Estimating the Mortality Impacts of Particulate Matter: What Can Be Learned from Between-Study Variability?

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Epidemiologic studies of the link between particulate matter (PM) concentrations and mortality rates have yielded a range of estimates, leading to disagreement about the magnitude of the relationship and the strength of the causal connection. Previous meta-analyses of this literature have provided pooled effect estimates, but have not addressed between-study variability that may be associated with analytical models, pollution patterns, and exposed populations. To determine whether study-specific factors can explain some of the variability in the time–series studies on mortality from particulate matter ≤ 10 μm in aerodynamic diameter (PM_{10}), we applied an empirical Bayes meta-analysis. We estimate that mortality rates increase on average by 0.7% per 10 μg/m^3 increase in PM_{10} concentrations, with greater effects at sites with higher ratios of particulate matter ≤ 2.5 μm in aerodynamic diameter ($PM_{2.5}$)/PM_{10}. This finding did not change with the inclusion of a number of potential confounders and effect modifiers, although there is some evidence that PM effects are influenced by climate, housing characteristics, demographics, and the presence of sulfur dioxide and ozone. Although further analysis would be needed to determine which factors causally influence the relationship between PM_{10} and mortality, these findings can help guide future epidemiologic investigations and policy decisions. *Key words*: **air pollution, confounding, empirical Bayes, epidemiology, hierarchical linear models, meta-analysis, mortality, particulate matter.** *Environ Health Perspect* **108:109–117 (2000). [Online 27 December 1999]**
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Although the link between particulate matter (PM) and mortality has been investigated for some time, the interpretation of this connection remains controversial. Early cross-sectional studies (*1–3*) found that PM had a significant association with mortality rates, measured as total suspended particles (TSP), sulfates, or other particle size distributions [including particulate matter ≤ 10 μm in aerodynamic diameter (PM_{10})]. These studies were bolstered by more recent time–series studies, many of which found statistically significant increases in all-age and all-cause mortality associated with increases in ambient PM concentrations (*4–24*). However, some recent studies found that the PM–mortality relationship was statistically insignificant at the 95% confidence level (*25–28*), whereas others found both significant and insignificant relationships, depending on the study setting (*29–32*). In addition, some reanalyses of previous studies argued that reported positive findings could be explained by correlated gaseous pollutants, weather, season, or the analytical model used (*33–35*). Studies that considered multiple particle sizes have come to different conclusions about which size range is largely responsible for increased mortality, with recent evidence on the role of fine particles (*31*) and on stronger relationships with PM_{10} (*29*).

Although there is some toxicologic evidence that supports the role of PM in human mortality (*36–38*), the mechanisms of action are not yet well understood, placing epidemiologic evidence at the center of the debate. The variability among epidemiologic findings and their interpretations played a major role in the contentious debate (*39*) over the revised National Ambient Air Quality Standard for PM (*40*).

Because the epidemiologic studies differ in a number of ways, the variability in findings could be a function of site-specific differences, analytical decisions, or simply random variation. In these studies, PM concentrations were measured in a number of ways, with conversion between measurements impeded by geographic and temporal variability in particle size distributions. These studies were set in different geographic regions, with a wide range of ambient pollution concentrations and correlations between PM and gaseous pollutants. The study sites differed in their demographic compositions, residential environments, and baseline mortality rates and patterns. The studies used different statistical models, including different lag times and averaging times, controls for confounding pollutants, and consideration of climate and season. Finally, the studies were conducted by a limited number of research groups, suggesting potential correlations related to analytical methods and choices.

In this study, we focused on whether any of these characteristics can explain some of the differences in effect estimates, and we attempted to determine the magnitude of the independent relationship between PM_{10} and mortality (both at specific sites and averaged across sites). Previous reviews and meta-analyses have not adequately answered these questions because of analytical limitations. Many review articles have relied on qualitative descriptions of pros and cons for a subset of studies, discussing the credibility of the evidence related to potential confounding by climate or correlated pollutants. Although these analyses are valuable, the lack of a quantitative base leads these reviews to very different conclusions depending on the studies chosen and the points argued; some authors conclude that the existing epidemiologic evidence clearly shows a causal relationship (*41–44*), but others feel that this relationship is spurious (*45,46*).

Past meta-analyses have used methods such as averages of central estimates (*47*) and variance-weighted averages of percentage increases in mortality per unit of pollution (*48*) or of PM_{10}-mortality elasticities (*49*). All of these models implicitly assume fixed effects, in which each effect estimate β_i is a random sample from a single underlying distribution $N(\mu_i, \sigma_i^2)$. The U.S. Environmental Protection Agency (EPA) criteria document (*50*) used random effects models to estimate PM mortality, assuming that each β_i is drawn from $N(\mu_i, \sigma_i^2)$, where the μ_i are random values drawn from $N(\mu, \tau^2)$, accounting for between-study variability. This is an appealing concept because of the expected heterogeneity among sampling sites.

Although random effects models quantify the amount of residual variance that can be explained by study-specific factors, they cannot determine what these factors are or how they would influence the effect estimates. Because of the number of potential confounders and effect modifiers for PM mortality, these factors must be quantitatively evaluated before determining the true relationship between PM and mortality.

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To evaluate these factors, we conducted a screening analysis by applying random effects models to stratifications of study estimates. We evaluated confounders in a multivariate context using empirical Bayes (EB) meta-analysis, which considers mixed effects in a two-stage hierarchical linear model, decomposing within-study and between-study variability. We used this model because of its ability to incorporate both specified study characteristic differences and random effects, and because it can provide posterior site-specific estimates using information from all studies. We can use these estimates to determine the mortality impacts directly attributable to PM, to pinpoint confounding variables, and to estimate the expected effects in new settings. These findings would be useful for externality assessment or benefit–cost analysis of PM remediation; if effect estimates vary across populations, this information could be incorporated with demographics and emission profiles for use in site-specific impact analyses.

