



## Practice of Epidemiology

# Estimating Causal Associations of Fine Particles With Daily Deaths in Boston

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Many studies have reported associations between daily particles less than 2.5  $\mu\text{m}$  in aerodynamic diameter ( $\text{PM}_{2.5}$ ) and deaths, but they have been associational studies that did not use formal causal modeling approaches. On the basis of a potential outcome approach, we used 2 causal modeling methods with different assumptions and strengths to address whether there was a causal association between daily  $\text{PM}_{2.5}$  and deaths in Boston, Massachusetts (2004–2009). We used an instrumental variable approach, including back trajectories as instruments for variations in  $\text{PM}_{2.5}$  uncorrelated with other predictors of death. We also used propensity score as an alternative causal modeling analysis. The former protects against confounding by measured and unmeasured confounders and is based on the assumption of a valid instrument. The latter protects against confounding by all measured covariates, provides valid estimates in the case of effect modification, and is based on the assumption of no unmeasured confounders. We found a causal association of  $\text{PM}_{2.5}$  with mortality, with a 0.53% (95% confidence interval: 0.09, 0.97) and a 0.50% (95% confidence interval: 0.20, 0.80) increase in daily deaths using the instrumental variable and the propensity score, respectively. We failed to reject the null association with exposure after the deaths ( $P = 0.93$ ). Given these results, prior studies, and extensive toxicological support, the association between  $\text{PM}_{2.5}$  and deaths is almost certainly causal.

causal model; instrumental variables; mortality; particulate pollution; propensity score

Abbreviation:  $\text{PM}_{2.5}$ , particles less than 2.5  $\mu\text{m}$  in aerodynamic diameter.

Hundreds of time-series studies reporting on associations of daily changes in air pollution and subsequent daily changes in deaths have been published worldwide (1–15). Many of these have been large multicity studies (2, 5, 16, 17). Their most consistent finding was an association of ambient particles and daily deaths. For example, a study of 5,609,349 deaths in 112 US cities over the years 1999–2005 reported strong associations with particles less than 2.5  $\mu\text{m}$  in aerodynamic diameter ( $\text{PM}_{2.5}$ ) (5).

As in most observational epidemiology investigations, these have been associational studies, and arguments for causality of the association have followed in the path of Hill's criteria (18). The studies were relatively consistent, exposure preceded outcome, and they were biologically plausible. Arguments for biological plausibility have focused on animal studies, showing that particle exposure can induce lung and systemic inflammation (19, 20), produce autonomic changes (21), accelerate atherosclerosis (22–27), and destabilized

atherosclerotic plaque (28). In addition, human studies have reported changes in biomarkers of risk, such as increased risk of ventricular arrhythmia, thrombotic processes, increased system inflammation, oxidative stress, increased blood pressure, and decreased plaque stability (28–41).

What has mostly been missing from this wealth of air pollution epidemiology studies is the use of causal modeling. Although the time-series design is itself quasiexperimental, more formal approaches would provide increased assurance that the observed associations are indeed causal. In this paper, we use 2 different approaches to causal modeling to examine the association between daily  $\text{PM}_{2.5}$  and daily deaths in the Boston, Massachusetts, metropolitan area.

## METHODOLOGICAL BACKGROUND

To establish causality, one requires a causal modeling framework, which in turn requires modeling in terms of potential

outcomes. Briefly, let  $Y_i^{A=a}$  be the outcome of an exposure  $A = a$  for the unit  $i$ , and  $Y_i^{A=a'}$  be the outcome if the unit  $i$  were instead exposed to an alternative exposure,  $A = a'$ . Causal modeling seeks to estimate the difference (or ratio) in the expected value of outcome in the population under the exposure they received versus what it would have been had they received an alternative exposure, that is,  $E(Y_i^{A=a})/E(Y_i^{A=a'})$ . Because only 1 potential outcome is observed, various methods seek legitimate surrogates for the unobserved potential outcome. Randomized trials fit this rubric because randomization means we can take the outcome in the group with the alternative exposure as a valid substitute for the outcome that would have occurred had the treated group received that alternative exposure. Causal methods in observational epidemiology seek alternative ways to estimate a substitute for the second potential outcome (42). One approach relies on natural experiments, or other sources of exposure variation believed to be independent of outcome except through exposure, as a surrogate variable for exposure that is independent from measured and unmeasured confounders and relies on the untestable assumption that the surrogate is randomly assigned with respect to confounders. Another approach uses formal modeling to make the exposure independent of all measured predictors and relies on the untestable assumption of no unmeasured confounding (43, 44). In this paper, we will apply both approaches, which we introduce below.

