



ORIGINAL CONTRIBUTIONS

Harvesting and Long Term Exposure Effects in the Relation between Air Pollution and Mortality

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While time series analyses have demonstrated that airborne particles are associated with early death, they have not clarified how much the deaths are advanced. If all of the pollution-related deaths were advanced by only a few days, one would expect little association between weekly averages of air pollution and daily deaths. The author used the STL algorithm to classify data on air pollution, daily deaths, and weather from Boston, Massachusetts (1979–1986) into three time series: one reflecting seasonal and longer fluctuations, one reflecting short term fluctuations, and one reflecting intermediate patterns. By varying the cutoff point between short term and intermediate term, it was possible to examine harvesting on different time scales. For chronic obstructive pulmonary disease, there was evidence that most of the mortality was displaced by only a few months. For pneumonia, heart attacks, and all-cause mortality, the effect size increased with longer time scales. The percentage increase in all deaths associated with a 10- $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ rose from 2.1% (95% confidence interval: 1.5, 4.3) to 3.75% (95% confidence interval: 3.2, 4.3) as the focus moved from daily patterns to monthly patterns. This is consistent with the larger effect seen in prospective cohort studies, rather than harvesting's playing a major role. *Am J Epidemiol* 2000;151:440–8.

air pollution; mortality

Editor's note: An invited commentary on this article appears on page 449.

A large body of literature has shown associations between particulate air pollution and daily mortality and morbidity (1–29). These associations have been demonstrated in locations or seasons where ozone and sulfur dioxide concentrations were essentially nonexistent, making confounding by these other pollutants implausible (30). As a result, national (31, 32) and international (33) bodies have concluded that these associations should be treated as causal and have recommended implementation of tighter air quality standards. While the association between particulate matter and daily mortality is generally accepted, considerable controversy exists about the extent to which deaths are advanced by higher air pollution levels. Some have argued that it is inappropriate to use regression coeffi-

cients from these studies to estimate the attributable risk of air pollution, because it is not clear how many of the deaths are occurring only a few days early among persons who were already dying (34). This is usually referred to as “harvesting,” or mortality displacement. If all of the deaths associated with particulate air pollution were only being displaced by a few days, this would obviously have implications for the extent of public health concern that should be given to the associations.

On the other hand, the existing studies have only examined the association between air pollution exposure on the same day or during the previous few days and mortality and morbidity. Exposure of animals to combustion particles indicates that such particles produce inflammatory damage in the lung, at least partially by the generation of oxidants (35–38). This suggests that exposure over time intervals of weeks may have some additional cumulative effect that is not captured in the current short term regression analyses. Furthermore, studies showing that air pollution is associated with increased severity of illness (14–29) suggest that it can increase the pool of persons at high risk of dying (by moving people from moderate to severe illness) as well as deplete it. The net effect on the size of the susceptible pool is not clear a priori. Finally, prospective cohort studies of particulate air pollution and daily numbers of

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Abbreviations: COPD, chronic obstructive pulmonary disease; ICD-9, *International Classification of Diseases*, Ninth Revision; PM, particulate matter.

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deaths (39, 40) have reported substantially greater effects of long term exposure to, e.g., $10 \mu\text{g}/\text{m}^3$ of fine particles than are indicated by the daily time series studies. Those authors have suggested that the difference may represent an effect of chronic exposure. This investigation sought to examine how the association between particulate air pollution and mortality and morbidity varies as the time scale of exposure varies.

MATERIALS AND METHODS

Data

This paper used mortality data from Boston, Massachusetts, for the years 1979–1986; details have been published previously (12). Briefly, between 1979 and 1986, dichotomous virtual impactor samplers were placed at a central, residential monitoring site in the Boston metropolitan area as part of the Harvard Six Cities Study. Separate samples of fine particles (particulate matter with a diameter ≤ 2.5 microns ($\text{PM}_{2.5}$)) and the coarse mass were collected. This analysis was restricted to the fine particle data.