Data Collection and Evaluation

We gathered time–series studies for this analysis from the EPA criteria document (*50*), previously published meta-analyses or review articles, and Medline (National Library of Medicine, Bethesda, MD), and Current Contents (Institute for Scientific Information, Philadelphia, PA) searches for studies including the key words "mortality" and "particle" or "particulate matter." We excluded studies if they did not contain basic population and concentration data or if they lacked gravimetric measures of PM (although studies that conducted on-site calibration between optical measures and gravimetric measures were included). We also excluded studies that only calculated elasticities without considering absolute concentrations, that did not report sampling variability, that did not report single-pollutant estimates, or that focused only on respiratory or elderly mortality. Finally, we excluded studies if the same authors reanalyzed the data in an updated article. Analyses of the same site and time period by different authors are all included, with the potential effects of double-counting considered in the analysis.

For our models, we assumed that these studies were independent samples from a random distribution of the conceivable population of studies. Clearly, given potential overweighting of sites and multiple studies conducted by the same authors using the same methodology, this assumption was difficult to support. To determine whether our results were sensitive to study selection, we conducted analyses with different subsets of studies in the sensitivity analysis. We also assessed the assumption of random selection by comparing the characteristics of our sample with the population at large.

In total, we selected 29 estimates of the PM-mortality link from 21 published studies. Of these 29 estimates, 14 were from PM_{10} analyses in the United States, 4 were from PM_{10} analyses outside the United States, 5 were from TSP analyses in the United States, and 6 were from TSP analyses outside the United States. We converted all of the TSP estimates to PM_{10} using reported values [0.50; (*18*)] or a default value of 0.55. Because of errors associated with this conversion, we considered PM_{10} and TSP studies both separately and in conjunction.

With these 29 estimates, we used reported effect estimates that did not analytically control for correlated gaseous pollutants. This was mandated by the fact that only 11 of the 29 single-pollutant estimates were accompanied by multivariate estimates (many authors controlled for confounding by choosing sites with minimal concentrations of key pollutants or by studying multiple sites with a range of pollution patterns). These effect estimates also allowed us to use the EB model to estimate confounding by gaseous pollutants. When studies gave multiple effect estimates, we chose the estimate that was presented by the authors as most reasonable considering all short- and long-term time trends, as well as climate and seasonal factors.

We considered three basic categories of predictors that might act as confounders or effect modifiers for biologic or physical reasons: pollution-related variables, demographic/site characteristics, and analytical factors (Table 1). In the first category, we derived ambient PM concentrations from the study text to account for possible dose–response nonlinearities. In addition, we wanted to estimate the relationship between PM concentrations and concentrations of gaseous pollutants, which may be independently linked with premature mortality [ozone (O_3), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), and carbon monoxide (CO)]. To estimate these relationships, we gathered daily average gaseous pollutant and PM concentrations for the relevant time periods from the Aerometric Information Retrieval System (AIRS; U.S. EPA, Washington, DC) and from the Harvard Six Cities Study (*51*). With these data, we ran univariate linear regressions with PM as the independent variable to estimate the magnitude of gaseous pollutant concentration change associated with a 1-μg/m^3 increase in PM concentrations. These regression coefficients are more informative than correlations because they account for concentration magnitudes as well as relationships between pollutants. We also estimated ratios of particulate matter ≤ 2.5 μm in aerodynamic diameter ($PM_{2.5}$)/PM_{10} from study texts (*29,31*), AIRS data covering the study sites and time periods, the EPA criteria document (*50*), or by using data collected from nearby sites.

We extracted baseline mortality rates from the studies. We also used data on the percentage of the population older than 65 years of age and the percentage of the population in poverty from the 1990 U.S. Census (U.S. Census Bureau, Suitland, MD). The census data were used to incorporate factors such as age-dependent mortality and accessibility of health care. Because personal exposures can be affected by indoor air quality and air exchange rates, we included multiple housing characteristics in the analysis (prevalence of central air conditioning, gas stoves, and warm air furnaces). These characteristics were taken from the American Housing Survey conducted by the U.S. Census Bureau, using data from the nearest metropolitan area for the relevant study years. We estimated heating and cooling degree days

Table 1. Predictors used in the EB model and the primary reasons for their inclusion.

Predictors	Primary reasons for inclusion
O_3, SO_2, NO_2, CO regression coefficients	Potential independent relationship between gaseous pollutants and acute mortality
$PM_{2.5}/PM_{10}$ ratio	Hypothesized role of fine particles because of their ability to enter the respiratory tract
Ambient PM_{10} concentration	Possibility of nonlinear concentration–response function (threshold or saturation effect)
Baseline mortality rate, population older than 65 years of age (%), population in poverty (%)	Areas with a higher percentage of sick or elderly people might have a greater effect if people with preexisting illness are affected
Gas stove prevalence	Potential indoor air quality influence on mortality
Warm air furnace prevalence	Potential indoor air quality influence on mortality, influence on penetration of outdoor particles
Central air conditioning prevalence	Influence on penetration of outdoor particles, activity patterns
Heating and cooling degree days	Influence on secondary particle formation, activity patterns, health effects related to heat or cold
Averaging time and lag time	Time period of exposure influencing acute mortality unknown

Abbreviations: CO, carbon monoxide; NO_2, nitrogen dioxide; O_3, ozone; SO_2, sulfur dioxide; $PM_{2.5}$, particulate matter ≤ 2.5 μm in aerodynamic diameter.

for all sites from the International Station Meteorological Climate Summary (*52*) to approximate differences in climate. Averaging time and lag time were extracted from each study to incorporate the influence that analytical decisions can have on the PM-mortality relationship.

Analytical methodology. In this paper, we focused our analysis on standard random effects and EB models. For both models, the derivations we present are only meant to provide familiarity with the underlying assumptions and terminology. More comprehensive model derivation can be found in papers by DerSimionian and Laird (*53*) and Raudenbush and Bryk (*54*).

We determined pooled central estimates using the random effects model (RE) derived by DerSimionian and Laird (*53*). This model assumes that β_i (the reported effect from study *i*) is comprised of a true effect μ_i with a sampling error e_i that is $N(0, s_i^2)$ for all $i = 1, ..., n$. The true effect μ_i is decomposed into the mean population effect μ and a between-study variability term δ_i that is $N(0, \tau^2)$.

