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The Temporal Pattern of Respiratory and Heart Disease Mortality in Response to Air Pollution

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Short-term changes in ambient particulate matter with aerodynamic diameters < 10 μm (PM_{10}) have been associated with short-term fluctuations in mortality or morbidity in many studies. In this study, we tested whether those deaths are just advanced by a few days or weeks using a multicity hierarchical modeling approach for all-cause, respiratory, and cardiovascular deaths, for all ages and stratifying by age groups, within the APHEA-2 (Air Pollution and Health: A European Approach) project. We fit a Poisson regression and used an unconstrained distributed lag to model the effect of PM_{10} exposure on deaths up to 40 days after the exposure. In baseline models using PM_{10} the day of and day before the death, we found that the overall PM_{10} effect (per 10 μg/m³) was 0.74% [95% confidence interval (95% CI), –0.17 to 1.66] for respiratory deaths and 0.69% (95% CI, 0.31–1.08) for cardiovascular deaths. In unrestricted distributed lag models, the effect estimates increased to 4.2% (95% CI, 1.08–7.42) for respiratory deaths and to 1.97% (95% CI, 1.38–2.55) for cardiovascular deaths. Our study confirms that most of the effect of air pollution is not simply advanced by a few weeks and that effects persist for more than a month after exposure. The effect size estimate for PM_{10} doubles when we considered longer-term effects for all deaths and for cardiovascular deaths and becomes five times higher for respiratory deaths. We found similar effects when stratifying by age groups. These larger effects are important for risk assessment. *Key words:* air pollution, heart disease, hierarchical models, lung disease, mortality displacement. *Environ Health Perspect* 111:1188–1193 (2003). doi:10.1289/ehp.5712 available via *http://dx.doi.org/* [Online 6 March 2003]

The association between daily deaths for all causes (Hoek et al. 1997; Ostro et al. 1996; Pope et al. 1995a; Saldiva et al. 1995; Schwartz 1994; Schwartz and Dockery 1992; Touloumi et al. 1994) or cause-specific mortality (Hoek et al. 2001; Ostro et al. 1999b; Rossi et al. 1999; Simpson et al. 2000; Wordley et al. 1997) and airborne particles has been reported in many studies over the last decade, and multicity analyses have confirmed these findings (Biggeri et al. 2001; Katsouyanni et al. 1997, 2001; Samet et al. 2000; Schwartz 2000a; Zanobetti et al. 2000a).

Early studies reported the association between daily deaths and pollution concentrations on the same day or 1–2 days before. Often the "best" lag was chosen in each analysis. This has been criticized as possibly tending to an overestimate of the effect.

However, several studies have demonstrated that air pollution levels, not just for the current day but for several preceding days, affect counts of daily deaths on a given day (Katsouyanni et al. 1990; Kelsall et al. 1997; Schwartz and Dockery 1992). In these studies, multiday averages of pollution are found to be better predictors of daily death counts than is a single day's exposure (even the best single day), and some have examined the shape, or distribution, of the lagged effect (Schwartz 2000b; Zanobetti et al. 2000a).

Some researchers have speculated that air pollution kills those who would have died in a few days anyway. This could occur if air pollution hastened the deaths of persons who were extremely frail. If air pollution did not simultaneously increase the number of people who become frail, the size of the frail pool would decrease after an air pollution episode. On subsequent days, a smaller frail pool would result in a reduction in daily deaths. Hence, this "harvesting" hypothesis implies a negative correlation between pollution concentrations and daily deaths at longer lags. This harvesting effect has been described previously (Zanobetti et al. 2000b, 2002).

A number of studies have examined this issue using several different methodologies (Schwartz 2000c, 2001; Zeger et al. 1999). All of them reported increased, rather than decreased, effects when longer lags were examined, but only one of them examined the correlation at multiple lags in a multicity hierarchical model.

Among the studies that analyzed the associations between air pollution and cause-specific mortality (Hoek et al. 2001; Ostro et al. 1999b; Rossi et al. 1999; Simpson et al. 2000; Wordley et al. 1997), Rossi et al. (1999) reported different lags for different causes in Milan, Italy. One possible reason for this is that different causes of death are affected by air pollution with different latency periods. The use of a multicity analysis that cancels out the noise by averaging over many estimates would provide a more reliable estimate of the effect and differences in the lag structure. Recently, Braga et al. (2001) reported differences in the lag structure

pattern between particulate matter with aerodynamic diameters < 10 μm (PM_{10}) and cause-specific mortality in a multicity hierarchical model. Only one study (Schwartz 2000c) has looked at mortality displacement with regard to cause-specific deaths.

Some studies found an association between airborne particles and mortality by age groups (Bremner et al. 1999; Goldberg et al. 2000; Ostro et al. 1999a; Ponka et al. 1998; Verhoeff et al. 1996), but again, none analyzed the distribution of the effect over time since exposure and whether the mortality displacement is short term.