Daily numbers of deaths in Norfolk, Suffolk, and Middlesex counties, which are the metropolitan counties proximate to the monitoring site, were extracted from annual detail mortality tapes obtained from the National Center for Health Statistics for the same time period. Deaths due to accidents and other external causes (*International Classification of Diseases*, Ninth Revision (ICD-9) (41), codes 800–999) were excluded. Separate counts were also computed for deaths from ischemic heart disease (ICD-9 codes 410–414), congestive heart failure (ICD-9 code 428), pneumonia (ICD-9 codes 480–486), and chronic obstructive pulmonary disease (COPD) (ICD-9 codes 490–496).

Meteorologic data were obtained from the National Center for Atmospheric Research. The hourly measures were collapsed over 24-hour periods to obtain a mean value for ambient temperature and dew point temperature. The initial paper (12) reported an association between daily number of deaths and the average amount of air pollution exposure on the same day and previous days. The association was seen after data were controlled for weather using nonparametric smooth functions of temperature and humidity and controlled for season using a nonparametric smooth function of time with a smoothing window of about 125 days. The initial paper also examined how the association varied with different particle measures, which is not the topic of this analysis.

Methods

If air pollution only advances deaths by a few days, we would expect an increase in daily numbers of deaths due

to air pollution to be followed shortly by a decline. If we averaged the numbers over 1 week, the two effects would cancel out (or partially cancel out, if some of the deaths were brought forward by a longer period). In other words, the association between air pollution and daily deaths would be concentrated in high frequency fluctuations, those with periods of only a few days. A multiday average of daily deaths would no longer be associated with air pollution, since the air pollution effect and the rebound from it would have been smoothed over by the averaging. If we can separate the correlation between air pollution and daily deaths into characteristic frequency ranges, the existence of an association at lower frequencies would demonstrate that not all of the air pollution-associated deaths are being advanced by only a few days. This is the basis of the analysis. Contrawise, if there were cumulative effects of exposure that were not captured in the daily regression analyses, or if air pollution increased the pool of susceptibles, the association between longer period fluctuations in air pollution and daily deaths would have a larger effect size than was seen in the original analysis. By examining this association in different frequency ranges, one can examine the existence of harvesting and effects of longer term exposure on a range of time scales from several days to approximately 1–2 months. Examination of much longer time scales is difficult because of the need to control for season.

Cleveland et al.'s STL algorithm (42) was used to separate the time series of daily deaths, air pollution, and weather into long wavelength components (representing time trends and seasonal fluctuations), midscale components, and residual very short time scale components. This analysis used the midscale components of each time series to assess the association between air pollution and mortality on that scale, having removed the potentially confounding effect of season (long scale) and the component susceptible to short term harvesting (short scale). The STL algorithm uses LOESS smoothing to separate the series into these components.

All analyses used the same cutoff point for the long wavelength component. A LOESS smooth with a window of 120 days was used to fit and remove the seasonal and long term time trends. The LOESS smooth uses a weighted moving regression within the 120-day window to estimate the seasonal component of variation for each time series (i.e., deaths, $\text{PM}_{2.5}$, temperature, and dew point). The weights decrease to zero at the ends of the window as the cube of the fraction of the distance from the center to the end (see the Appendix), and are near 1 only for approximately the central 40 percent of the window. Hence, the effectiveness of a 120-day window in a LOESS smooth in removing long wavelength patterns is similar to a simple unweighted moving average of approximately 60

days. The LOESS smooth is preferred because the weighted smoothing produces less distortion in the high frequency components. Smaller window sizes (e.g., 90 days) induce short term serial correlation in the data that is not present in the original series.

Because the goal of the analysis was to examine the association in different frequency ranges, several different midscale components were examined separately. These midscale smoothing windows were 15, 30, 45, and 60 days. For each midscale window, the analysis was repeated, removing the seasonal and short term patterns from the data. Regression analysis was then performed among the midscale variations in deaths, pollution, and weather for each of the four choices of midscale variation.

To maintain comparability with the original study, the same generalized additive model and choice of lag times were used in these analyses. A log-linear regression was fitted relating the logarithm of the filtered daily number of deaths (with the mean added back) to LOESS smooth functions of temperature, dew point, and a linear PM_{2.5} term for each of the different midscale frequency ranges. The smooth functions of temperature and dew point used approximately 5 df each. (See the Appendix for more details.) The results for each of these windows were compared with results from the original regressions. This allows for a comparison of the effect sizes as we sequentially exclude longer and longer term harvesting from the analysis.

