The Concentration–Response Relation between Air Pollution and Daily Deaths

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Studies on three continents have reported associations between various measures of airborne particles and daily deaths. Sulfur dioxide has also been associated with daily deaths, particularly in Europe. Questions remain about the shape of those associations, particularly whether there are thresholds at low levels. We examined the association of daily concentrations of black smoke and SO_2 with daily deaths in eight Spanish cities (Barcelona, Bilbao, Castellón, Gijón, Oviedo, Valencia, Vitoria, and Zaragoza) with different climates and different environmental and social characteristics. We used nonparametric smoothing to estimate the shape of the concentration–response curve in each city and combined those results using a metasmoothing technique developed by Schwartz and Zanobetti. We extended their method to incorporate random variance components. Black smoke had a nearly linear association with daily deaths, with no evidence of a threshold. A 10 μg/m^3 increase in black smoke was associated with a 0.88% increase in daily deaths (95% confidence interval, 0.56%–1.20%). SO_2 had a less plausible association: Daily deaths increased at very low concentrations, but leveled off and then decreased at higher concentrations. These findings held in both one- and two-pollutant models and held whether we optimized our weather and seasonal model in each city or used the same smoothing parameters in each city. We conclude that the association with particle levels is more convincing than for SO_2, and without a threshold. Linear models provide an adequate estimation of the effect of particulate air pollution on mortality at low to moderate concentrations. *Key words:* **air pollution, daily mortality, dose–response relationships, hierarchical models, particulate matter.** *Environ Health Perspect* **109:1001–1006 (2001). [Online _____]**
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Starting in the late 1980s, a series of studies reported associations between daily concentrations of air pollution and daily deaths (*1–3*). Since then, studies have been done in multiple locations, and recently a number of large, multicity studies (*4–7*) have been reported. These studies have consistently found associations between airborne particles, measured in various ways, and daily deaths. In addition, studies in Europe have reported associations with sulfur dioxide concentrations. In contrast, no consistent association with SO_2 has been reported in the United States (*7*). Other gaseous air pollutants have been less consistently reported to be associated with daily deaths, although, again in Europe, ozone has been more consistently associated (*8*).

Most of these studies have assumed linear associations between air pollution and daily deaths, although in cases where concentrations reached high levels, logarithmic transformations have frequently been used (*4*). However, the shape of the concentration–response relationship is critical for public health assessment, and in particular, some have speculated that thresholds might exist. Although thresholds are commonly assumed in toxicologic studies of identical animals, the general human population is diverse both genetically and with respect to predisposing conditions. Biologically, a relatively linear population concentration–response relationship at low doses would be expected if the mortality were due to exacerbation of underlying illnesses, and the sensitivity to air pollution varied with genetics and the extent of the predisposing condition (*9*). This question has been explored using a variety of approaches in individual cities, and roughly linear associations were identified in all of them (*9–11*). Recently, two studies have explored this question for particulate air pollution, using multicity studies in the United States. One used data from 20 U.S. cities, 5 of which had daily measurements of PM_{10} (particulate matter ≤ 10 μm), with the rest having measurements only 1 day in 6 (*12*). The researchers used regression splines to model the concentration–response curve in each city and combined the results across cities. They found no evidence for a threshold. In fact, the concentration–response relation was quite linear across the entire range of exposure. The other report (*13*) used 10 cities, all of which had daily measurements of PM_{10}, resulting in slightly more days of study. It used nonparametric smoothing to model the concentration–response curve between air pollution and daily death in each city and combined the results across cities. Again, a linear, no-threshold relationship was seen. Schwartz and Zanobetti (*13*) also performed simulations to confirm the ability of this approach to detect thresholds and other types of nonlinearity.

To date, no similar study has been done outside of North America or for pollutants other than PM_{10}. Particle characteristics differ considerably between Europe and the United States, and the high number of diesel engines make mobile sources a much more important source of urban particles in Europe. Here we report results of analyses in eight cities in Spain, examining the concentration–response relation between daily deaths and both SO_2 and airborne particles. These analyses are part of the EMECAM project, a Spanish multicenter study on air pollution and health that seeks to evaluate, using a standardized methodology, the short-term effects of air pollution on health in 14 Spanish cities (*14,15*). Eight of those cities used a common method for measuring airborne particles and are analyzed here.