We assessed homogeneity of the studies with Cochran's *Q*-statistic, defined as

$$Q = \Sigma w_i(\beta_i - \beta^*)^2 \qquad [1]$$

where w_i is $1/s_i^2$ and β^* is the weighted average of the effect estimates, weighted by w_i. Under the null hypothesis of homogeneity, *Q* is approximately a χ^2 statistic with $n - 1$ degrees of freedom. Given this calculation, τ^2 can be estimated as

$$\tau^2 = \max\left[0, \left(\frac{(Q - (n-1))}{\sum w_i - \frac{\sum w_i^2}{\sum w_i}}\right)\right] \qquad [2]$$

Finally, we define w_i^* as $1/(s_i^2 + \tau^2)$, and the estimate of μ is the weighted average of the effect estimates, weighted by w_i^*. This methodology is an extension of simple variance weighting, incorporating study heterogeneity.

We incorporated study characteristics using a mixed effects EB model derived by Raudenbush and Bryk (*54*). With all variables defined as above, μ_i is assumed to be a function of both known study characteristics and random error. Thus, rather than defining $\mu_i = \mu + \delta_i$, we define $\mu_i = W_i'\gamma + \delta_i$, where W_i is a $(q \times 1)$ vector of characteristics varying by study, and γ is a $(q \times 1)$ vector of coefficients estimated to describe between-study variability. In this model, τ^2 is determined by maximum likelihood methods, where the log of the likelihood function is proportional to:

$$-\Sigma\log(s_i^2 + \tau^2) - \log|\Sigma(s_i^2 + \tau^2)^{-1} W_i W_i'| - \Sigma(s_i^2 + \tau^2)^{-1}(\beta_i - W_i'\gamma^*)^2 \qquad [3]$$

In Equation 3, γ^* is the maximum likelihood estimate for the vector of derived coefficients, defined as $(\Sigma \lambda_i W_i W_i')^{-1} \Sigma \lambda_i W_i \beta_i$, where λ_i is $\tau^2/(s_i^2 + \tau^2)$.

Given these iteratively derived estimates, the maximum likelihood estimate for μ_i is the weighted average of the reported estimate β_i and the between-study variability estimate $W_i'\gamma^*$, where the weight on β_i is $\tau^2/(\tau^2 + s_i^2)$ and the weight on $W_i'\gamma^*$ is $s_i^2/(\tau^2 + s_i^2)$. As explained by Raudenbush and Bryk (*54*), this allows data drawn from completely homogeneous populations to be described by study characteristics, whereas data drawn with no knowledge of other studies are best described by the prior effect estimates. For other scenarios, a weighted average of these values that minimizes squared-error loss is most appropriate. Thus, EB provides posterior estimates for each study, in contrast to RE, in which the sole output is the pooled effect estimate.

Results

Summary of study findings. The effect estimates from all of the studies are presented in Table 2 as the percentage change in daily mortality associated with a 10-$\mu g/m^3$ increase in PM_{10} concentrations. The central effect estimates ranged from a low of -0.5% to a high of 2.6%. For these studies, the pooled random effects estimate is 0.73% [95% confidence interval (CI), 0.59–0.87%], with significant heterogeneity in effect estimates ($p < 0.01$). The pooled estimates were similar when the studies were stratified by location and particle measure, with estimates of 0.63 and 0.83% for PM_{10} and TSP, respectively, and 0.70 and 0.80% for U.S. and non-U.S. studies, respectively. Stratifying across both dimensions, we found pooled estimates of 0.67% for PM_{10}/U.S., 0.57% for PM_{10}/non-U.S., 0.77% for TSP/U.S., and 0.93% for TSP/non-U.S. studies. Because of the relative stability of estimates from studies within the United States and the uniformity of data sources, we focused our analytical efforts on these 19 study estimates. Thus, our central random effects estimate was 0.70% (CI, 0.54–0.86%), with marginal heterogeneity in effect estimates ($p = 0.1$). In comparison, previous meta-analyses have estimated pooled values of 1.0% (*47,48,55*) and 0.5–1.0% (*50*), using different subsets of studies.

For these 19 effect estimates, the relationship between daily average PM_{10} concentrations and gaseous pollutant concentrations varied widely (Table 3). There appeared to be some geographic variability, with higher SO_2 coefficients in the East Coast and Rust Belt and higher O_3 coefficients in the Midwest. If any of these pollutants were independently related to increased mortality, this would imply differences in the PM_{10}-mortality relationship by site. The relationships between coefficients are similar if high-hour gaseous pollutant concentrations are considered in lieu of daily average concentrations.

Figure 1 shows the relationships between effect estimates and potential confounders/effect modifiers. To better understand the univariate relationships, we stratified the 19 effect estimates across some of these variables. This stratification shows a strong relationship between the $PM_{2.5}/PM_{10}$ ratio and PM_{10} mortality rates, with weaker relationships for a number of other variables (Table 4). However, some of these relationships are counterintuitive, which may be a result of confounding due to strong correlations between predictors (Table 5).

EB model. If we apply the EB model to our 19 U.S. study estimates, a model without predictors yields an estimated grand mean of 0.70% (CI, 0.54–0.85%), similar to the random effects estimate. To add predictors to the model from a large set of potential candidates, given a small number of studies and correlated predictors, we followed the methodology of Bryk and Raudenbush (*56*). We used the "*t*-to-enter" statistic, which was based on a simple linear regression of the predictor in question on the EB residuals. Like forward regression, predictors were entered one at a time, using a threshold of $t = 1$.

For these studies, the predictor with the greatest "*t*-to-enter" was the warm air furnace prevalence ($t = 1.43$). Adding this predictor to the model decreased τ^2 from 0.032 to 0.020, indicating that unexplained heterogeneity remained. Additional variables were added, yielding six other significant predictors, which entered the model in the order that they are presented in Table 6. The $PM_{2.5}/PM_{10}$ ratio was the most statistically significant covariate in the final model. With these predictors, τ^2 was reduced to 0.00006, indicating that much of the between-study heterogeneity was explained. The value of τ^2 was slightly lower if only the first three predictors were included in the model. Interaction terms (e.g., between air conditioning prevalence and cooling degree days) were tested and were not significant.

To assess confounding with gaseous pollutants other than SO_2, despite the lack of statistical significance, we also generated an EB model with all of the significant predictors and gaseous pollutant regression coefficients. As shown in Table 6, these coefficients are statistically insignificant and only the O_3 coefficient has any explanatory power.

We can use our EB model to make posterior estimates for these 19 studies, and we can also estimate the degree to which the association between mortality and PM_{10} is influenced by correlated gaseous pollutants.