RESULTS

Table 1 shows the mean values for the Boston environmental and mortality data. Air pollution levels were low to moderate. The total number of deaths per day averaged 60. Figure 1 shows the 120-day LOESS smooth, which appears to capture seasonal variation and some shorter term structure in the mortality data. Figure 2 shows the residuals after removal of this pattern from the mortality data, confirming that no seasonal pattern was left in the data. In fact, the partial autocorrelation function was reduced to white noise by a 150-day LOESS smooth, and to be conservative the 120-day window was used. Figure 3 shows what data filtered in such a manner look like. It shows the residual daily number of deaths from ischemic heart disease, after removal of both seasonal and short term fluctuations, over time. The mean is zero in the figure, but the mean was added back in to perform the log-linear regressions. Figure 4 shows the estimated increase in deaths from COPD associated with a 10- $\mu\text{g}/\text{m}^3$ increase in PM_{2.5} as originally estimated, and with each of the four filters. Figures 5 and 6 show the estimated increases for pneumonia and ischemic heart disease deaths. These three cause-specific plots illustrate different patterns of association.

TABLE 1. Mortality and environmental data used in a study of air pollution, Boston, Massachusetts, 1979–1986*

	Mean	Standard error
Mortality (deaths per day)		
All-cause	60	9.6
Pneumonia	2.7	1.9
Chronic obstructive pulmonary disease	1.4	1.4
Ischemic heart disease	17.9	5.3
Environmental data		
Temperature (°C)	10.6	9.6
PM _{2.5} † ($\mu\text{g}/\text{m}^3$)	15.6	9.2
Dew point (°C)	4	10.7

* Data were obtained from Schwartz et al. (12).

† PM_{2.5}, particulate matter with a diameter ≤ 2.5 microns.

The results for COPD show a pattern similar to what has been hypothesized about mortality displacement. The effect size first increases when a 15-day smoothing window is used and then decreases to zero with a 60-day smoothing window. This suggests that the deaths due to COPD are only being advanced by a few weeks or a few months.

Pneumonia, in contrast, shows some sign of short term harvesting: There is a lower effect size with a 15-day smoothing window, but then the effect size grows to more than twice the original estimate by the time a 60-day smoothing window is reached. This pattern is not consistent with most of the deaths' being advanced by a few days to a few months.

For ischemic heart disease death, the effect size is unchanged using the 15-day window. With larger averaging windows, the effect size increases monotonically. For the 60-day window, which focuses the association on correlations with a 30- to 100-day time scale, the effect of air pollution is almost twice as great as in the original regression.

The results for all-cause mortality most strongly resemble those for ischemic heart disease. The 15-day smoothing window results in little change, but the effect size then increases steadily with increasing averaging times. This is indicated in figure 7.

DISCUSSION

These results provide some evidence of both some short term harvesting effects and larger effects when short term harvesting is excluded. These latter effects may reflect the impact of longer term average pollution concentrations or increased recruitment into the susceptible pool caused by air pollution. When making comparisons with the original regression results, we should recall that once seasonal patterns are removed, the greatest variation in the air pollution data occurs