### Time series as quasiexperimental

First, consider the nature of time-series studies of daily deaths. Imagine instead that we followed the Boston population individually. We apply the Cox proportional hazard model for each person  $i$  and follow-up day  $t$ , as shown below:

$$\text{Log}(\lambda_{it}) = \log(\lambda_0(t)) + X_{it}\beta,$$

where  $X_{it}$  represents the usual suspects—blood pressure, lipids, smoking, alcohol, diet, and so on.  $\lambda_{it}$  is the hazard for person  $i$  at time  $t$ , and  $\lambda_0(t)$  is the baseline hazard in the population for unit  $i$  at time  $t$ . Let us divide the  $X$ 's into 2 groups. The first,  $S_{it}$ , represents variables such as body mass index and pack-years that change slowly over time, that is, on timescales of months to years. The second,  $F_{it}$ , represents the more rapidly changing predictors, such as daily smoking, alcohol consumption, acute triggers of plaque rupture or arrhythmias, acute exposures that might impair pulmonary defenses, and so on. Because  $\lambda_0(t)$  represents the baseline risk independent of key risk factors included in  $S_{it}$  and  $F_{it}$ , we assume it to vary slowly over timescales of months to years. Now, suppose we fit  $\log(\lambda_{it})$  to a flexible function of time with sufficient degrees of freedom in order to capture fluctuations in  $\log(\lambda_{it})$  over timescales of months or longer. Then, the above equation can be transformed as follows:

$$\text{Log}(\lambda_{it}) = g(t) + F_{it}\delta,$$

where  $g(t)$  is the flexible function of time with, for example, 4 df per year of study, and  $F_{it}\delta$  represents the effects of the rapidly varying exposures. That is,  $g(t)$  captures both the time variation of  $\lambda_{0t}$  and of  $S_{it}$ . The mean effects of  $\lambda_{0t}$  and  $S_{it}$

are captured by the intercept, so the only potential confounding remaining is due to  $F_{it}$ . The rapidly changing covariates can be divided into 2 general types. The first type is environmental exposures, such as temperature and air pollution. The second type is day-to-day variability in cigarette smoking or engaging in other risky behaviors. Day-to-day fluctuations in air pollution in North America are mostly unapparent to the general population, except in a few cities, making it unlikely that people modify other behavioral risk factors in response to them. If short-term fluctuations in air pollution are unapparent and generally unrelated to other risky behaviors, then we have a quasiexperimental setting in which exposure is randomly assigned, suggesting causality.

### Instrumental variables

Let  $Y_t^{A=a}$  be the potential outcome (aggregated number of deaths) in the population exposed to  $A = a$  on day  $t$ , and let  $Y_t^{A=a'}$  be the potential outcome under the alternative exposure  $a'$ . We would like to estimate  $E(Y_t^{A=a})/E(Y_t^{A=a'})$ . As mentioned earlier, only  $Y_t^{A=a}$  is observed. Suppose the potential outcome depends on predictors in the following manner:

$$\text{Log}(E(Y_t^a)) = \theta_0 + a\theta_1 + \Phi_t, \quad (1)$$

where  $Y_t^a$  represents the potential outcome at time  $t$  under exposure  $a$ ,  $\theta_0$  and  $\theta_1$  are the intercept and the slope of exposure, and  $\Phi_t$  represents the impact of all other variables on the outcome. Usually,  $E(A_t\Phi_t) \neq E(A_t)E(\Phi_t)$ , hence  $E(\Phi_t|A = a) \neq E(\Phi_t|A = a')$ , and we have confounding. If all of the confounders are not measured, standard methods including standard approaches to causal modeling will give biased estimates of  $\theta$ . However, many exposures including air pollution have multiple sources of variation. Now suppose that we can find a variable  $Z$  that is one such source of variation in exposure, such that  $Z$  is associated with  $Y$  only through  $A$ .  $Z$  is called an instrumental variable or an instrument for  $A$ . Then,  $A_t$  can be expressed as follows:

$$A_t = Z_t\delta + \eta_t, \quad (2)$$

where  $\eta_t$  represents the other sources of variations in exposure and, in particular, all of the exposure variations that are associated with other measured or unmeasured predictors of outcome. This follows from  $Z$ 's being related to  $Y$  only through  $A$ . Formally,

$$\begin{aligned} E(\eta_t\Phi_t) &\neq E(\eta_t)E(\Phi_t) \text{ and thus } E(\eta_t\Phi_t) \neq 0, \\ \text{but } E(Z_t\Phi_t) &= 0 \text{ because of the instrument assumption.} \end{aligned} \quad (3)$$

Then, let  $Z1$  and  $Z2$  be equal to  $Z$ , so that the following relationships are satisfied:  $E(A|Z1) = a$ , and  $E(A|Z2) = a'$ . Then,

$$E(Y_t^{Z=Z1}) = \exp(\theta_0 + \theta_1 a + \Phi_t)$$

and

$$E(Y_t^{Z=Z2}) = \exp(\theta_0 + \theta_1 a' + \Phi_t) \quad (4)$$

Then,

$$E(Y_t^{Z=Z1})/E(Y_t^{Z=Z2}) = \exp(\theta_1(a - a')). \quad (5)$$

Consequently, if we use  $Z$  as an instrument for  $A$ , we can recover a causal estimate for  $\theta_1$ , which is the log rate ratio.

Nothing is for free. We have traded the untestable common assumption made in most causal analyses (that there are no omitted confounders) for a different untestable assumption (that the instrument is not associated with any of the confounders). In addition, we must assume that the instrument is not a modifier of the exposure. In different cases, one or the other of these assumptions (no omitted confounders vs. no association of the instrument with confounders) will seem more plausible. In addition, if  $Z$  explains little of the variation in  $A$ , it may be a valid instrument but lack power to detect an association.

In our case, we believe that we can identify a valid instrument, which is implausibly associated with other predictors of mortality, and which explains enough of the day-to-day variation in particulate air pollution to have reasonable power.

Particulate matter is a complex mixture of chemical compounds in the solid and/or liquid phase. It is composed of primary particles directly emitted from sources and secondary particles that are formed in the atmosphere by a series of reactions. If dry deposition is the predominant removal mechanism of  $PM_{2.5}$ , then the residence time of  $PM_{2.5}$  in the atmosphere is on the order of days to weeks. Wet deposition can accelerate particle removal, but it occurs only during precipitation events. Therefore, at a given location and time, a considerable fraction of  $PM_{2.5}$  in the air is transported from elsewhere. Boston and the Northeastern Region are mostly impacted by pollution transported from different regions of the United States and Canada. On average, transported  $PM_{2.5}$  could represent from  $\frac{1}{2}$  to  $\frac{2}{3}$  of total  $PM_{2.5}$ . In a previous study in Boston, we have shown that, when air masses originate from less polluted regions, the  $PM_{2.5}$  concentration levels are lower compared with those originating from polluted ones (45). More recently, we used National Oceanic and Atmospheric Administration data and their Hybrid Single-Particle Lagrangian Integrated Trajectory model to track the back trajectories of air masses over Boston for a 6-year period, for up to 96 hours previously (46). We believe these back trajectories are good instruments for  $PM_{2.5}$ , because 1) they represent emissions transported from elsewhere and, thus, they are not influenced by the behavior of people in Boston; 2) people in Boston are unaware of the origin of transported pollutants and, hence, do not modify their behavior in response to changes in air mass trajectories; 3) there is no plausible connection between them and changes in other behavior that influences short-term mortality rates such as number of cigarettes smoked, daily changes in diet, alcohol consumption, and so on.