In our previous study of the APHEA-2 (Air Pollution and Health: A European Approach) project (Zanobetti et al. 2002), we examined mortality displacement between air pollution and all daily deaths. The goal of that analysis was to estimate the dependence of daily deaths on day t on PM_{10} on that day, and up to the previous 40 days using an unconstrained distributed lag model. As a sensitivity analysis, in that study we used a fourth-degree polynomial and a cubic distributed lag model, and all the models showed similar results.

In the present study, within the APHEA-2 project, we examined mortality displacement by age, and we looked at the differences between cardiovascular and respiratory deaths compared with all causes of deaths. Following the same approach as in our previous analysis, we applied a fourth-degree polynomial and unconstrained distributed lag models in a multicity hierarchical framework.

Data and Methods

Health data. The APHEA-2 project was a multicenter study of 30 cities across Europe and adjacent countries (e.g., Istanbul, Turkey, and Tel Aviv, Israel). The goal of the APHEA-2 project was to examine the effects of air pollution on daily mortality. Details on APHEA-2 data have been reported previously (Katsouyanni et al. 2001).

To maximize the power of the study, we chose the largest cities in the project, subject to the constraint that only one city be chosen in each country. The 10 cities selected were Athens, Greece; Budapest, Hungary; Lodz, Poland; London, United Kingdom; Madrid, Spain; Paris, France; Prague, Czech Republic; Rome, Italy; Stockholm, Sweden; and Tel Aviv. Together, they comprise a population of about 28 million people, which is two-thirds of the population in the full study, and represents Northern Europe, Central Europe, and the Mediterranean region.

The data that we analyzed in this study included daily counts of all-cause mortality, excluding deaths from external causes [*International Classification of Disease, 9th Revision* (*ICD-9*) code > 800), daily counts of deaths from cardiovascular disease (CVD) (*ICD-9* code 390–429), and daily counts of respiratory mortality (*ICD-9* code 460–519). In all cities, the mortality counts were also divided in the following age groups: 15–64, 65–74, and ≥ 75 years.

The years of study were 1990 through 1997; however, mortality data in most cities were available only through 1995 or 1996.

Air pollution data were available as daily averages of the monitoring stations in each city. Particulate matter was measured as PM_{10} in four cities, as PM_{13} in Paris and PM_{15} in Rome. The Paris data were assumed to be equivalent to PM_{10} in this study. In Rome, Athens, Lodz, and Budapest, the data were converted from other measurements into PM_{10} using city-specific conversion factors. Further details have been published previously (Katsouyanni et al. 2001; Zanobetti et al. 2002).

We first analyzed respiratory and heart mortality; then, we examined deaths from all causes and stratified respiratory and cardiovascular deaths by age groups.

Methods. In the first step of the analysis, generalized additive regression models (Hastie and Tibshirani 1990) were fit in each of the 10 cities, and the models were built following the APHEA-2 methodology. Details on the models for all-cause mortality have been published (Katsouyanni et al. 2001).

Separate models were built in each city because of the substantial variability in seasonal patterns and weather between, for example, Stockholm and Tel Aviv.

In the generalized additive model, the outcome is assumed to depend on a sum of non-parametric smooth functions for each variable. This allows us to better model the nonlinear dependence of daily deaths on weather and season. The model is of the form

$$\log[E(Y_t)] = \alpha_0 + S_1(X_1) + S_i(X_i) + \ldots + S_p(X_p),$$

where $E(Y_t)$ is the expected value of the daily count of deaths Y_t, and S_i is the smooth function of the covariate X_i. The covariates we examined were weather, influenza epidemics, holidays, and day of the week. The locally weighted running-line smoother (Cleveland and Devlin 1988) was chosen to estimate the smooth function.

All models controlled for temperature and relative humidity on the same day using non-parametric smooth functions. In addition, we examined nonparametric functions and linear weather variables on the previous day or up to 3 previous days or the average of a few days. We chose the variables that minimized Akaike's Information Criterion (Akaike 1973) for the model. This approach has been used and discussed previously (Katsouyanni et al. 2001; Schwartz 1999; Schwartz et al. 1996).

To remove seasonal and long-term fluctuations, we used a smooth function of time. Seasonal patterns are controlled because there are unmeasured predictors of death, such as diet, which have long-term trends over time and vary seasonally. Because air pollution also shows seasonal variations, and often long-term trends, this creates a potential for confounding. Day-to-day fluctuations in diet are unlikely to be correlated with air pollution.

To model seasonality, we chose the smoothing parameter that minimized the sum of the autocorrelation of the residuals while removing seasonal patterns.

In some models, it was necessary to introduce autoregressive terms to eliminate the remaining serial correlation from the residuals (Brumback et al. 2000). This approach has been used in a number of recent studies (Rossi et al. 1999; Schwartz 1999, 2000a).