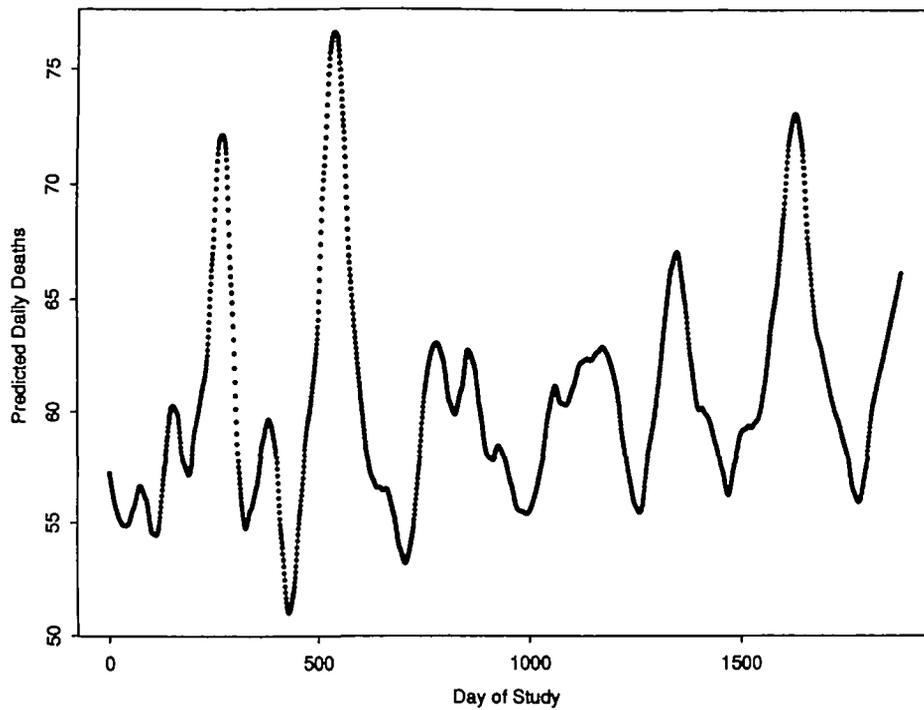


FIGURE 1. Results of the 120-day window LOESS smooth function of daily deaths in Boston, Massachusetts, for the period 1979–1986. This smooth was removed from the data to control for season and trend in all of the subsequent analyses.

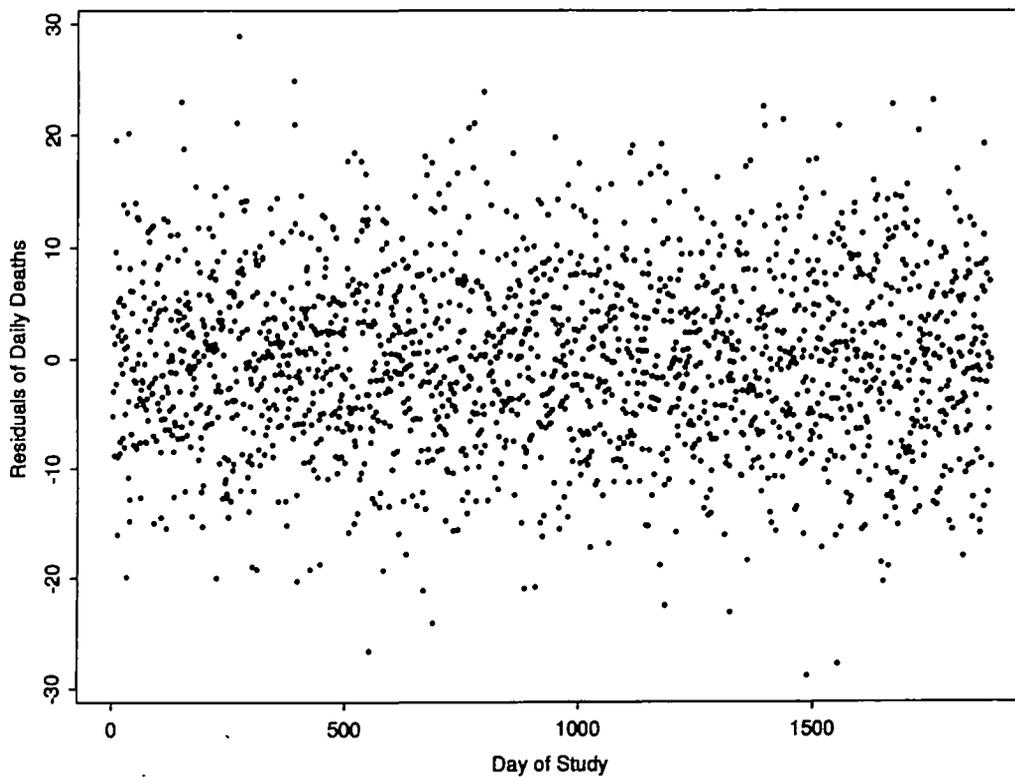


FIGURE 2. Residuals from the seasonal smooth depicted in figure 1. No seasonality is apparent in the residuals.

