimates of PM_{10} effects on total mortality from nonexternal causes at lag 1.

deviation among cities of the true relative rate under models 1, 2, and 3. A profile likelihood shows the weight of the evidence about the amount of heterogeneity. This profile likelihood gave the largest weights (heights of the histogram) at values close to zero, indicating homogeneity or almost no heterogeneity. The marginal posterior distributions of the between-city standard deviations under models 1 and 3 are similar to the profile likelihood. The larger posterior mean of between-city standard deviation under model 2 reflects the assumption of regional heterogeneity (that is, a larger total variance).

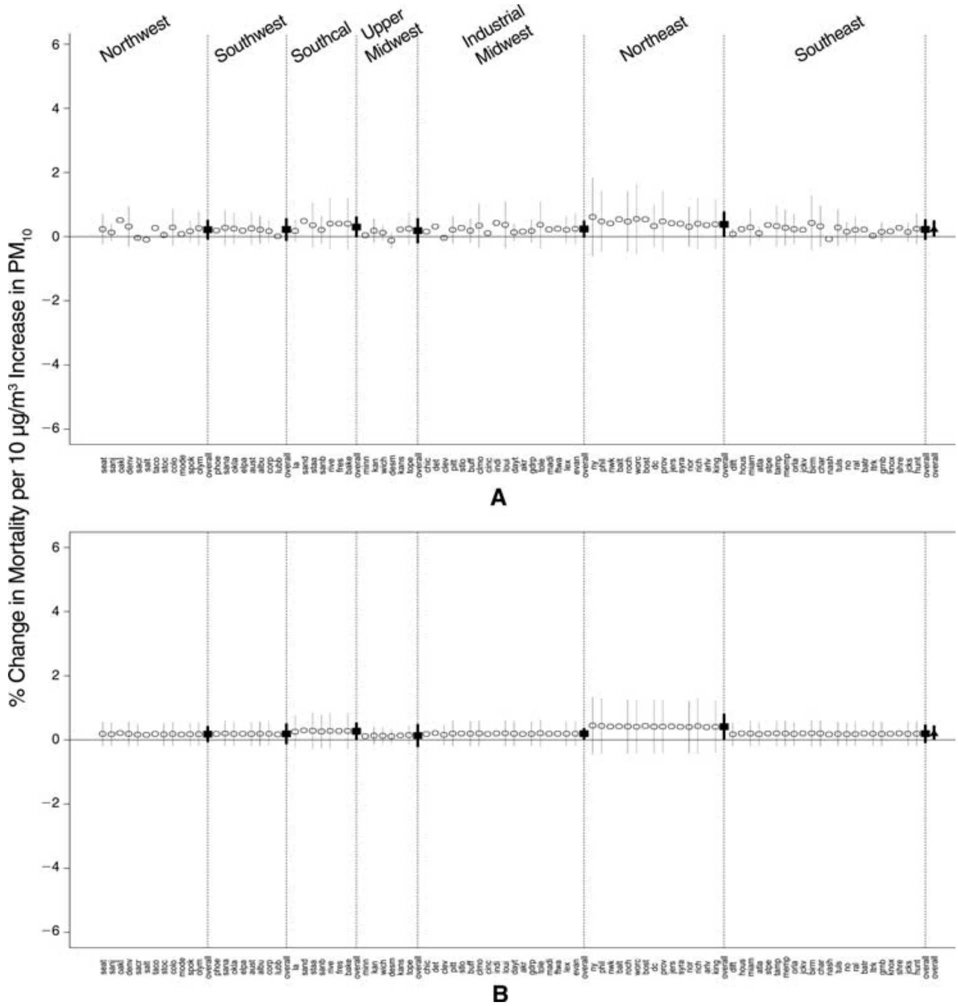

FIGURE A.2. City-specific posterior means and 95% posterior regions at lag 1 for each of 88 locations under both priors (model A, more heterogeneity within regions; B, noninformative about heterogeneity).

Prior Distributions for Heterogeneity Parameters Under a Three-Stage Regional Model

In combining the data across cities, it is necessary to make assumptions concerning the extent of heterogeneity in the effect of air pollution on mortality among the locations. The consequences of this assumption are explored below.

Let σ^2 and τ^2 denote the variance within region and the variance across regions, respectively, of the true air pollution effects. In our baseline analyses (prior model B), we allow a range from little or no to more substantial heterogeneity, and we assume noninformative priors on σ^2 and τ^2 (gamma [0.001, 0.001] for $1/\sigma^2$ gamma [0.001, 0.001] for $1/\tau^2$).

In an alternative to our baseline analysis, which uses noninformative priors, we assume heterogeneity of the city-specific effects within regions (prior model A). More specifically, in prior model A, we allow the assumption that there is heterogeneity across cities, possibly substantial in size, and exclude within-region homogeneity (inverse gamma [3,1] for σ^2). The effect of this prior assumption with respect to prior B is twofold: It produces city-specific relative risk estimates that draw less heavily on data from each city, and it yields slightly more conservative confidence bands on the overall relative risk.

Figure A.2 shows city-specific posterior means and 95% confidence regions for each of the 88 locations under the baseline prior (prior model B—noninformative about heterogeneity) and the alternative prior distribution (prior model A—assuming heterogeneity within regions). Also shown are the posterior estimates and 95% intervals for the regional and overall means. Estimates of the overall PM_{10} relative risk are similar for the two prior models (B: 0.22 [0.02, 0.43], A: 0.25 [0.03, 0.47]). Note that under the baseline prior B, the city-specific and region-specific estimates are more like one another. This is because the posterior distributions for the within-region and between-region standard deviations of the true air pollution effects (σ and τ) are centered at mean 0.08 and 0.16, respectively, indicating a small degree of heterogeneity of the effects within a region and across regions. For example, a median value of $\sigma = 0.08$ corresponds to 95% of cities having the PM_{10} relative risks of $\pm 2 \times 0.08 = \pm 0.16$ or approximately ±40% of the overall relative risk.

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