Recently several authors have pointed out that there are problems with the implementation of generalized additive models in current statistical packages (Dominici et al. 2002; Ramsay et al. 2003). One is the lax default convergence criterion in generalized additive models in S-PLUS software (MathSoft, Inc., Seattle, WA). A more serious problem is that this program does not properly estimate standard errors. To deal with the underestimation of the parameters' variances, we calculated standard errors for the estimated regression coefficients using the nonparametric bootstrap (Efron and Tibshirani 1993). In particular, we generated 250 bootstrap samples each consisting of n values drawn with replacement from the observed data, where n was the number of observations in each city. The model of interest was run for each generated data set, and the sample standard deviation of the resulting regression coefficients serves as the bootstrap standard error.

We examined the dependence of daily deaths on PM_{10} of that day and of preceding days, up to the previous 40 days, using first an unconstrained distributed lag model and then a fourth-degree polynomial distributed lag model.

If the pollution-related deaths are only being advanced by a few days to a few weeks, we would see this "harvesting" effect expressed by negative associations between air pollution and deaths several days to weeks afterward. The effect of air pollution, net of any such short-term rebound up to 40 days, is the sum of the effect estimates for all 41 days.

For Poisson regression, the unconstrained distributed lag model can be written as

$$\log[E(Y_t)] = \alpha + \text{covariates} + \beta_0 Z_t \quad [1]$$
$$+ \beta_1 Z_{t-1} + \ldots + \beta_q Z_{t-q}$$

The unconstrained distributed lag model is too noisy to provide any information about

the shape of the effect versus lag, but it does give an unbiased estimate of the overall effect, computed as the sum of the β_j. To be able to have an idea of the shape of the curve, it is preferable to constrain the coefficients to vary smoothly with lag number (Almon 1965). A polynomial distributed lag constrains the β_j to follow a polynomial pattern in the lag number; that is,

$$\beta_j = \sum_{k=0}^{d} \eta_k \, j^k, \quad \text{for } j = 0\ldots q, \quad [2]$$

where j is the number of lags and d is the degree of the polynomial.

Too much constraint risks bias, producing a distorted shape, whereas too little constraint produces estimates that are too noisy to be informative.

To fit a fourth-degree polynomial distributed lag model with 40 days of delay, in equation 2 we would have $d = 4$ and $j = 0, \ldots, 40$.

In the first stage of the analysis, a separate distributed lag model was fit for each of the 10 cities. The coefficients $\hat{\beta}_j$ by lag for the distributed lag model were obtained from equation 2,

and because we used the bootstrap method, we computed the sum of the effect estimates for all 41 days in each city. In the second stage, we combined the city-specific results using inverse variance weighted averages.

In our primary analysis we used an unconstrained distributed lag, because it makes the fewest assumptions. We used the polynomial distributed lag model as a sensitivity analysis because this gives more stable results and also allows us to examine the pattern of the mortality response over time.

To verify whether the longer lags really contribute to the overall pollution effect, we also analyzed the unconstrained distributed lag model with 20 and 30 days of delay.

Results

Table 1 shows, for the 10 cities, the mean and standard deviation of the daily number of total, cardiovascular, and respiratory deaths, in total and for the three age groups. It also shows the mean and standard deviation of the environmental variables. The mean of daily deaths for 15- to 64-year-olds is generally very

low when subdivided by cause. For respiratory mortality, the second age group is also small; therefore, we decided that the cause-specific analysis by age could be done for the two older groups for cardiovascular mortality, and in the oldest age group for respiratory mortality.

Table 2 shows the percentage increase for the combined effect estimates across all of the 10 cities of PM_{10} [per 10 μg/m³ and its 95% confidence interval (95% CI)] for the fourth-degree polynomial (sum of the β_j per 10 μg/m³), and the unconstrained distributed lag models when stratified by cause of death.

Figures 1 and 2 show plots of the residuals from the unconstrained distributed lag model for Athens and London, respectively, with no residual seasonality in the models.

We found a 4.2% increase (95% CI, 1.08–7.42) in respiratory deaths for a 10 μg/m³ increase in PM_{10} concentration using the unconstrained distributed lag model. Similar results, but with tighter confidence intervals, were found with the polynomial distributed lag models. In contrast, the mean of PM_{10} on the same and previous day was associated with only

Table 1. Study period, population, and mean ± SD of the number of daily deaths and the environmental variables in the 10 cities.