Methods

Air pollution and daily death data were collected from eight cities in Spain during the years 1990–1996. The cities were Barcelona, Bilbao, Castellón, Gijón, Oviedo, Valencia, Vitoria, and Zaragoza. Airborne particle

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concentrations were measured as black smoke, a measure of black combustion particles common in Europe during the data collection period. Black smoke is a good measure for particles from traffic and has been shown to be more strongly correlated with daily deaths than PM_{10} in a number of cities in Western Europe (*4*). In Europe, black smoke appeared to be a good indicator of diesel exhaust (*16*) [which was an important source of ultrafine particles (*17*)] as well as a good indicator of distance from the motorways (*18*). Air pollution measurements used standardized instruments, siting criteria, and quality-control protocols in all of the cities (*12*).

The association between air pollution and daily mortality in each city was investigated using Poisson regression in a generalized additive model (*19*). Robust regression was used to reduce the effect of any extreme observations on the regression results (*20*). The generalized additive model allows regressions to include nonparametric smooth functions to model the potential nonlinear dependence of daily mortality on weather and season. A Loess smooth function was used (*21*). Loess estimates a smooth function by fitting a weighted regression within a moving window (or fraction of the data) centered about each value of the predictor variable. The weights are close to one for the central third of the window and decline to zero rapidly outside that range. Outside of the window, the weights are all zero. This window is often called the span. The use of generalized additive models for time series of counts was first introduced in 1993 (*22*). This approach has become standard in air pollution epidemiology.

Because the weather patterns varied across the cities from those with more moderate to those with more extreme conditions, it was necessary to fit different weather models in each location. The variables controlled for (temperature, previous days' temperature, and relative humidity) were not allowed to vary, but the number of degrees of freedom used to fit them was. The size of the smoothing window was chosen to minimize Akaike's Information Criterion (AIC).

Temporal patterns were dealt with in two ways. One cause of temporal changes in daily deaths is influenza, which particularly influences winter peaks. Influenza is a reportable illness in Spain, and municipal health departments collect data from local physicians. We used a smooth function of daily counts of influenza cases to control for its influence on mortality, again choosing the smoothing parameter in each city to minimize AIC. We also used dummy variables for day of the week and for public holidays and a smooth function of time to capture seasonal patterns that remain after controlling for weather and influenza. The smoothing window for time was chosen to remove seasonality from the residual plots and minimize the serial correlation in the residuals. If significant serial correlation remained, autoregressive Poisson models were fit (*23*).

Once the baseline models were fit, a smooth function of the mean of air pollution concentration on the day of death and the previous day was added to the model. The smoothing window included 50% of the data, which corresponds to between 4 and 5 degrees of freedom for the air pollution relationship in each city. Because the two air pollutants are correlated, we first used single-pollutant models. We then put smoothed functions of both air pollutants in the model to assess how the dose response changed when potential confounding by the other pollutant was considered.

To combine the smooth curves across cities, we applied the approach of Schwartz and Zanobetti (*13*). In each city, the predicted log relative risk and its pointwise standard error was computed for each 2 μg/m^3 increment in exposure above the reference category. The reference level was chosen to be 0–20 μg/m^3 for black smoke and 0–9 μg/m^3 for SO_2. A pointwise meta-analysis was then computed for each exposure category.

It is possible that heterogeneity is present in the effects of pollution across cities. To allow for this, we estimated a random variance component using the method of moments. Again, this was done at each exposure increment. However, the small number of observations in each 2 μg/m^3 increment in exposure makes the estimated random variance component at each increment unstable. Heterogeneity may vary by exposure level, but likely varies smoothly. Therefore we smoothed these estimated random variance components versus pollution concentration, again using Loess. This gave us more stable estimates of the random variance component at each exposure level. The pointwise meta-analysis was computed using inverse variance weighting, including the estimated random variance component.

The use of automatic span selection criteria, such as AIC, is subject to the same criticism as stepwise regression. Often choices

Table 1. Mean levels of environmental factors in eight Spanish cities.