Using the optimum model, the posterior EB estimates for the 19 studies have reduced heterogeneity, with values largely ranging between 0.6 and 1.0%. The heterogeneity is further reduced if the model is limited to three predictors. To estimate average confounding by gaseous pollutants, we used the EB model with all of the gaseous pollutant terms forced into the model. When we used this model with the mean population characteristics for all predictors, the average mortality effect was 0.7%. If we control for correlated pollutants by setting the gaseous pollutant regression coefficients to zero, our estimate is reduced to 0.2%. Because forcing insignificant terms into the model may result in overmodeling, we also estimated confounding using our optimum model, which only considered confounding from SO_2. Using this model, the effect for a site with mean study characteristics is reduced from 0.7 to 0.4%.

Sensitivity analysis. Because of the small number of study estimates and uncertainties in many dimensions, a detailed sensitivity analysis is needed before conclusions can be made about potential causal predictors of the PM_{10}-mortality relationship. We tested the sensitivity of our findings to study selection and model selection.

First, to test whether the inclusion of studies measuring TSP induced estimation errors or changed the variables entering the model, we considered only the 14 PM_{10}/U.S. studies. For these studies, we found that the $PM_{2.5}/PM_{10}$ ratio entered the EB model first, followed by heating degree days, central air prevalence, gas stove prevalence, the O_3 regression coefficient, and averaging time. For the terms in common, all of the coefficients were similar in magnitude and direction to the optimum model. When all of the gaseous pollutants were forced into the model, the O_3 and SO_2 regression coefficients remained the most statistically significant gaseous pollutant terms.

We also expanded the analysis to include all 29 study estimates. Because we only have data for a subset of predictors for all studies, we could not make direct comparisons with our 19-study model. We considered the subset of predictors that included ambient PM_{10} concentration, averaging time and lag time, percent of the population older than 65 years of age, baseline mortality rate, heating and cooling degree days, and dummy variables for PM_{10}/TSP and U.S./non-U.S. studies. Of these predictors, only baseline mortality rate entered the EB model, with significant unexplained heterogeneity ($p = 0.005$). The grand mean estimate was similar to that of the 19-study model (0.72%).

We also tested the sensitivity of our findings to the decision to include multiple studies of the same location, to avoid the potential effects of double counting. We reduced the sample size to 13, with 48 potential study combinations, when we considered only one study per city. The $PM_{2.5}/PM_{10}$ ratio was the only predictor that entered the EB model for all combinations of studies. In addition, gas stove prevalence, the SO_2 and O_3 regression coefficients, warm air furnace prevalence, heating degree days, and percent of the population older than 65 years of age appeared in at least two-thirds of study combinations (in descending order of frequency). The $PM_{2.5}/PM_{10}$ ratio was the first predictor that entered the regression for 56% of the study combinations.

Finally, we tested the sensitivity of our findings to the choice of an EB model for the inclusion of study characteristics. We applied a random effects regression model (*57*) to the 19

Table 2. Summary of estimates from PM-mortality studies.

Site	Study period	Change in daily mortality (%)/10 μg/m³ increase in PM_{10} (CI)	PM measurement[a]	Reference
Birmingham, AL	1985–1988	1.0 (0.2–1.9)	PM_{10}	(*8*)
Boston, MA	1979–1986	1.2 (0.7–1.7)	PM_{10}	(*31*)
Cook County, IL	1985–1990	0.5 (0.3–0.7)	PM_{10}	(*12*)
Cook County, IL	1985–1990	0.5 (0.1–0.9)	PM_{10}	(*30*)
Knoxville, TN	1980–1987	0.9 (0.1–1.8)	PM_{10}	(*31*)
Knoxville, TN	1985–1986	1.6 (-1.3–4.6)	PM_{10}	(*29*)
Los Angeles, CA	1985–1990	0.5 (0.0–1.0)	PM_{10}	(*25*)
Portage, WI	1979–1987	0.7 (-0.4–1.7)	PM_{10}	(*31*)
Salt Lake, UT	1985–1990	-0.2 (-1.1–0.6)	PM_{10}	(*29*)
St. Louis, MO	1979–1987	0.6 (0.1–1.0)	PM_{10}	(*31*)
St. Louis, MO	1985–1986	1.5 (0.1–2.9)	PM_{10}	(*29*)
Steubenville, OH	1979–1987	0.9 (0.1–1.6)	PM_{10}	(*31*)
Topeka, KS	1979–1988	-0.5 (-2.0–0.9)	PM_{10}	(*31*)
Utah Valley, UT	1985–1989	1.3 (0.2–2.5)	PM_{10}	(*15*)
Birmingham, UK	1992–1994	1.1 (0.1–2.1)	PM_{10}	(*23*)
Brisbane, Australia	1987–1993	0.8 (0.3–1.4)	PM_{10}	(*22*)
Amsterdam, The Netherlands	1986–1992	0.6 (-0.1–1.4)	PM_{10}	(*28*)
Santiago, Chile	1989–1991	0.3 (0.1–0.6)	PM_{10}	(*14*)
Philadelphia, PA	1974–1988	0.6 (0.2–1.0)	TSP	(*21*)
Steubenville, OH	1974–1984	0.5 (0.1–0.9)	TSP	(*35*)
Steubenville, OH	1974–1984	0.6 (0.2–1.0)	TSP	(*6*)
Philadelphia, PA	1973–1980	1.2 (0.7–1.7)	TSP	(*7*)
Cincinnati, OH	1977–1982	1.1 (0.5–1.7)	TSP	(*10*)
Mexico City, Mexico	1990–1992	1.0 (0.6–1.3)	TSP	(*18*)
Toronto, Canada	1980–1994	0.7 (0.3–1.0)	TSP	(*24*)
Rotterdam, The Netherlands	1983–1991	1.0 (0.2–1.8)	TSP	(*19*)
Koln, Germany	1975–1985	0.3 (-0.2–0.9)	TSP	(*32*)
Zurich, Switzerland	1984–1989	0.7 (0.0–1.4)	TSP	(*17*)
Basel, Switzerland	1984–1989	2.6 (1.6–3.6)	TSP	(*17*)

[a]All TSP estimates are converted to PM_{10} using a factor of 0.55 unless a conversion factor is provided in the article [0.50; Mexico City, (*18*)].