City/age group (years)	Years of study	Mortality Total	Mortality CVD	Mortality Respiratory	PM_{10} (mg/m³)	Temperature	Humidity
Athens	1992–1996	72.9 ± 13.2	35.9 ± 8.7	4.6 ± 2.4	42.7 ± 12.9	17.8 ± 7.4	61.7 ± 13.6
15–64		8.3 ± 3	2.9 ± 1.7	0.4 ± 0.6			
65–74		21.3 ± 5.2	9.3 ± 3.4	1.1 ± 1.1			
≥ 75		42.4 ± 9.6	23.7 ± 6.7	3.2 ± 1.9			
Budapest	1992–1995	80 ± 11.6	40.1 ± 8	3.1 ± 2	41 ± 9.1	12.8 ± 8.8	70.1 ± 12.6
15–64		22.1 ± 4.7	6.8 ± 2.7	0.6 ± 0.8			
65–74		19.5 ± 4.6	9.5 ± 3.2	0.7 ± 0.8			
≥ 75		37.6 ± 7.9	23.7 ± 6	1.7 ± 1.4			
Lodz	1990–1996	29.5 ± 6.3	16.8 ± 4.6	1.2 ± 1.1	53.5 ± 15.5	8.4 ± 8.4	79 ± 12.4
15–64		8.9 ± 3.2	3.7 ± 2	0.3 ± 0.5			
65–74		8.1 ± 3	4.5 ± 2.2	0.3 ± 0.6			
≥ 75		12.2 ± 3.9	8.7 ± 3.2	0.5 ± 0.8			
London	1992–1996	168.5 ± 25.2	71.4 ± 12.9	29 ± 11	28.8 ± 13.7	11.8 ± 5.4	69.3 ± 11.3
15–64		28.8 ± 5.7	9.5 ± 3.2	2.4 ± 1.7			
65–74		37 ± 7.4	15.7 ± 4.5	4.6 ± 2.6			
≥ 75		101.7 ± 18.5	46.1 ± 9.6	21.8 ± 8.9			
Madrid	1992–1995	60.8 ± 11.1	21.7 ± 6.1	6.1 ± 3.1	37.8 ± 17.7	14.5 ± 7.4	61.8 ± 16.7
15–64		13.7 ± 3.9	3.1 ± 1.8	0.7 ± 0.9			
65–74		13 ± 3.8	4 ± 2.1	1.1 ± 1.1			
≥75		33.4 ± 7.7	14.6 ± 4.6	4.2 ± 2.5			
Paris	1992–1996	123.3 ± 15.7	37.9 ± 7.5	9 ± 3.8	22.5 ± 11.5	12.1 ± 6.5	75.6 ± 12.5
15–64		30.7 ± 5.7	4.1 ± 2	0.9 ± 0.9			
65–74		20.8 ± 5	5.4 ± 2.5	1.2 ± 1.1			
≥ 75		69.9 ± 11.8	28.3 ± 6.4	6.9 ± 3.2			
Prague	1992–1995	38.2 ± 7.2	22.2 ± 5.2	1.4 ± 1.2	76.2 ± 45.7	11 ± 8	69.4 ± 14.1
15–64		7.5 ± 3	2.8 ± 1.7	0.3 ± 0.5			
65–74		10.2 ± 3.2	5.3 ± 2.3	0.4 ± 0.6			
≥ 75		20.1 ± 5.1	14.1 ± 4.2	0.7 ± 0.9			
Rome	1992–1996	56.2 ± 10.4	23.2 ± 6.4	3.1 ± 2	58.7 ± 17.4	16.8 ± 6.7	61.6 ± 11.9
15–64		11.3 ± 3.6	2.7 ± 1.7	0.2 ± 0.5			
65–74		13.4 ± 4	4.5 ± 2.3	0.6 ± 0.8			
≥ 75		30.9 ± 7.5	16 ± 5.1	2.2 ± 1.7			
Stockholm	1994–1996	28.9 ± 6.1	14 ± 4.1	2.5 ± 1.7	15.5 ± 7.9	7.7 ± 8.1	71.4 ± 15.8
15–64		3.7 ± 2	1 ± 1.1	0.1 ± 0.4			
65–74		5.3 ± 2.4	2.2 ± 1.6	0.3 ± 0.6			
≥ 75		19.7 ± 5.1	10.7 ± 3.5	2 ± 1.5			
Tel Aviv	1993–1996	27.4 ± 6.3	11.5 ± 4.1	1.4 ± 1.4	50.3 ± 57.5	20.6 ± 5.4	65.6 ± 11
15–64		4 ± 2	1 ± 1.1	0.1 ± 0.4			
65–74		5.8 ± 2.5	2.3 ± 1.5	0.2 ± 0.5			
≥ 75		17.2 ± 4.9	8.2 ± 3.3	1 ± 1.2			

a 0.74% increase (95% CI, –0.17 to 1.66) in respiratory mortality.

We found a 1.97% (95% CI, 1.38–2.55) increase in CVD deaths using the unconstrained distributed lag model. Again, the results for the polynomial distributed lag models were similar, whereas the results for the mean of lag 0 and 1 of PM_{10} were lower (0.69% increase, 95% CI, 0.31–1.08).

Overall, the estimated effect of PM_{10} was doubled for CVD when the lagged effects were considered; the effect was five times larger for respiratory mortality.

Table 3 shows the percentage increase for the combined effect estimates across all of the 10 cities for PM_{10} (per 10 µg/m^3 and its 95% CI) derived by applying the unconstrained distributed lag model with 20, 30, and 40 days of delay. The results show a clear increasing trend with increasing numbers of lags.