City	Years of study	Population	Humidity	Temperature (°C)	Daily deaths	Black smoke (μg/m^3)	SO_2 (μg/m^3)
Barcelona	1991–1995	1,643,545	75	16	43	40	11
Bilbao	1992–1996	667,034	80	15	14	26	25
Castellón	1991–1995	134,213	71	17	2.9	25	16
Gijón	1993–1996	261,724	79	14	6.3	52	34
Oviedo	1993–1996	198,050	78	13	4.5	29	44
Valencia	1994–1996	749,796	63	19	16.1	44	26
Vitoria	1990–1994	214,148	76	12	3.5	51	18
Zaragoza	1991–1995	572,212	64	15	12.5	47	21

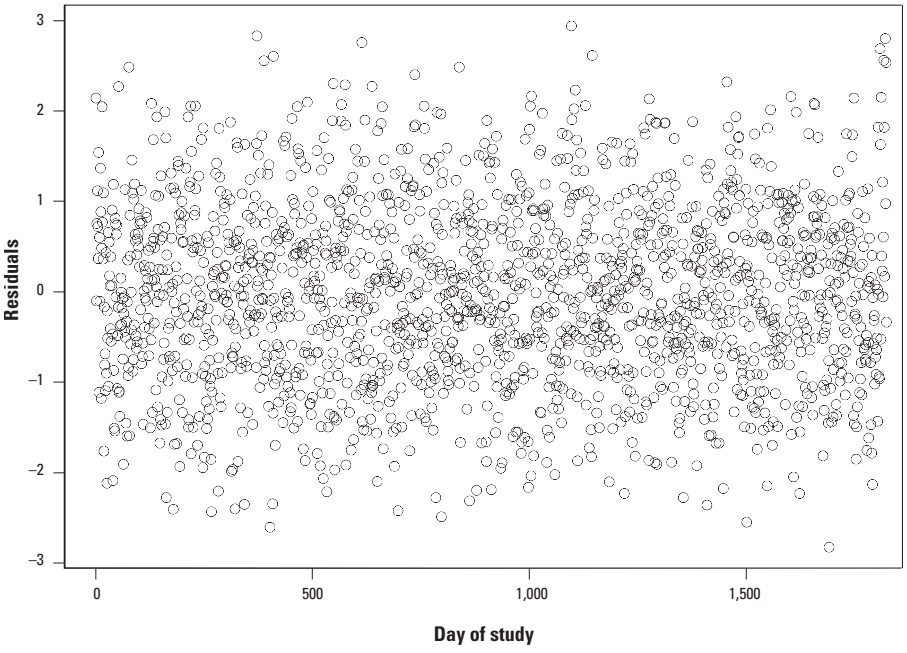

Figure 1. Deviance residuals of the regression model for daily deaths in Barcelona. Controlling for weather, influenza, and season has removed seasonality from the data.

are dictated by noise in the data, and AIC is known to be biased toward using excessive degrees of freedom. We chose to use different spans in different cities because climatic conditions varied across our cities. However, as a sensitivity analysis, we repeated our analyses for the two-pollutant model using the same span for each term in each city. These were taken to be 50% of the data for the weather variables and influenza and to be a span of 200 days for the smooth function of time. We then compared the results to our original approach.

Results

Table 1 shows the mean concentrations of black smoke, SO_2, daily deaths, temperature, and humidity in each of the eight cities. The range of weather conditions was substantial across these locations. For example, the range of relative humidity across the eight locations included locations with higher humidity than in a recent U.S. study (*11*), and, with the exception of one outlier desert community in the U.S. study, it included lower relative humidity as well. The mean temperatures of the cities varied by 5°C. Table 1 also shows the years for which data were available in those cities. Mean levels of pollutants show different sources' patterns (e.g., in most of cities there is a predominance of particulates, but in others SO_2 levels equal or exceed the mean concentrations of black smoke).

The weather terms generally used 3–4 degrees of freedom each, and the smooth function of influenza counts about 4 degrees of freedom. The span for the seasonal pattern averaged 300 days. Figure 1 shows the residual from the model for Barcelona plotted versus day of study, illustrating that seasonality has been removed.