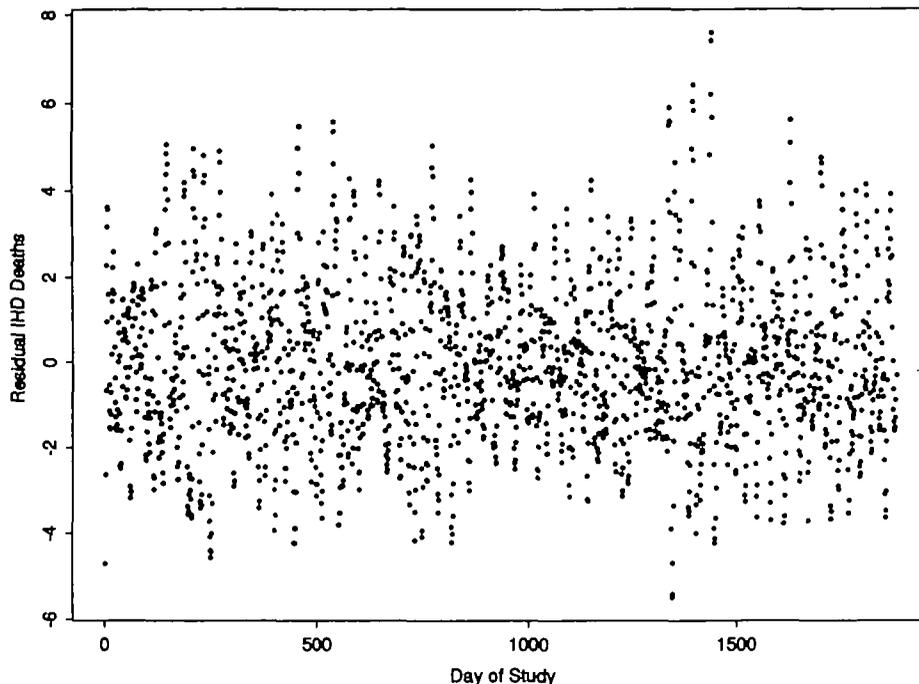


FIGURE 3. Residuals of ischemic heart disease (IHD) deaths versus day of study, after removing seasonality using a 120-day LOESS filter and short term fluctuations using a 15-day LOESS filter.

with time scales of less than a week. Hence, the regression is presumably dominated by results on that time scale. As we move to regressing the filtered time series, we switch the dominant time scale first to variations over a few weeks and eventually to variations

over a few months. By that time, for COPD, the effect of air pollution has disappeared. This suggests that the COPD deaths are mostly being brought forward by a few months. Note that these results apply to deaths for which COPD is listed as the underlying cause. COPD

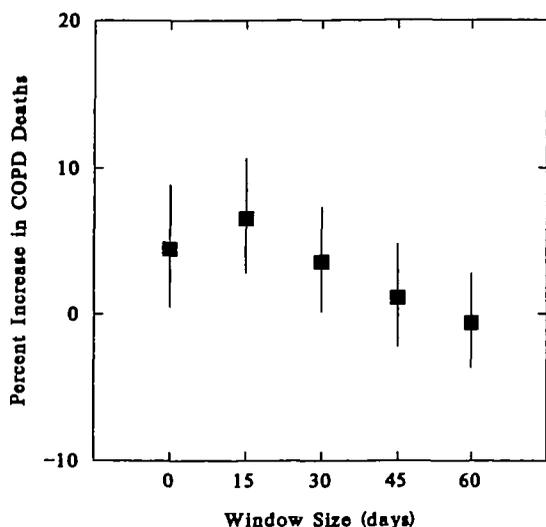


FIGURE 4. Estimated effect of a 10- $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ concentration on daily mortality from chronic obstructive pulmonary disease (COPD) in Boston, Massachusetts, in the original published article (12) and the four analyses carried out in this study, using windows of 15, 30, 45, and 60 days.