Figure 3 shows the estimated effect of PM_{10} at each lag (and its confidence interval) for CVD deaths. PM_{10} has a major immediate impact, declining rapidly to near 0 with a lag of 1 week. It then shows a prolonged, slight elevation in risk for the next month.

The pattern for respiratory deaths is quite different, as shown in Figure 4. The estimated immediate effect of PM_{10} decreases much more slowly than it does for CVD deaths. It again rises to a second smaller peak about a month later, before decreasing again by lag 40.

We then repeated the same analyses stratifying by age groups. Table 4 shows the results for all the outcomes by age group. Within each age group, we found similar results using the constrained and unconstrained distributed lag models. When looking across the age groups, we found that the risks increase. For example, using the fourth-degree polynomial distributed lag model, we found a –0.25% (95% CI, –0.876 to 0.36) increase in total mortality in the 15- to 64-year-olds, a 0.78% (95% CI, 0.23–1.33) increase in the 65- to 74-year-olds, and a 1.84% (95% CI, 0.92–2.78) increase in the ≥ 75-year-old group.

Applying the fourth-degree polynomial distributed lag model, we found a 2.06% increase (95% CI, 1.05–3.09) in CVD mortality for the 64- to 75-year-olds for a 10 µg/m^3 increase in PM_{10}. For the ≥ 75 year group, we obtained a 2.35% (95% CI, 1.42–3.29) increase in CVD deaths. We found a 4.57% (95% CI, 1.25–7.99) increase in respiratory disease for the ≥ 75 year group, which is similar to the results for all ages.

Discussion

Recent discussions of the effects of airborne particles on deaths have distinguished between effects within days of exposure and effects of chronic exposures seen in prospective cohort studies.

In the present study we report an analysis of the effects of PM_{10} on an intermediate time scale, and the potential for short-term mortality displacement by specific causes of death, by specific age groups, and for age groups by cause in 10 European cities, within the APHEA-2 project. Rather than finding that most of the effect of air pollution is due to "harvesting" individuals on the brink of death anyway, our study shows that the effect size estimate for airborne particles doubles for cardiovascular deaths when we look at the first 40 days after exposure, and increases 5-fold for respiratory deaths. We found a different pattern of mortality risk over time for cardiovascular and respiratory deaths, with the elevation in risk of death after exposure declining more slowly over time for respiratory than cardiovascular deaths. Zelikoff et al. (1999) have shown that exposure to urban particles exacerbates pneumonia. In a broad population of individuals with varying susceptibility, we

Table 2. Results for the combined estimated PM_{10} effect for the fourth degree and unrestricted models, with 40 days of delay using bootstrap methods.

	CVD		Respiratory disease	
	Percent	95% CI	Percent	95% CI
Mean lag 01	0.69	0.31–1.08	0.74	⁻0.17–1.66
Distributed lag				
Fourth degree	1.99	1.44–2.54	4.21	1.70–6.79
Unrestricted	1.97	1.38–2.55	4.20	1.08–7.42

Increases are for a 10 µg/m^3 increase in PM_{10}.

Figure 1. CVD mortality in Athens: plot of the residuals from the unconstrained distributed lag model showing no residual seasonality in the models.
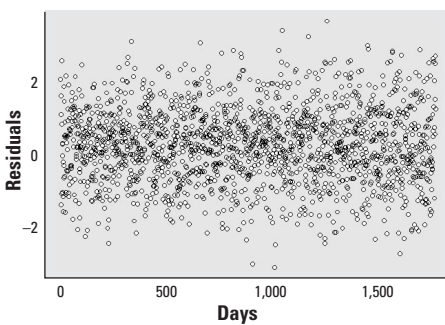
Figure 2. CVD mortality in London: plot of the residuals from the unconstrained distributed lag model showing no seasonality left in the models.

Table 3. Results for the combined estimated PM_{10} effect for the unrestricted models, with 20, 30, and 40 days of delay, using bootstrap methods.

	CVD		Respiratory disease	
	Percent	95% CI	Percent	95% CI
Unrestricted distributed lag				
20 lags	1.34	0.89–1.79	1.71	⁻0.65–4.12
30 lags	1.72	1.20–2.25	2.62	0.19–5.11
40 lags	1.97	1.38–2.55	4.20	1.08–7.42

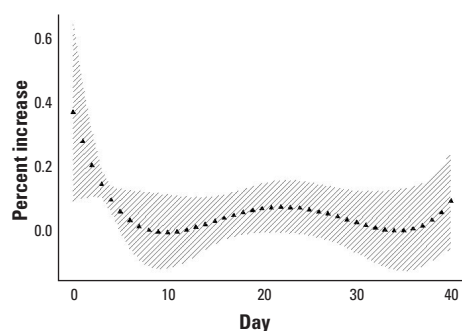Increases are for a 10 µg/m^3 increase in PM_{10}.