When air pollution was assumed to have a linear concentration–response relationship with daily deaths, a significant association was found with black smoke [0.88% increase in daily deaths for a 10 μg/m^3 increase in black smoke, 95% confidence interval (CI), 0.56–1.20%) in a single-pollutant model. SO_2 showed substantially weaker evidence of an association in these cities (0.27% increase in daily deaths for a 10 μg/m^3 increase in exposure, 95% CI, 0.18–0.73%), also in a single-pollutant model.

Figure 2 shows the estimated concentration–response relationship between black smoke and daily deaths in the eight Spanish cities, considering black smoke as the only pollutant. The association is essentially linear, with no evidence of a threshold. An increase from 17 μg/m^3 to 67 μg/m^3 is associated with a 5% increase in daily deaths, which is almost identical with the results of the linear model. Figure 2 shows the estimated pointwise confidence intervals for the concentration–response curve at each point and what the estimated confidence interval would have been if the random variance component had been set to zero. This is the fixed effect estimate, assuming no heterogeneity in response. The difference represents the additional uncertainty in the overall population concentration–response curve due to the heterogeneity in results across cities.

In contrast, Figure 3 shows a very different pattern for SO_2. The risk increases until SO_2 concentrations of about 20–30 μg/m^3 and then levels out and begins to decline with further increases in concentration. The same 50 μg/m^3 increase from the baseline is associated with only a 0.5% increase in daily deaths, which is only 40% of what would have been predicted based on fitting a linear concentration–response relation. Again, there was heterogeneity in response, and the open circles show what the confidence intervals would have been had we used a fixed effect model.

Figures 4 and 5 show the same dose–response relationships, except in this case the effects of each pollutant are estimated simultaneously. The relationship with black smoke was little changed by controlling for SO_2. In contrast, the association with SO_2 now shows little evidence of any association.

Figure 6 shows three dose–response relations between black smoke and daily deaths. The first is from the single-pollutant model, the second controls for SO_2, and the third uses the same span for smoothing the weather and seasonal variables in each city and controls for SO_2. There is little change in the association across the three approaches, although controlling for SO_2 does result in a somewhat steeper slope.

Figure 7 shows the same plots for SO_2. The evidence for an SO_2 association diminishes when black smoke is controlled for, but again there is little sensitivity to how weather, season, or influenza are controlled.

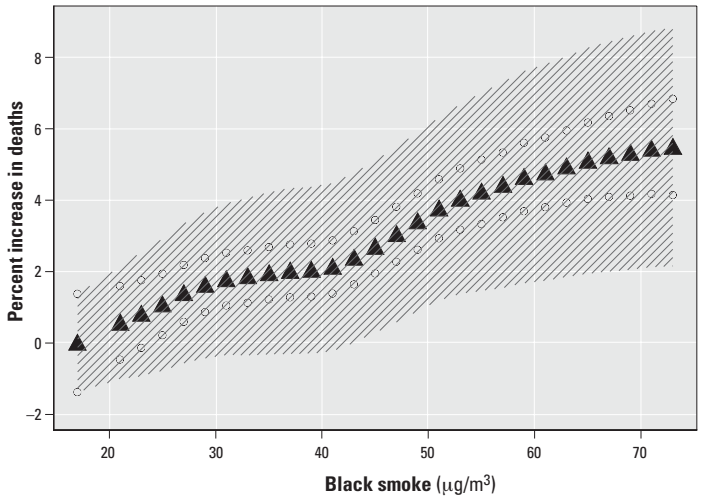

Figure 2. The metasmooth of the concentration–response relation between black smoke and daily deaths (on a percent scale). Each triangle represents the meta-analysis of the estimated effect in that 2 μg/m^3 increment in exposure from each of the eight cities, incorporating a random variance component. The shaded lines denote the pointwise 95% CI for each estimate. The circles show what the 95% CI would have been had a random variance component not been estimated. The difference indicates the increased variance in the estimate due to heterogeneity among the cities in the response to particles. The association is essentially linear across its entire range.