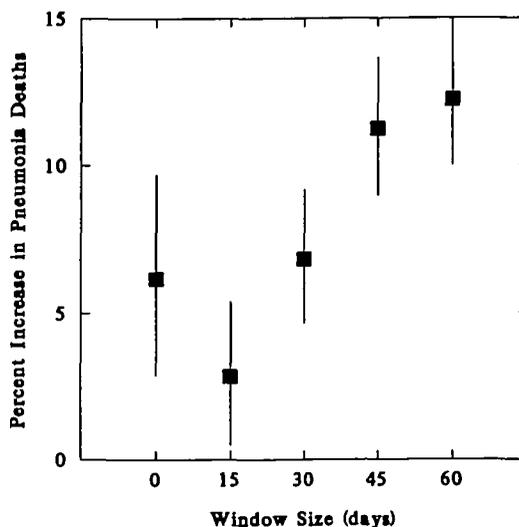


FIGURE 5. Estimated effect of a 10- $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ concentration on daily mortality from pneumonia in Boston, Massachusetts, in the original published article (12) and the four analyses carried out in this study, using windows of 15, 30, 45, and 60 days.

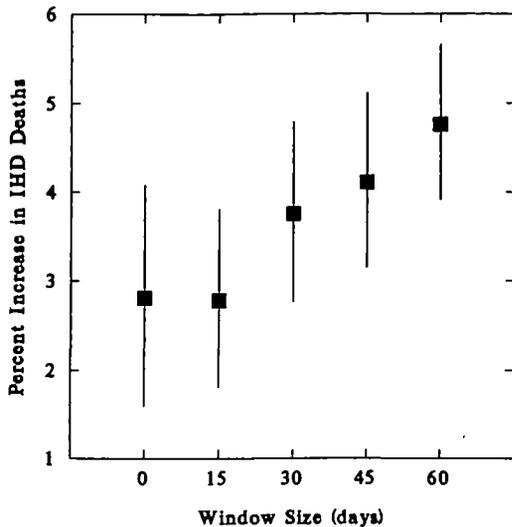


FIGURE 6. Estimated effect of a $10\text{-}\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ concentration on daily mortality from ischemic heart disease (IHD) in Boston, Massachusetts, in the original published article (12) and the four analyses carried out in this study, using windows of 15, 30, 45, and 60 days.

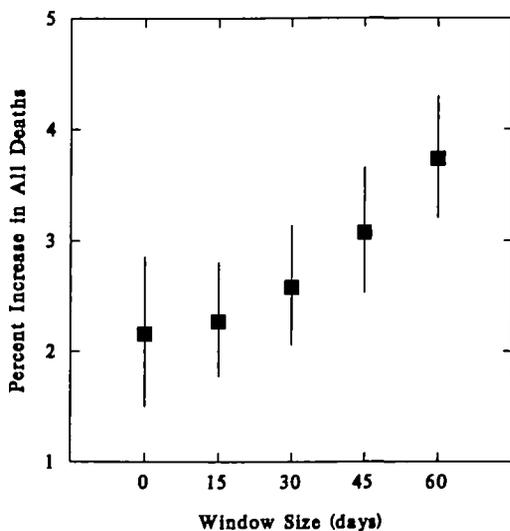


FIGURE 7. Estimated effect of a $10\text{-}\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ concentration on all-cause mortality in Boston, Massachusetts, in the original published article (12) and the four analyses carried out in this study, using windows of 15, 30, 45, and 60 days.

may be a contributing cause of death for deaths with other underlying causes listed, and the pattern may differ in those cases. In a recent study (43), rats with COPD had excessive mortality when exposed to $200\text{--}300\ \mu\text{g}/\text{m}^3$ of particles in exposure chambers; however, they died in their sleep without signs of respiratory distress, and the deaths may have been due to cardiovascular effects.