Figure 3. The estimated shape of the association of PM_{10} for each lag with daily deaths for CVD with a fourth-degree distributed lag model with random effect in 10 cities (percentage increase in deaths for a 10 µg/m^3 increase in PM_{10}). The shaded area represents the 95% CIs.
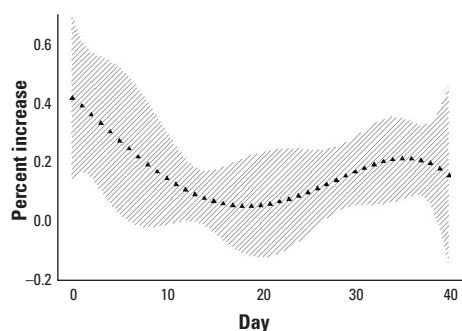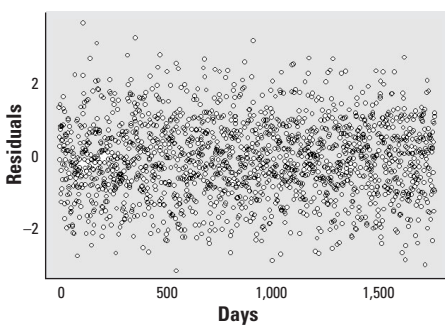

Figure 4. The estimated shape of the association of PM_{10} for each lag with daily deaths for respiratory disease with a fourth-degree distributed lag model with random effect in 10 cities (percentage increase in deaths for a 10 µg/m^3 increase in PM_{10}). The shaded area represents the 95% CIs.

Table 4. Results for the combined estimated PM$_{10}$ effect for the fourth-degree and unrestricted models, with 40 days of delay, by age groups using bootstrap methods.

Distributed lag	15–64 years		65–74 years		≥ 75 years	
	Percent	95% CI	Percent	95% CI	Percent	95% CI
Total mortality						
Fourth degree	−0.25	−0.87–0.36	0.78	0.23–1.33	1.84	0.92–2.78
Unrestricted	−0.01	−0.76–0.75	0.74	0.02–1.45	1.94	1.07–2.81
Cardiovascular mortality						
Fourth degree	—	—	2.06	1.05–3.09	2.35	1.42–3.29
Unrestricted	—	—	1.62	0.54–2.70	2.52	1.57–3.48
Respiratory mortality						
Fourth degree	—	—	—	—	4.57	1.25–7.99
Unrestricted	—	—	—	—	4.52	0.89–8.28

Increases are for a 10 μg/m^3 increase in PM$_{10}$.

would expect a distribution of times until the exacerbation required hospitalization, which might account for this pattern. We also found an increasing PM$_{10}$ effect with increasing age.

Up to now, no study has examined long distributed lags or short-term mortality displacement for specific ages and causes of death. This study confirms the basic finding of the previous analysis on mortality displacement (Schwartz 2000c, 2001; Zanobetti et al. 2002; Zeger et al. 1999), because we did not find any net short-term harvesting. Rather, our results are consistent with the report of higher risk estimates in cohort studies (Dockery et al. 1993; Pope et al. 1995b), although still smaller in magnitude. However, there may be short-term displacement for some, but this is outweighed by the longer-term effect.

This study provides insight into the shape of the longer-term responses to particulate air pollution. In particular, it suggests that the adverse response to pollution persists to a month or longer after exposure not only for total mortality but also for respiratory and cardiovascular mortality. This was also observed in the 1952 London smog episode (Anderson 1999).

If we focus on assessing the difference in the lag pattern between particulate matter and cause-specific mortality, we can identify two different patterns. For respiratory deaths, the decline in impact of particle exposure over time is noticeably slower than that for cardiovascular deaths. For both causes, there is a small elevation of death risk that persists for about another month. The confidence intervals prevent us from drawing strong conclusions about the shape of the curves.

Based on the biologic plausibility, the differences on the lag structure here observed are admissible. CVD presents an acute response to trigger agents, and both experimental (Godleski 2000) and human (Peters et al. 2000) studies have supported this point. On the other hand, a wider and more lagged structure can be expected for respiratory diseases such as pneumonia and chronic disease, because these events have slower progression.

The APHEA-2 project was one of three large multicity studies of the effects of particulate air pollution that have recently been reported. The largest study (National Mortality and Morbidity Air Pollution Study) examined 90 U.S. cities (Samet et al. 2000). Because of the limitations of U.S. monitoring networks, results were reported only for 24-hr PM exposure. Those results were quite similar to the main APHEA-2 results (Katsouyani et al. 2001) but slightly lower. The APHEA-2 main results used the mean of PM exposure over 2 days (Katsouyani et al. 2001).

Another U.S. study restricted to 10 U.S. cities with daily PM monitoring showed a gradient in effect size when comparing 1-day averages, 2-day averages, and a 5-day distributed lag (Schwartz 2000a).

Our results, taken together with the reports described above, as well as other approaches to the harvesting question, confirm that estimates of the effects of subchronic exposure to air pollution that rely on 24- or 48-hr exposure measures seriously underestimate the impact of particle exposure.