Table 3. Coefficients of univariate regressions of daily average concentrations of ozone, nitrogen dioxide, sulfur dioxide, and carbon monoxide on daily average PM_{10} concentrations for 19 U.S. studies (all pollutants measured in micrograms per cubic meter).

Site	Study period	Reference	O_3 β	O_3 SE	NO_2 β	NO_2 SE	SO_2 β	SO_2 SE	CO β	CO SE
Birmingham, AL	1985–1988	(*8*)	0.21	(0.025)	0.41	(0.098)	0.077	(0.015)	17.0	(0.67)
Boston, MA	1979–1986	(*31*)	0.41	(0.064)	0.57	(0.040)	0.63	(0.047)	8.4	(3.2)
Cook County, IL	1985–1990	(*12,30*)	0.35	(0.061)	0.43	(0.072)	0.37	(0.048)	6.9	(1.5)
Knoxville, TN	1980–1987	(*31*)	0.29	(0.041)	0.25	(0.019)	0.082	(0.026)	24.8	(4.9)
Knoxville, TN	1985–1986	(*29*)	0.23	(0.10)	0.18	(0.044)	0.0048	(0.050)	29.1	(4.7)
Los Angeles, CA	1985–1990	(*25*)	0.11	(0.061)	1.64	(0.14)	0.14	(0.016)	43.3	(3.5)
Portage, WI	1979–1987	(*31*)	0.67	(0.14)	0.18	(0.061)	0.11	(0.048)	18.6	(6.9)
Salt Lake, UT	1985–1990	(*30*)	-0.39	(0.033)	0.90	(0.055)	0.43	(0.020)	47.5	(5.6)
St. Louis, MO	1979–1987	(*31*)	0.69	(0.043)	0.33	(0.025)	0.37	(0.032)	10.8	(3.2)
St. Louis, MO	1985–1986	(*29*)	0.87	(0.093)	0.24	(0.046)	0.34	(0.055)	9.1	(6.4)
Steubenville, OH	1979–1987	(*31*)	0.09	(0.035)	0.32	(0.016)	1.30	(0.052)	16.5	(2.3)
Topeka, KS	1979–1988	(*31*)	0.71	(0.044)	0.17	(0.019)	0.067	(0.014)	-3.8	(4.2)
Utah Valley, UT	1985–1989	(*15*)	0.13	(0.057)	0.72	(0.026)	0.43	(0.020)	19.7	(1.7)
Philadelphia, PA	1974–1988	(*21*)	0.36	(0.030)	1.34	(0.042)	1.55	(0.030)	25.9	(0.74)
Steubenville, OH	1974–1984	(*6,35*)	0.12	(0.01)	0.23	(0.21)	0.60	(0.019)	4.3	(0.48)
Philadelphia, PA	1973–1980	(*7*)	0.16	(0.036)	1.35	(0.075)	1.89	(0.045)	31.6	(1.1)
Cincinnati, OH	1977–1982	(*10*)	0.26	(0.030)	1.04	(0.63)	0.37	(0.037)	15.5	(0.70)

U.S. study estimates, which estimated a grand mean value of 0.71% (CI, 0.54–0.87%), which was nearly identical to EB. When all predictors from the optimum model were included, the coefficients and standard errors were nearly identical to the EB model, with similar posterior effect estimates.

Discussion

Clearly, interpretation of the above findings is the most difficult portion of this analysis. Of all of the variables tested, the $PM_{2.5}/PM_{10}$ ratio appears to be the strongest predictor of the relationship between PM_{10} and mortality. The positive coefficient for the $PM_{2.5}/PM_{10}$ ratio provides additional evidence of the role of fine particles in increased mortality rates.

Although not as robust, other variables entering the model could have some interesting implications if proven valid. The significance of the SO_2 regression coefficient (and