### Propensity score

Propensity score, which is the conditional probability of exposure assignment given a vector of observed covariates, has been advised in observational studies to remove bias due to all observed covariates (47). The idea is to group subjects that have comparable chances of being assigned to the

treatment (exposure) group versus the control (unexposed) group on the basis of their measured characteristics. That is, we compare exposed people who had a 10% chance of being exposed with unexposed people who had a 10% chance of being exposed. Since in both cases the covariates predict the same exposure risk, the differences in outcomes by actual exposure should not be due to confounders and, hence, should be causal. This can be extended to continuous exposures by modeling the exposure in a linear rather than logistic regression. This produces a propensity score that is the predicted values of the exposure given all of the measured confounders. Although one can control for this score directly, it is more usual to divide the data into quintiles or deciles of the propensity score and to perform the analysis of association between exposure and outcome only within these quintiles, since that does not require correctly specifying the relationship between outcome and propensity score. Because the comparison is among subjects with comparable association of covariates with exposure, exposure is effectively random with respect to covariates in these deciles. Importantly, this approach still provides valid estimates of the average causal association of exposure if the set of covariates includes effect measure modifiers.

## METHODS

### Mortality data

We analyzed data from the Boston, Massachusetts, metropolitan area, which we defined as Middlesex, Norfolk, and Suffolk counties. Mortality data were obtained from the Massachusetts Department of Public Health for the years 2004–2009. The mortality files provided information on the exact date of death and the underlying cause of death. Our outcome was all-cause nonaccidental daily mortality (*International Classification of Diseases, Ninth Revision*, codes 0–799) chosen to have sufficient statistical power.

### Air quality data

$PM_{2.5}$  measurements were conducted at the Harvard Supersite located on the roof of the Countway Library of the Harvard Medical School near downtown Boston.

Back-trajectory paths were calculated by using the Hybrid Single-Particle Lagrangian Integrated Trajectory model (version 4.9) developed by the National Oceanic and Atmospheric Administration. The meteorological archive used was the Eta Data Assimilation System with 40-km resolution. For every hour of every day from 2004 to 2009, a 96-hour back-trajectory was computed from the starting coordinates of the Countway Library site and a vertical height of 750 m. The vertical movement of air parcels within the system was modeled by using an isentropic assumption (48, 49).

*Instrumental variable approach.* We created an instrument for  $PM_{2.5}$  as follows. We excluded the first 8 hours of back-trajectory locations as possibly being related to activity in Boston. For the remaining 88 hours, we used their latitude, longitude, and the elevation of the air mass that ended up at 750 m in Boston as inputs to predict daily  $PM_{2.5}$  in Boston. To this we added 2 other variables, wind speed and sea level pressure. As noted above, it is difficult to see how where the

air mass was 42 hours ago or, outside of extreme weather events, what the wind speed or pressure was could be related to almost any other predictor of mortality besides air pollution, with 1 exception (temperature), and possibly season. Clearly, where the air mass comes from also influences today's temperature and may vary by season.

To address this, we adopted a 2-stage approach. First, we fit penalized splines predicting  $PM_{2.5}$  as a nonlinear function of both today's and yesterday's temperatures and a 24-df spline of date. We saved the residuals of this model, which are the variations in  $PM_{2.5}$  that were independent of variations in temperature, season, and time trend, for use in the next stage. We did the same for the 1-day lag of  $PM_{2.5}$ .

In the second stage, we reduced the dimensions of our instruments from the hundreds of measurements at different hours to a single instrument to predict the variations in  $PM_{2.5}$  (independent of temperature) identified above. We used a support vector machine to perform the predictions. We regressed those predictions against the residuals of the measured  $PM_{2.5}$  (controlling for temperature and time as above) to ensure that they explained enough of the variation to avoid the problems of weak instruments. These back-trajectory-based temperature independent predictions were used as our instrument. These predictions are on the same scale as  $PM_{2.5}$ , allowing a direct interpretation of the coefficient in terms of  $PM_{2.5}$  changes.