In contrast, the results for pneumonia suggest that there may be some deaths brought forward by a few days—which produces the diminished effect on a time scale of a few weeks—but the effect is overwhelmed by the larger effect sizes when all longer term filters are applied. On a time scale of 1 or 2 months, the effect of air pollution on pneumonia deaths seems substantially larger than originally reported. This is not surprising; people with pneumonia rarely linger on the edge of death for months. If the pneumonia is potentially life-threatening, it usually remains so for a limited period, followed by either recovery or death. If a patient recovers from the pneumonia, he or she is probably safe until the next episode, which is likely to occur a year or more in the future. I have confirmed this by examining pneumonia hospital admissions in Chicago, Illinois, for 1992. Of the persons aged 65 years or older who were admitted to hospitals in January and February, only 8 percent had a readmission in the next 6 months. Hence, a pattern of some deaths' being brought forward by a few days, but not most of them, makes sense. The possibility that longer term exposures to particulate air pollution may exacerbate pneumonia deaths is also plausible, since particulate exposure is associated with inflammatory processes. Moreover, the association between particulate air pollution and pneumonia hospital admissions (42–44) suggests that the pool of persons at risk of dying from pneumonia may be increased by particulate air pollution, not decreased. Animal studies have shown that exposure to combustion particles exacerbates *Staphylococcus pneumonia* in rats (44) and influenza infections in mice (45), lending further credence to this association. Of course, it is still possible that the deaths of some of these individuals, particularly at older ages, are only being brought forward by a few months, which is still a modest amount. However, the natural history of pneumonia suggests that most of the people who recover from pneumonia will not contract another case until the next pneumonia season.

For ischemic heart disease mortality and all-cause mortality, excluding short term changes definitely leads to an increase in the estimated effect of air pollution. If one thinks of heart attacks as Poisson events in vulnerable populations, then it is not surprising that if an event is avoided on a given day, the expected displacement of mortality will be greater than months. Of course, the effect of air pollution might be primarily to exacerbate a myocardial infarction brought on by other stimuli. Here also the analysis cannot exclude the possibility that the deaths are only being brought forward by, e.g., 3 months. However, since the 5-year survival rate for people who survive the first 48 hours of a heart attack is quite high, this is unlikely to be the case for

most of the avoided early deaths. Again, among elderly persons admitted to a hospital for myocardial infarction in January and February of 1992, only 6 percent had a second admission for myocardial infarction in the next 6 months. In a prospective follow-up study involving most of the urban areas in the United States, Pope et al. (40) examined the relation between fine particle exposure on a scale of years and deaths. They reported that a $10\text{-}\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ concentration was associated with a 6.6 percent increase in all-cause mortality. They attributed the difference between that effect estimate and results such as the 2.1 percent estimate seen in the original time series study (12) as suggesting a greater effect of long term exposure, possibly due to the development of chronic disease. For example, other studies have indicated that particulate exposure is a risk factor for the development of COPD (46, 47). Some have argued that the higher slope reflects the higher exposures that existed 20 years earlier in their study locations (48). This analysis indicates that moving from a time scale of days to one of months captures approximately half of the difference between the daily time series and the prospective cohort study. This suggests that most of the increase in slope occurs over relatively short time scales and does not take 20 years of exposure to develop. Of course, it is also possible that the higher slope in the cohort studies results from uncontrolled confounding.

There is a developing body of literature on potential mechanisms by which particulate air pollution might affect the cardiovascular system. Exposure of dogs to $100\text{--}200\ \mu\text{g}/\text{m}^3$ of fine particles in an exposure chamber for 6 hours per day for 3 days resulted in electrocardiographic changes that are risk factors for arrhythmia (49). These changes were enhanced in the presence of preexisting angina (49). In another recent study (50), instillation of 250 μg of combustion particles into the lungs of rats produced arrhythmia and death. In humans, particulate air pollution has been associated with increases in plasma viscosity (51), an increased risk of elevated heart rate (52), and changes in heart rate variability (53).

Obviously, it would be of interest to examine whether the deaths associated with particulate air pollution continue to increase as the averaging time increases further. In particular, how long does it take to reach the levels seen in the prospective cohort studies? However, seasonality acts as an impediment to examining this further using time series data. The use of a filter to remove seasonality prevents us from examining longer term averaging periods. One alternative would be to use a larger window to control for season, but this would increase the risk of confounding by inadequately controlling for season, and hence repre-

sents an inherent limitation of such time series analyses. Another limitation of the study is the choice of lag times for the exposure variables. The original study chose a priori to use the mean of the pollution levels on the same day and the previous day at all six locations studied (12). I repeated that choice here in order to maintain comparability. The original paper also used weather variables for the same day for each city studied. Further examination in Boston could reveal a better fit from a different weather model. Again, I used the same model to maintain comparability. Because of this, differences in effect size estimates can be uniquely attributable to discarding the higher frequency variations in the data. Kelsall et al. (54) reported that the association between airborne particles and daily deaths in Philadelphia, Pennsylvania, was insensitive to variations in control for season and weather.