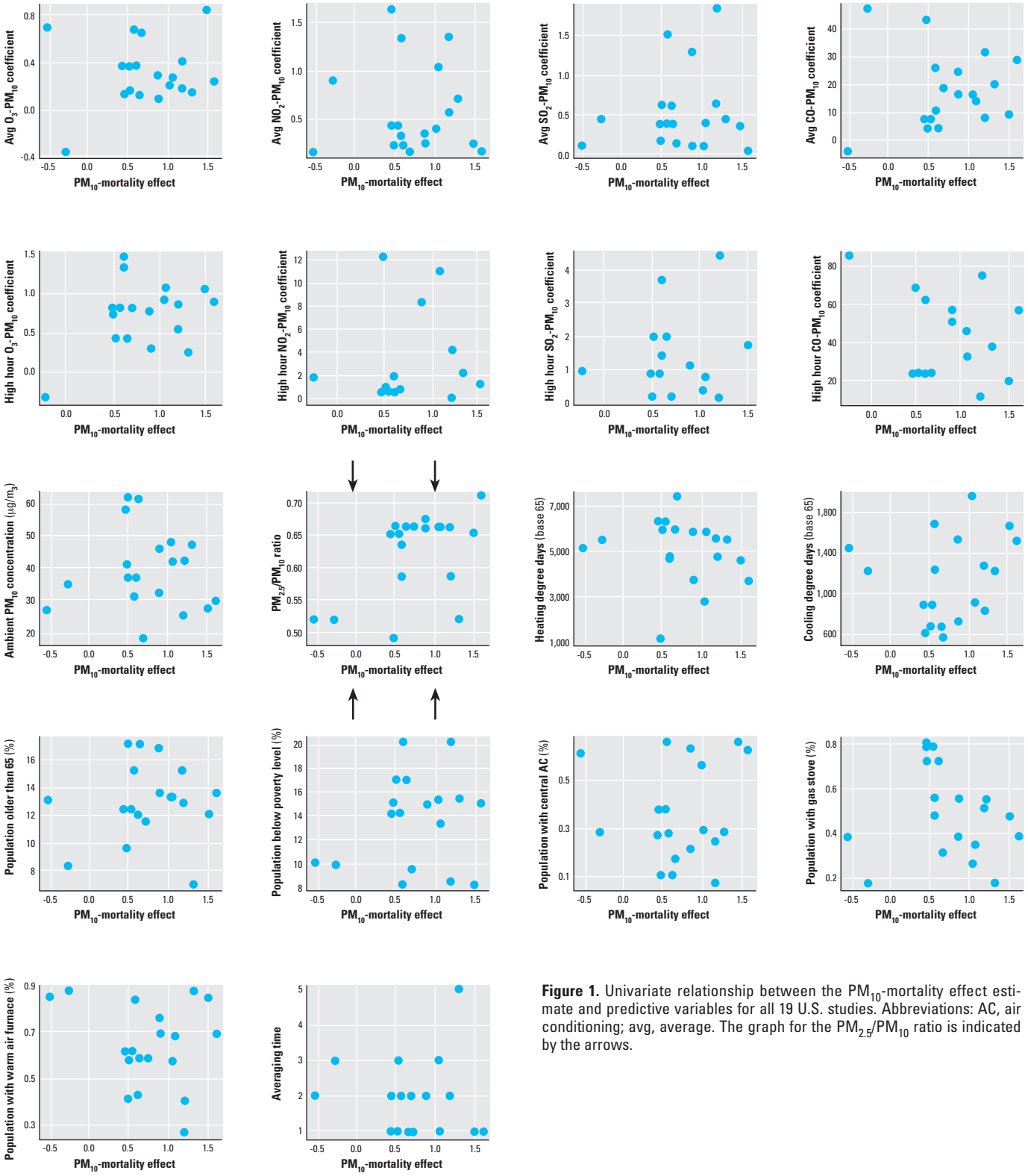

Figure 1. Univariate relationship between the PM_{10}-mortality effect estimate and predictive variables for all 19 U.S. studies. Abbreviations: AC, air conditioning; avg, average. The graph for the $PM_{2.5}/PM_{10}$ ratio is indicated by the arrows.

the O_3 regression coefficient in many subanalyses) might imply an independent link with mortality for these pollutants, with the SO_2 term potentially linked to sulfate particles as well as gaseous pollutant effects. The negative coefficient for heating degree days could imply a greater mortality effect in warmer climates, possibly related to more rapid conversion of NO_2 and SO_2 to fine particles, heat-related phenomena, or activity patterns. The negative coefficient for warm air furnace prevalence could be related in part to its correlation with central air conditioning, with the two components together influencing the penetration of particles from the outdoors.

The negative coefficient for gas stove prevalence is puzzling because there is no evidence of beneficial health effects from increased exposure to combustion pollutants related to gas stoves. This coefficient may be a proxy for terms that are strongly correlated with gas stove presence. For example, gas stove prevalence is higher in cities with fewer cooling degree days; therefore, a negative coefficient would imply a positive relationship with cooling degree days (supporting the greater effects in warmer climates). Similarly, the negative coefficient for the percentage of elderly is counterintuitive, but may be related to a strong positive correlation with terms such as the $PM_{2.5}/PM_{10}$ ratio and the SO_2 regression coefficient.

Although these explanations are plausible, there are a number of barriers that made it difficult to reach definitive conclusions. The model findings are often dependent on a few studies, leading different variables to enter the model with different subsets of studies. Because the $PM_{2.5}/PM_{10}$ ratio is the only variable that is significant across nearly all of the study combinations, the validity of other terms can be questioned. The magnitude of the EB coefficient, even for the $PM_{2.5}/PM_{10}$ ratio, depends on the variables included in the model, given a limited number of studies and high correlations between predictors.

Although multivariate analyses are needed to help distinguish among numerous potential predictors, the lack of independence can pose problems, particularly with a large number of predictors. If we use only three predictors in the EB model, the coefficient for the $PM_{2.5}/PM_{10}$ ratio is reduced from 8.7 to 2.3, demonstrating this influence. Similarly, findings such as the negative coefficients for the percentage of elderly or for gas stove prevalence may be a function of these correlations. These problems are exacerbated by our inability to conduct a complete analysis on all 29 study estimates.

We did not include all analytical differences in our model; study authors used analytical models and methods of controlling for weather that differed in a number of ways which could not be captured quantitatively. Because analytical methods to deal with climate have been targeted as crucial in understanding the true PM effect, this omission is a limitation of our analysis. Analytical methodology could also significantly influence the correlations among study findings because of the dependence of model selection on the author and the time period when the study was conducted.

In addition, some of the predictors that we included in the model may not measure the desired dimensions or may not represent the actual characteristics of the site. Heating and cooling degree days are crude proxies for climate, as weather patterns related to humidity or temperature extremes might be more likely to influence mortality rates. Our housing characteristic data were drawn from the nearest metropolitan area, which may not properly represent nonurban settings. The gaseous pollutant coefficients may not capture the complete relationship between pollutants, particularly if the dose–response relationships are nonlinear or have thresholds, or if peak exposures are more important than daily averages. To test the latter premise, we ran the EB model with high-hour gaseous pollutant concentrations rather than daily average concentrations, and the findings were similar. In general, there may be differences between concentration patterns and exposure patterns, particularly if large populations are represented by a small number of monitors.

Because of the high correlations between predictors, it is difficult to attribute causality to any one variable. Many of the patterns in

Table 4. Stratified analysis of the 19 U.S. PM-mortality studies.

Category	Group	Value	CI
All studies	–	0.70	0.54–0.86
Pollutant measure	PM_{10}	0.67	0.46–0.88
	TSP	0.77	0.51–1.02
$PM_{2.5}/PM_{10}$ ratio	< 0.57	0.31	-0.35–0.97
	0.57–0.64	0.68	0.44–0.91
	> 0.65	0.81	0.61–1.01
Heating degree days	< 5,000	0.78	0.56–1.01
	> 5,000	0.65	0.43–0.86
Averaging time	1 day	0.65	0.46–0.84
	> 1 day	0.73	0.49–0.97
Population > 65 years of age (%)	< 0.13	0.64	0.39–0.88
	> 0.13	0.77	0.57–0.97
With central air conditioning (%)	< 0.30	0.76	0.54–0.98
	> 0.30	0.57	0.39–0.74
With gas stove (%)	< 0.50	0.74	0.40–1.08
	> 0.50	0.69	0.51–0.87
With warm air heating (%)	< 0.60	0.77	0.56–0.99
	> 0.60	0.63	0.40–0.86
O_3 regression coefficient	< 0.30	0.76	0.53–1.00
	> 0.30	0.64	0.43–0.86
SO_2 regression coefficient	< 0.40	0.60	0.44–0.75
	> 0.40	0.76	0.48–1.04
CO regression coefficient	< 16	0.66	0.46–0.86
	> 16	0.76	0.49–1.03
NO_2 regression coefficient	< 0.40	0.64	0.43–0.85
	> 0.40	0.74	0.50–0.99

Abbreviations: Pooled estimates are presented as the percentage change in mortality per 10 μg/m^3 increase in PM_{10}, as determined by random effects models.