For our final analysis, we fit a log-linear quasi-Poisson regression to the daily deaths in Boston. We used the mean of the instrument on the day of and the day before death as our exposure, because studies of the acute associations of  $PM_{2.5}$  on daily deaths usually use a similar 2-day mean. Although the instrumental variable should be independent of confounders, the mean of daily deaths in Boston varies over time, which would result in substantial overdispersion if not addressed. We therefore included natural splines of time with 30 df and the 2-day mean of the instrument in the model. This model was not overdispersed.

**Propensity score.** We conducted an alternative analysis using the propensity score approach. We modeled  $PM_{2.5}$  in a linear regression with natural splines of time (24 df), temperature (3 df), yesterday's temperature (3 df), dummy variables for day of the week, and linear terms for the co-pollutants ozone, nitrogen dioxide, sulfur dioxide, and carbon monoxide. The predicted  $PM_{2.5}$  from this model is the propensity score. We trimmed the days with the highest and lowest 5% of the propensity scores, divided the remainder into deciles, and analyzed the association within deciles. Because our analysis is performed within sets of observations matched on the same propensity score, we have effectively eliminated confounding by those measured covariates. Specifically, we again fit a quasi-Poisson model with dummy variables for the deciles of propensity score and the 2-day mean  $PM_{2.5}$ .

Finally, we performed a sensitivity analysis to further test the causality of the association. It follows on the ideas in Granger causality and, more recently, the work of Flanders et al. (50). Suppose that some omitted variable is, contrary to assumption, associated with both our instrument and our outcome. Unless the omitted variable is a direct cause of the back-trajectories, which we think is implausible, the correlation is an accident of similar temporal variations. In that

**Table 1.** Descriptive Statistics of the Data From Boston, Massachusetts, 2004–2009

Percentile	No. of Daily Deaths	$PM_{2.5}$ , $\mu\text{g}/\text{m}^3$	Temperature, $^{\circ}\text{C}$	Ozone, ppb	Wind Speed, knots <sup>a</sup>
Minimum	30	1	−16.9	1	2.5
25	47	6	4.2	17	7.0
50	53	7.8	11.9	24	8.7
75	59	11.1	19.4	31	11.1
100	82	33.9	31.5	73	26

Abbreviation:  $PM_{2.5}$ , particles less than 2.5  $\mu\text{m}$  in aerodynamic diameter.

<sup>a</sup> One knot = 1.852 km/hour.

case, it is likely that the correlation of the omitted variable with our instrument 2 days after the date of death is nearly as high as it is for the day of death. In that case, we would find an association between future values of our instrument and today's value of daily deaths. We tested this assumption.

## RESULTS

Table 1 presents descriptive statistics of the data. During the study period,  $PM_{2.5}$  never exceeded the current daily National Ambient Air Quality Standard of 35  $\mu\text{g}/\text{m}^3$ . We first applied the instrumental variable approach. The model removing season and weather from  $PM_{2.5}$  prior to creating the instrument used splines for current day's and prior day's temperatures and a spline for date, as described in Methods, and explained 38% of the variation in  $PM_{2.5}$ . The support vector machine prediction model based on the back-trajectories explained 56% of the remaining variation in  $PM_{2.5}$ , or 34% of the total variation. We note that the support vector machine prediction puts the instrument on the same scale as  $PM_{2.5}$  (i.e.,  $\mu\text{g}/\text{m}^3$ ), so the coefficient can be interpreted as the marginal impact of a unit change in  $PM_{2.5}$ . When that prediction was used as an instrument in the Poisson regression for all natural cause mortality, we found a significant association, with a 1- $\mu\text{g}/\text{m}^3$  increase in  $PM_{2.5}$  associated with a 0.53% (95% confidence interval: 0.09, 0.97) increase in daily deaths. When instead, we used the exposure 2 days after the date of death, we failed to reject the null hypothesis ( $P = 0.93$ ; 95% confidence interval: −0.43, 0.47).