Moreover, because part of the effect appears to involve triggering myocardial infarctions (Peters et al. 2001), the previous literature showing persons surviving for a month after their infarct have a life expectancy measured in years, suggests that deaths associated with air pollution include many that are advanced by a considerable amount.

Together with previous studies, this study suggests that risk assessment based on the short-term associations likely underestimate the number of early deaths that are advanced by a significant amount, and that estimates based on the cohort studies, or studies such as this one, would more accurately assess the public health impact.

REFERENCES

Akaike H. 1973. Information theory and an extension of the maximum likelihood principal. In: Second International Symposium on Information Theory (Petrov BN, Csaki F, eds). Budapest:Akademiai Kaiado, 267–281.

Almon S. 1965. The distributed lag between capital appropriations and expenditures. Econometrica 33:178–196.

Anderson HR. 1999. Health effects of air pollution episodes. In: Air Pollution and Health (Holgate ST, Samet JM, Koren HS, Maynard RL, eds). London:Academic Press, 461–482.

Biggeri A, Bellini P, Terracini B, Italian MISA Group. 2001. Meta-analysis of the Italian studies on short-term effects of air pollution. Epidemiol Prev 25(2 suppl):1–71.

Braga AL, Zanobetti A, Schwartz J. 2001. The lag structure between particulate air pollution and respiratory and cardiovascular deaths in 10 US cities. J Occup Environ Med 43:927–933.

Bremner SA, Anderson HR, Atkinson RW, McMichael AJ, Strachan P, Bland JM, et al. 1999. Short-term associations between outdoor air pollution and mortality in London 1992–4. Occup Environ Med 56:237–244.

Brumback BA, Ryan LM, Schwartz J, Neas LM, Stark PC, Burge HA. 2000. Transitional regression models with application to environmental time series. J Am Stat Assoc 95(449):16–28.

Cleveland WS, Devlin SJ. 1988. Robust locally-weighted regression and smoothing scatterplots. J Am Stat Assoc 74:829–836.

Dockery DW, Pope CA III, Xu X, Spengler JD, Ware JH, Fay ME, et al. 1993. An association between air pollution and mortality in six U.S. cities. New Engl J Med 329:1753–1759.

Dominici F, McDermott A, Zeger SL, Samet JM. 2002. On the use of generalized additive models in time-series studies of air pollution and health. Am J Epidemiol 156:1–11.

Efron B, Tibshirani R. 1993. An Introduction to the Bootstrap. New York:Chapman & Hall.

Godleski JJ, Verrier RL, Koutrakis P, Catalano P, Coull B, Reinisch U, et al. 2000. Mechanisms of morbidity and mortality from exposure to ambient air particles. Res Rep Health Eff Inst 91:5–88.

Goldberg MS, Bailar JC III, Burnett RT, Brook JR, Tamblyn R, Bonvalot Y, et al. 2000. Identifying subgroups of the general population that may be susceptible to short-term increases in particulate air pollution: a time-series study in Montreal, Quebec. Res Rep Health Eff Inst 97:7–113.

Hastie T, Tibshirani R. 1990. Generalized Additive Models. London:Chapman & Hall.

Hoek G, Brunekreef B, Fischer P, van Wijnen J. 2001. The association between air pollution and heart failure, arrhythmia, embolism, thrombosis, and other cardiovascular causes of death in a time series study. Epidemiology 12:355–357.

Hoek G, Schwartz J, Groot B, Eilers P. 1997. Effects of ambient particulate matter and ozone on daily mortality in Rotterdam, The Netherlands. J Arch Environ Health 52:455–463.

Katsouyanni K, Hatzakis A, Kalandidi A, Trichopoulos D. 1990. Short term effects of atmospheric pollution on mortality in Athens. Arch Hellen Med 7:126–132.

Katsouyanni K, Touloumi G, Samoli E, Gryparis A, Le Tertre A, Monopolis Y, et al. 2001. Confounding and effect modification in the short-term effects of ambient particles on total mortality: results from 29 European cities within the APHEA2 project. Epidemiology 12:521–531.

Katsouyanni K, Touloumi G, Spix C, Schwartz J, Balducci F, Medina S, et al. 1997. Short term effects of ambient sulphur dioxide and particulate matter on mortality in 12 European cities: results from time series data from the APHEA project. Br Med J 314:1658–1663.

Kelsall JE, Samet JM, Zeger SL, Xu J. 1997. Air pollution and mortality in Philadelphia: 1974–1988. Am J Epidemiol 146:750–762.

Ostro B, Chestnut L, Vichit-Vadakan N, Laixuthai A. 1999a. The impact of particulate matter on daily mortality in Bangkok, Thailand. J Air Waste Manag Assoc 49:100–107.

Ostro B, Hurley S, Lipsett MJ. 1999b. Air pollution and daily mortality in the Coachella Valley, California: a study of PM$_{10}$ dominated by coarse particles. Environ Res 81:231–238.

Ostro B, Sanchez JM, Aranda C, Eskeland GS. 1996. Air pollution and mortality: results from a study of Santiago, Chile. J Expo Anal Environ Epidemiol 6:97–114.