Overall, this analysis suggests that the time series study results which have been published underestimate rather than overestimate the number of early deaths that are associated with air pollution and that are brought forward by nontrivial amounts of time.

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APPENDIX

The STL algorithm as applied in this analysis takes each time series (daily deaths, daily PM_{2.5}, daily mean temperature, and daily mean dew point temperature) and decomposes it into three parts. The first part represents seasonal and other longer term fluctuations, and was fitted by applying a LOESS filter to the data with a window of 120 days. The residuals from this process are then filtered again, using a LOESS filter with a second window size. In the initial analysis, this was set at 15 days. The residuals of this second filter represent fluctuations of less than 15 days. Subtracting these residuals from the residuals of the first filter gives us the fluctuations in the original time series that have both long term and very short term fluctuations removed. For example, we would decompose daily fluctuations in PM_{2.5} as follows:

$$PM_{2.5} = PM_{2.5\text{long}} + PM_{2.5\text{mid}} + PM_{2.5\text{short}}$$

The subsequent regression analyses are conducted on the midrange components of each series.

LOESS is a nonparametric running line smoother. For each window, it divides the data into variations that are commensurate with a little more than half the window size or larger, and shorter term variations. This is done by fitting a running regression within each window to estimate the value of the longer frequency component. The regression is weighted with tricubic weights, defined as follows. Let t be the time in days since the beginning of the study, t_{mid} the midpoint of the window, i.e., the day for which a smoothed estimate is being computed, and d half the width of the smoothing window (e.g., 60 days for the 120-day smooth that controls for season). Then define u as the fraction of the distance between the midpoint and the end of the window for any observation in the window. That is,

$$u = (t - t_{\text{mid}})/d.$$

So u ranges from 0 (at the center of the window) to ± 1 at the ends. Then the weights are:

$$w = (1 - |u|^3)^3.$$

These weights fall rapidly to zero at the ends of the window and are near 1 for the central 40 percent of the window. This is shown in figure A1.

Once all four series were filtered, the following regression was fitted:

$$\text{Log}(\text{death}_{\text{mid}} + \text{mean}(\text{death})) =$$

$$s(\text{temp}_{\text{mid}}) + s(\text{dew}_{\text{mid}}) + PM_{2.5\text{mid}}.$$

Here, s stands for a nonparametric smooth function, which was used to assure that nonlinearities in the dependence on weather were adequately modeled. LOESS smoothing was used for this as well, using a span of 50 percent of the data, which corresponded to approximately 5 df for each weather variable. A log-linear model was fitted to maintain comparability with the original study (12). Similarly, temperature and dew point temperature on the concurrent day were used, as in the original paper, and the smoothing window for each weather factor was the same as in the original paper. This maintains maximum comparability with the original results, allowing us to interpret differences in effect size as being due to the exclusion of the very short term fluctuations in the data from the regressions. To examine the longer windows, the entire process was repeated, using a midscale window of first 30 days, then 45 days, and finally 60 days.

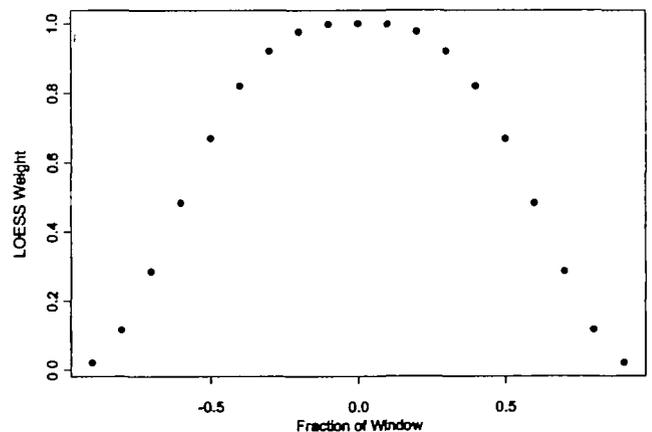


FIGURE A1. Weights assigned to points in the LOESS smooth as a function of their distance from the center of the smoothing window. The distance is expressed as a fraction of half the window size, and ranges from -1 to 1 .