In the propensity score analysis, the propensity score explained 63% of the variation in  $PM_{2.5}$ . Controlling for deciles of propensity score, we found that each 1- $\mu\text{g}/\text{m}^3$  increase in  $PM_{2.5}$  was associated with a 0.50% (95% confidence interval: 0.20, 0.80) increase in daily deaths.

## DISCUSSION

We have used 2 complementary approaches to causal modeling—instrumental variables and propensity scores. The first provides protection against unmeasured as well as measured confounding, based on certain assumptions. The second provides protection against confounding by measured covariates and interactions, based on a different set of assumptions.

These 2 approaches yielded essentially identical results, providing key evidence of the causality of the observed association.

The key question in an instrumental variable analysis is whether or not the instrument is indeed independent of all other predictors of mortality. This can only be addressed on the basis of prior knowledge of those predictors and the instrument. In our case, we were looking at predictors of mortality rates in the next few days, not long-term mortality. The major deaths elevated in studies of particulate air pollution are cardiovascular and respiratory. Acute triggers of myocardial infarction include consumption of alcohol, tobacco products, marijuana and cocaine, episodes of anger, sexual activity, and so on. However, it is not expected that changes in these triggers would be related to the origins and trajectories of air masses reaching Boston. Similarly, although respiratory epidemics are airborne, they are not generally windborne. Hence, pneumonia deaths seem implausibly associated with the origins and trajectories of air masses impacting Boston air quality. The only disadvantage of using back-trajectories as an instrument is the association between their characteristics and temperature, which is independently a predictor of short-term mortality rates. We have addressed this potential limitation by removing nonlinear associations with temperature, humidity, time trends, and season from the PM<sub>2.5</sub> variable and fitting instruments for the remaining variation in PM<sub>2.5</sub> that is independent of weather, season, and time. Under these conditions, we believe that we have used a valid instrument.

Assuming that our instrument is valid, we have demonstrated a causal association between PM<sub>2.5</sub> and daily deaths. This finding is also confirmed by using the entirely different approach of propensity score analysis, which yielded an effect measure size that is essentially identical. Assuming that there are no unmeasured variables that are correlated with both exposure and mortality rates within strata of propensity score, this analysis also provides a causal estimate. We have argued in the introduction that there are actually few confounders, primarily weather and other pollutants, both of which are included in the propensity score. Although variables such as smoking and diet also vary from day to day, there is no reason to believe that variation is correlated with PM<sub>2.5</sub>, particularly within strata of time trend, season, temperature, and other pollutants. Because the first approach provides more protection against unmeasured confounders and the second greater protection against measured potential confounders, these approaches can be considered complementary.

Further, assuming that exposure 2 days subsequent to the day of death is a valid surrogate for omitted time-varying covariates, failing to reject the null association with 2 days' subsequent value of the instrument suggests that the instrumental variable is indeed independent of covariates that vary over time on the timescale of days to weeks. Taken together, we believe that this provides strong evidence that we have identified a causal association.

Our findings are supported by an extensive toxicological literature. For example, studies have shown associations of PM<sub>2.5</sub> exposure with accelerated development and destabilization of atherosclerotic plaque, more severe ischemia under experimental protocol, lung inflammation and remodeling, increased reactive oxygen species in the lung and heart, increased blood pressure, decreased phagocytosis by lung

macrophages, and so on (19, 23, 27, 51–70). In controlled human exposure studies, a randomized study of air filtration in the elderly has shown improvements in microvascular function following a 48-hour exposure to filtered air versus sham filtration (unfiltered air) (71). Furthermore, volunteers walking an urban route had lower blood pressure when using a particle filter mask than without a mask (72). Finally, participants exposed to diesel exhaust versus filtered air had higher blood pressure and more arterial stiffness when exposed to the diesel exhaust exposure (69). The plentiful toxicological data on acute responses to PM<sub>2.5</sub> leave little doubt that the associations reported between PM<sub>2.5</sub> and acute changes in mortality rates are causal.

Another key result is that these causal associations occurred during a period in Boston when particle concentrations never exceeded the current 24-hour National Ambient Air Quality Standard of 35 µg/m<sup>3</sup>. Hence, all of the excess deaths from these exposures occurred at currently permissible levels of pollution.

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