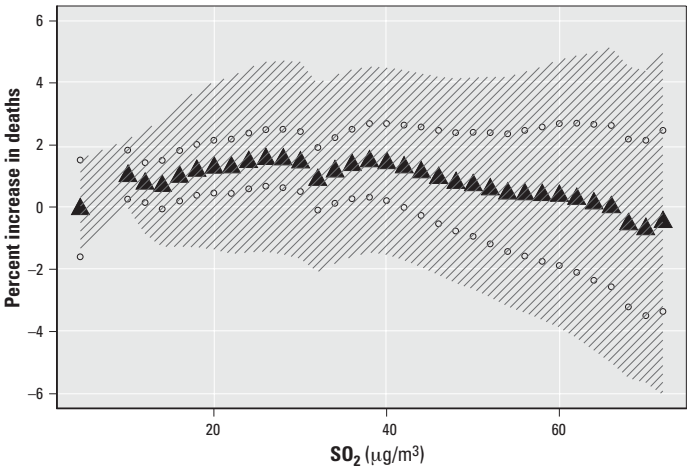

Figure 3. The metasmooth of the concentration–response between SO_2 and daily deaths (on a percent scale). Each triangle represents the meta-analysis of the estimated effect in that 2 μg/m^3 increment in exposure from each of the eight cities, incorporating a random variance component. The shaded lines denote the pointwise 95% CI for each estimate. The circles show what the 95% CI would have been had a random variance component not been estimated. The difference indicates the increased variance in the estimate due to heterogeneity among the cities in the response to SO_2. There is little evidence of a causal concentration–response relation.

Discussion

We have confirmed in Europe the findings recently reported in the United States—that the dose–response relation between airborne particles and daily deaths is essentially linear, at least at low to moderate concentrations. This was done using data from eight cities in Spain with substantial variation in climatic patterns and concentrations of black smoke. This is consistent with the two prior reports examining particulate matter concentration–response (*12,13*). In addition, another recent study of six U.S. cities excluded all days with particle concentrations above 25 μg/m^3 and reported a significant association with daily deaths (*5*). Another recent study looked at hospital admissions versus PM_{10} in 10 U.S. cities (*24*). Excluding days with PM_{10} concentrations above 50 μg/m^3, they reported a significant association with PM_{10}. Given the broad range of locations and substantial number of cities examined in these studies, the evidence appears to be convincing. The magnitude of the association seen here is also consistent with previously published results for black smoke (*4*) and broadly consistent with the results seen in many studies over the world (*2,6–8*) using a variety of measures of airborne particles.

We have also shown that the association is insensitive to variation in how weather and season is controlled for. When we used the same span for season, which was one-third less than the average of the spans our optimization procedure chose in each city, and also used somewhat more degrees of freedom for weather and influenza, no appreciable change was seen in the dose–response relation. This does not mean that there were no changes in individual cities, but rather that they tended to cancel out when averaged over multiple cities. This insensitivity of multiple city studies has been noted before in a study assuming linear relations (*7*).

The results for SO_2 are less supportive of a causal association. The smooth plot does not suggest a consistent increase in daily deaths with exposure, and the confidence bands for a linear fit include no effect. In the two-pollutant models, the results are even more convincingly null. Again, this is

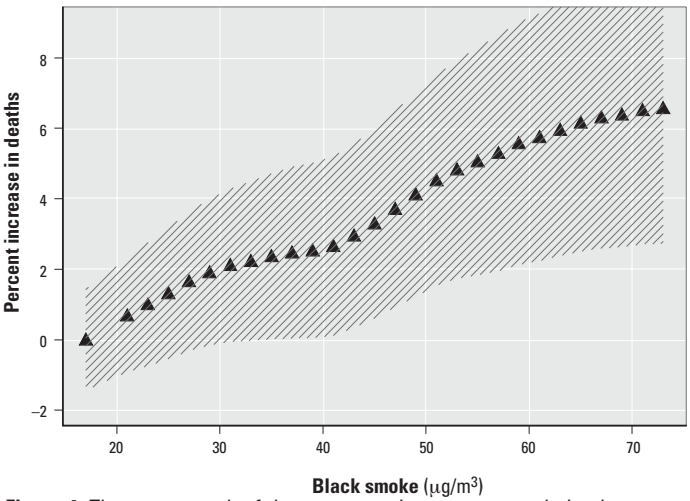

Figure 4. The metasmooth of the concentration–response relation between black smoke and daily deaths (on a percent scale) in a model that controlled for a smoothed function of SO_2. Each triangle represents the meta-analysis of the estimated effect in that 2 μg/m^3 increment in exposure from each of the eight cities, incorporating a random variance component. The shaded lines denote the pointwise 95% CI for each estimate. The association remains essentially linear across its entire range.