Table 5. Correlations between predictors considered in EB meta-analysis, for 19 U.S. studies (values greater than 0.5 in italics).

	Amb PM_{10}	$PM_{2.5}/PM_{10}$	O_3 coeff	NO_2 coeff	SO_2 coeff	CO coeff	Avg time	> 65 years (%)	In poverty (%)	HDD	CDD	Mort rate	Central AC	Gas stove	Warm air furn
Amb PM_{10}	1.00	-0.15	*-0.57*	0.28	0.20	0.05	-0.08	0.28	*0.64*	-0.23	-0.33	-0.40	-0.40	0.45	-0.17
$PM_{2.5}/PM_{10}$	–	1.00	0.25	*-0.58*	-0.08	-0.41	-0.35	*0.58*	-0.02	0.28	0.01	0.39	0.08	0.14	-0.15
O_3 coeff	–	–	1.00	-0.39	-0.22	*-0.59*	-0.23	0.06	-0.46	0.12	0.25	*0.56*	0.45	0.05	0.07
NO_2 coeff	–	–	–	1.00	0.46	*0.65*	-0.05	-0.25	0.41	-0.39	-0.16	-0.09	-0.32	0.12	-0.44
SO_2 coeff	–	–	–	–	1.00	0.14	-0.10	0.45	*0.55*	0.19	-0.18	0.32	-0.45	0.23	-0.37
CO coeff	–	–	–	–	–	1.00	0.07	-0.40	0.22	-0.48	0.05	-0.26	-0.06	-0.25	-0.10
Avg time	–	–	–	–	–	–	1.00	*-0.61*	-0.09	0.15	0.21	*-0.57*	0.02	-0.47	0.34
> 65 years (%)	–	–	–	–	–	–	–	1.00	0.44	0.17	-0.17	*0.57*	-0.19	0.45	-0.33
In poverty (%)	–	–	–	–	–	–	–	–	1.00	-0.18	-0.14	0.07	-0.29	0.33	-0.40
HDD	–	–	–	–	–	–	–	–	–	1.00	-0.45	-0.04	-0.43	-0.01	0.16
CDD	–	–	–	–	–	–	–	–	–	–	1.00	0.27	*0.84*	*-0.52*	0.39
Mort rate	–	–	–	–	–	–	–	–	–	–	–	1.00	0.39	0.22	-0.17
Central AC	–	–	–	–	–	–	–	–	–	–	–	–	1.00	-0.28	*0.52*
Gas stove	–	–	–	–	–	–	–	–	–	–	–	–	–	1.00	-0.49
Warm air furn	–	–	–	–	–	–	–	–	–	–	–	–	–	–	1.00

Abbreviations: AC, air conditioning; amb, ambient; avg, average; CDD, cooling degree days (base 65); furn, furnace; HDD, heating degree days (base 65); coeff, coefficient; mort, mortality.

both pollution concentrations and demographics can be related to geographic region, which may also influence PM_{10} composition in ways related to mortality effects. As detailed in the EPA criteria document (*58*), each city has a distinctive particle size distribution and chemical composition based on local sources and meteorologic patterns. For example, organics contribute a substantial fraction of fine particles in Los Angeles, California, whereas sulfates dominate in the Northeast. These complex chemical differences may contribute to differences in mortality impacts, and are not captured by our meta-analysis.

To test the potential effects of chemical composition, we examined sulfate concentrations. Because SO_4 concentration data are not available for all 19 U.S. estimates, we used data from the 10 estimates derived from the Six Cities studies (*6,29,31,35*).For these 10 estimates, the SO_4/PM_{10} ratio is highly correlated with both the mortality effect estimate (r = 0.84) and with the $PM_{2.5}/PM_{10}$ ratio (r = 0.70). If we conducted an EB regression on these 10 estimates, including both ratios, the SO_4/PM_{10} ratio would enter the equation and the $PM_{2.5}/PM_{10}$ ratio would not. Because of the high correlation and small sample size, it is difficult to draw conclusions from this analysis, but this demonstrates that constituent components of fine particles may act as stronger predictors of mortality.

It is also possible that we omitted relevant predictors that could explain the significance of the $PM_{2.5}/PM_{10}$ ratio. We did not include smoking prevalence and other lifestyle-related predictors (e.g., percentage of the population that is overweight or which leads a sedentary lifestyle) in our primary analysis because data were not available at the city or county level. We tested statewide average values for these variables, but none entered the optimum model, likely because of the variability in behaviors within states. To determine whether these omitted variables could plausibly explain our findings, we replicated an earlier experiment for cigarette smoking (*59*).

Smoking would need to be highly correlated with the $PM_{2.5}/PM_{10}$ ratio with sufficient variability among sites to explain the entire $PM_{2.5}/PM_{10}$ ratio effect. Using the optimum model (Table 6) and assuming ambient Los Angeles pollution conditions, the cities with minimum and maximum $PM_{2.5}/PM_{10}$ ratios (Los Angeles, 0.47; and Knoxville, TN, 0.70, respectively) would have a mortality difference of 2.5×10^{-6}/person/day if all other parameters were constant. Using the rate of 2 million cigarettes per death, as reported by Wilson et al. (*59*), this implies a consumption difference of approximately 5 cigarettes/person/day. This difference would be found if smokers in Knoxville smoked approximately 1 pack/day more than smokers in Los Angeles, or if the prevalence were 25% in Los Angeles and 46% in Knoxville with average consumption per smoker. Even if we use the lower $PM_{2.5}/PM_{10}$ coefficient associated with the three-parameter model, the necessary smoking differences are significant, and it is highly unlikely that differences of this magnitude are systematically correlated with $PM_{2.5}/PM_{10}$ ratios across multiple cities.