Peters A, Dockery DW, Muller JE, Mittleman MA. 2001. Increased particulate air pollution and the triggering of myocardial infarction. Circulation 103:2810–2815.

Peters A, Liu E, Verrier RL, Schwartz J, Gold DR, Mittleman M, et al. 2000. Air pollution and incidences of cardiac arrhythmia. Epidemiology 11:11–17.

Ponka A, Savela M, Virtanen M. 1998. Mortality and air pollution in Helsinki. Arch Environ Health 53:281–286.

Pope CA III, Dockery DW, Schwartz J. 1995a. Review of epidemiologic evidence of health effects of particulate air pollution. Inhal Toxicol 7:1–18.

Pope CA III, Thun MJ, Namboodiri M, Dockery DW, Evans JS, Speizer FE, et al. 1995b. Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. Am J Respir Crit Care Med 151:669–674.

Ramsay T, Burnett R, Krewski D. 2003. The effect of concurvity in generalized additive models linking mortality and ambient air pollution. Epidemiology 1:18–23.

Rossi G, Vigotti MA, Zanobetti A, Repetto F, Giannelle V,

Schwartz J. 1999. Air pollution and cause specific mortality in Milan, Italy, 1980–1989. Arch Environ Health 54:158–164.

Saldiva PH, Pope CA, Schwartz J, Dockery DW, Lichtenfels HJ, Salge JM, et al. 1995. Air pollution and mortality in elderly people: a time series study in Sao Paulo, Brazil. Arch Environ Health 50:159–163.

Samet JM, Dominici F, Curriero FC, Coursac I, Zeger SL. 2000. Fine particulate air pollution and mortality in 20 U.S. cities, 1987–1994. N Engl J Med 343:1742–1749.

Schwartz J. 1994. Air pollution and daily mortality: a review and meta analysis. Environ Res 64:36–52.

———. 1999. Air pollution and hospital admissions for heart disease in eight US counties. Epidemiology 10:17–22.

———. 2000a. Assessing confounding, effect modification, and thresholds in the association between ambient particles and daily deaths. Environ Health Perspect 108:563–568.

———. 2000b. The distributed lag between air pollution and daily deaths. Epidemiology 11:320–326.

———. 2000c. Harvesting and long-term exposure effects in the relationship between air pollution and mortality. Am J Epidemiol 151:440–448.

———. 2001. Is there harvesting in the association of airborne particles with daily deaths and hospital admissions? Epidemiology 12:55–61.

Schwartz J, Dockery DW. 1992. Increased mortality in Philadelphia associated with daily air pollution concentrations. Am Rev Respir Dis 145:600–604.

Schwartz J, Spix C, Touloumi G, Bacharova L, Barumamdzadeh T, Le Tertre A, et al. 1996. Methodological issues in studies of air pollution and daily counts of deaths or hospital admissions. J Epidemiol Community Health 50(suppl 1):S3–S11.

Simpson R, Denison L, Petroeschevsky A, Thalib L, Williams G. 2000. Effects of ambient particle pollution on daily mortality in Melbourne, 1991–1996. J Expo Anal Environ Epidemiol 10:488–496.

Touloumi G, Pocock SJ, Katsouyanni K, Trichopoulos D. 1994. Short-term effects of air pollution on daily mortality in Athens: a time-series analysis. Int J Epidemiol 23:957–967.

Verhoeff AP, Hoek G, Schwartz J, van Wijnen JH. 1996. Air pollution and daily mortality in Amsterdam. Epidemiology 7:225–230.

Wordley J, Walters S, Ayres JG. 1997. Short term variations in hospital admissions and mortality and particulate air pollution. Occup Environ Med 54:108–116.

Zanobetti A, Schwartz J, Dockery DW. 2000a. Airborne particles are a risk factor for hospital admissions for heart and lung disease. Environ Health Perspect 108:1071–1077.

Zanobetti A, Schwartz J, Samoli E, Gryparis A, Touloumi G, Atkinson R, et al. 2002. The temporal pattern of mortality responses to air pollution: a multicity assessment of mortality displacement. Epidemiology 13:87–93.

Zanobetti A, Wand MP, Schwartz J, Ryan L. 2000b. Generalized additive distributed lag models: quantifying mortality displacement. Biostatistics 1:279–292.

Zeger SL, Dominici F, Samet J. 1999. Harvesting-resistant estimates of air pollution effects on mortality. Epidemiology 10:171–175.

Zelikoff JT, Nadziejko C, Fang T, Gordon C, Premdass C, Cohen MD. 1999. Short term, low-dose inhalation of ambient particulate matter exacerbates ongoing pneumococcal infections in *Streptococcus pneumoniae*-infected rates. In: Proceedings of the Third Colloquium on Particulate Air Pollution and Human Health (Phalen RF, Bell YM, eds). Irvine, CA:Air Pollution Health Effects Laboratory, University of California, Irvine, 8:94–101.