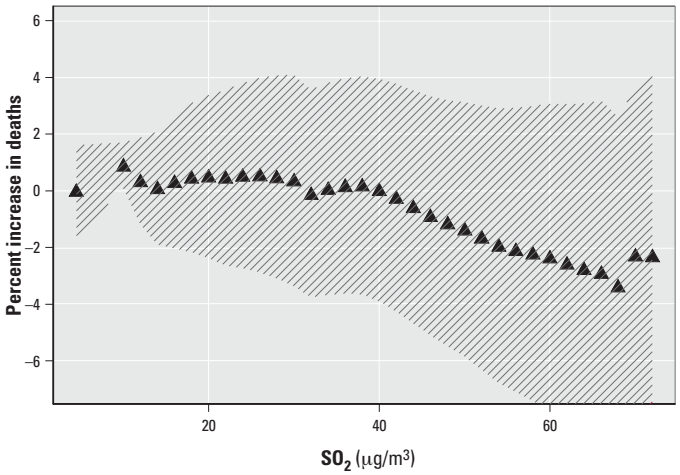

Figure 5. The metasmooth of the concentration–response relation between SO_2 and daily deaths in a model that controlled for a smoothed function of black smoke. Each triangle represents the meta-analysis of the estimated effect in that 2 μg/m^3 increment in exposure from each of the eight cities, incorporating a random variance component. The shaded lines denote the pointwise 95% CI for each estimate. The risk of death increases at very low SO_2 concentrations, and then plateaus and declines.

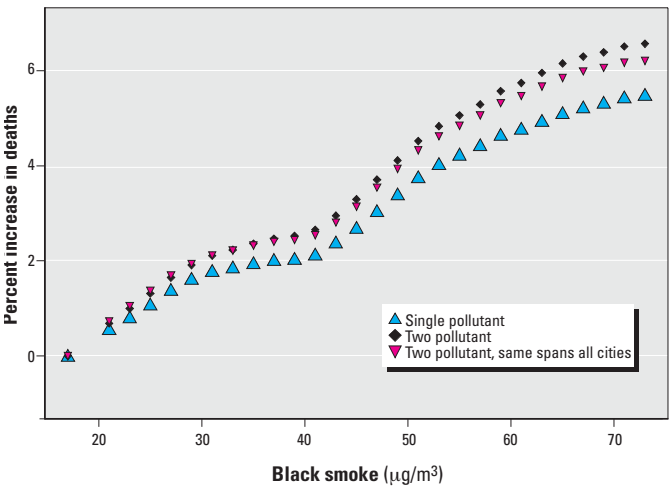

Figure 6. The concentration–response between black smoke and daily deaths in a single-pollutant model, a two-pollutant model, and a two-pollutant model with an alternative specification of the season and weather model that did not vary across cities.

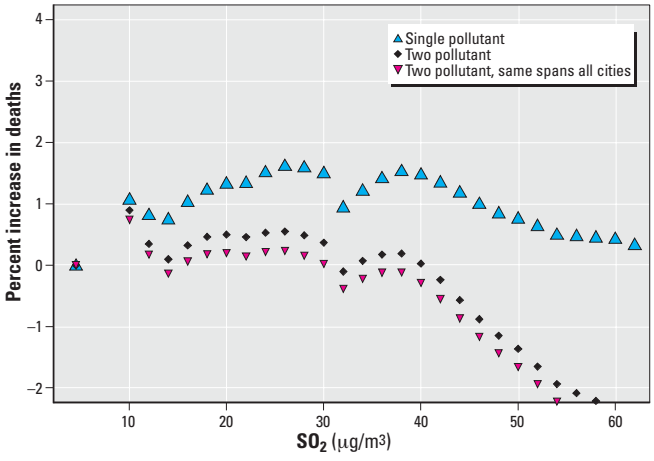

Figure 7. The concentration–response between SO_2 and daily deaths in a single-pollutant model, a two-pollutant model, and a two-pollutant model with an alternative specification of the season and weather model that did not vary across cities.