Even if the above barriers could be discounted, we also must deal with the issue of study selection bias, which is a problem in all meta-analyses. We tried to avoid selection bias by choosing all of the available studies that fulfilled our criteria, including multiple analyses of the same city when differences occurred. However, there is no meaningful way to avoid a possible "file drawer" phenomenon in which studies finding no significant relationship between PM_{10} and mortality may not have been published or submitted for publication. Although this phenomenon could potentially influence our EB predictors, a "file drawer" bias would not greatly affect the general findings of a significant PM-mortality link. Given the body of largely positive evidence, it would take 120 unpublished studies with central estimates of -0.1% and the median variance of our 29 study estimates, or 57 studies with these central estimates and the minimum variance of our study estimates, to yield a statistically insignificant grand mean estimate.

Selection bias could also arise if the sample cities in the analysis were not representative of the true family of conceivable studies. If a subset of cities that were more or less prone to PM health effects were chosen for epidemiologic analyses, this would undermine the generalizability of the analysis and the formulated models. For the 19 U.S. estimates, the percentages of the population younger than 65 years of age and below the poverty level are comparable to the U.S. average. However, many of these studies were conducted in cities in the eastern half of the United States, which may not represent the population at large. Nevertheless, the cities chosen have a wide range of ambient PM_{10} and gaseous pollutant concentrations and represent both rural and urban locations.

One of our study objectives was to determine the degree to which correlated gaseous pollutants confound the PM-mortality relationship. From our primary regression, SO_2 may act as a confounder of PM_{10} mortality, with some evidence of confounding from O_3 in the sensitivity analyses. One way to assess whether the EB model reasonably depicted the influence of confounding pollutants was to look at the six U.S. studies that analytically controlled for correlated gaseous pollutants. We compared the reported multipollutant estimates with posterior estimates from the EB model, forcing the pollutants controlled

Table 6. EB regression results for all 19 U.S. estimates.

	Optimum "*t*-to-enter" model		Model with all gaseous pollutants forced into regression	
Term	β	*t*-Statistic	β	*t*-Statistic
Intercept	-2.08	-1.63	-1.93	-0.88
Warm air furnace	-0.77	-1.48	-1.08	-1.54
Gas stove	-0.93	-2.11	-1.27	-2.43
$PM_{2.5}/PM_{10}$ ratio	8.65	3.06	8.33	2.77
HDD	-0.00014	-1.80	-0.00011	-0.89
SO_2 regression coefficient	0.58	2.26	0.70	2.15
Population > 65 years of age (%)	-0.13	-1.98	-0.17	-2.17
Ambient PM_{10} concentration	0.015	1.48	0.029	1.65
O_3 regression coefficient	–	–	0.65	0.83
NO_2 regression coefficient	–	–	-0.096	-0.23
CO regression coefficient	–	–	0.00029	0.02

HDD, heating degree days (base 65).

Table 7. Comparison between the multivariate PM_{10}-mortality effect estimates drawn from the studies and posterior estimates of the PM_{10}-mortality effect controlling for the given gaseous pollutants, drawn from the 19-study EB models.

Study site	Reference	Pollutants controlled	Univariate and multivariate estimates from study (%)	Univariate and multivariate posterior estimates from EB[a] (%)
Cook County, IL	(*12*)	O_3	0.5 – 0.4	0.5 – 0.4
Los Angeles, CA	(*25*)	CO	0.5 – 0.4	0.5 – 0.4
Philadelphia, PA	(*21*)	SO_2	0.6 – 0.6	0.8 – -0.1
Steubenville, OH	(*35*)	SO_2	0.5 – 0.3	0.6 – 0.5
Steubenville, OH	(*6*)	SO_2	0.6 – 0.5	0.6 – 0.5
Philadelphia, PA	(*7*)	SO_2	1.2 – 0.9	1.1 – 0.4

[a]EB estimates for each study are derived by running an EB model with all nongaseous pollutant terms from the optimum "*t*-to-enter" model in Table 6, with the listed pollutants forced into the model.

in each study into the model. The univariate and multivariate effect estimates were similar for all but the Philadelphia studies [Table 7; (*7,21*)]. The errors for the Philadelphia data may be a function of overmodeling, uncaptured site-specific characteristics, or errors in the SO_2–PM regression coefficients because of problems associated with the TSP/PM_{10} conversion. These errors did not occur when the three-parameter EB model was used, although there was more error associated with the univariate estimates.

Stratified random effects models and EB meta-analysis can provide valuable information both about the set of existing studies and about directions for future investigations. Many of the significant EB predictors are related either to the study location or to characteristics of the housing stock. To help unravel the effects of these correlated predictors, we recommend that future epidemiologic studies target sites that have a limited number of potential confounders or effect modifiers or contain a different mix of predictors than previously considered. For example, Seattle, Washington, has minimal central air and gas stove prevalence in a moderate climate, whereas Phoenix, Arizona, has significant central air prevalence in a warm climate with low sulfate concentrations (*58*). In general, a more comprehensive geographic spread and the consideration of urban and rural settings will help to determine causal predictors by reducing the correlations among variables. Future studies should consider the PM-mortality literature as a whole and should choose sites that consider variability across dimensions other than air pollution.

EB models and their posterior estimates can also show which studies might be outliers and in need of further analysis, and can be used to estimate the findings of new studies if site-specific information is known. As the number of epidemiologic studies on air pollution mortality increases, the statistical power will improve and will allow for the evaluation of more predictors. In particular, additional studies to consider both $PM_{2.5}$ and PM_{10}, as well as studies addressing the issues of gaseous pollutant confounding either analytically or by exclusion, will help update our initial estimates and verify whether the derived relationships are accurate. Once more comprehensive models for PM mortality have been created, they could be used to help target geographic regions where PM reductions could have greater impacts.

Conclusions

We applied an EB meta-analysis model to the time–series PM-mortality literature to determine whether variability in effect estimates can be explained by simple study-specific factors. We estimated that mortality rates increased by approximately 0.7% for a 10-μg/m^3 increase in PM_{10} concentrations. Our model finds compelling evidence that the PM_{10}-mortality relationship is stronger in locations with higher $PM_{2.5}/PM_{10}$ ratios, supporting the hypothesized role of fine particles. The significance of housing characteristics, climate, and correlated SO_2 and O_3 demonstrate that a number of factors have a measurable influence on the magnitude of the PM-mortality relationship. EB analysis of the PM_{10}-mortality literature is recommended on an ongoing basis, to better determine factors that contribute to heterogeneity and causal determinants of increased mortality.

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