consistent with the overall literature. SO_2 was consistently associated with daily deaths in the APHEA study (Air Pollution and Health: a European Approach), which included a wide range of cities in Europe (*4*). However, other European studies have failed to find effects (*25,26*). A recent analysis in the Netherlands by Buringh et al. (*27*) found that when stratified by time period, the effect size for SO_2 increases with increasing time period during which its mean concentration fell. This was consistent with either a steeper slope for SO_2 at lower exposures or with it standing as a surrogate for another pollutant. However, when they stratified the analyses geographically, they found lower effect sizes for SO_2 in the regions with lower exposure. They concluded that it was likely a surrogate. Sunyer et al. (*28*) found an association with black smoke but not SO_2 in a case-crossover study of a cohort with COPD in Barcelona.

The National Morbidity and Mortality Air Pollution Study (*7*) examined the association between both PM_{10} and SO_2 in 90 U.S. cities. Although positive associations between SO_2 concentrations and daily deaths were found in some cities, negative associations were found in others, and the overall effect size estimate was zero whether considered alone or in models with other pollutants. There seems to be no reason for such a strong finding in so many cities unless SO_2 was not a causal pollutant. How can this be resolved with the strong findings from the APHEA study (*4*)? The most reasonable conclusion from the body of evidence is that SO_2 in Europe may act as a surrogate for another pollutant, probably airborne particles. This has also been noted in a recent hierarchical analysis of season-specific regressions in Philadelphia (*29*). It is also consistent with the observation of Speizer and co-workers (*30*) in 1961 that more than 90% of inhaled SO_2 was stripped out in the upper airways. Hence SO_2 exposure generally does not reach the lung. Moreover, little of that was absorbed systemically; the SO_2 was released back into the air during exhalation. Thus it is unlikely that SO_2 could be a cause of mortality.

It must be acknowledged that nonlinearity can be difficult to distinguish from interactions. For example, if the effect of air pollution was linear, but with a different slope in cold than in warm weather, and if the mean concentrations also varied between cold and warm weather, a nonlinear relation would be apparent. It is difficult to imagine a combination of nonlinear relations and interactions happening to produce a linear association in a multicity study with varying levels of particles and weather patterns across cities. However, the nonlinear relation observed with SO_2 might be due to such a phenomena. Because the slope is actually negative at higher concentrations, we would have to assume a true causal relation that actually switched signs for this explanation to hold, and this seems less plausible biologically. Further, the pattern was insensitive to different controls for weather and season, making those unlikely confounders or effect modifiers.

These results are made more interesting by recent interest in the differential effects of particles from different sources and the substantial difference in the sources of particles between Spain and the United States. A recent study by Laden et al. (*31*) reported that both particles from traffic and long-range transport particles were independently associated with daily deaths. The U.S. cities studied by Daniels et al. (*12*) and Schwartz and Zanobetti (*13*) had greater contributions from secondary particles, formed by the reaction of gases in the atmosphere, than typical in the Spanish cities. These secondary particles are predominantly sulfates in the eastern United States and nitrates in the West. The United States has almost no cars or light trucks that use diesel engines, and hence mobile sources contribute a smaller fraction of total ambient particles in U.S. cities than in Spain. In contrast, essentially all trucks and many cars are diesel in Spain. This makes mobile sources a larger source of the urban particles. Hence the lack of a threshold for the effect of particles appears independent of the fraction of the pollutant that derives from traffic versus long-range transport of secondary particles (mostly from powerplants). This is of public policy interest, as it suggests that both sources are no-threshold pollutants.

The finding of no threshold for the effects of airborne particles has other implications for public health. One is that several percent of annual deaths in Spain may be occurring as a result of air pollution. This suggests that control of this problem will have major public health benefits. Second, the finding that the association is not just on high pollution days suggests that measures that attempt to lower routine air pollution concentrations will have greater public health benefits than measures that focus on a few days with the highest concentrations.

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