Is the Association of Airborne Particles with Daily Deaths Confounded by Gaseous Air Pollutants? An Approach to Control by Matching

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Although particulate air pollution has been associated with increased numbers of daily deaths in dozens of cities around the world, issues still remain about the association. Some have questioned the complex modeling used to control for season in Poisson regression or the role of gaseous air pollutants as potential confounders of the association. I examined the association between deaths and particulate matter with an aerodynamic diameter ≤ 10 μm (PM_{10}) using a case–crossover design. In this approach, the pollution on the day of each death is contrasted with the pollution level on control days when the subject did not die. Season and gaseous air pollutants were controlled by matching. Control days were chosen within the same month of the same year to control for season, and matched on either sulfur dioxide (SO_2; within 1 ppb), nitrogen dioxide (within 1 ppb), maximum ozone (within 2 ppb), or carbon monoxide (within 0.03 ppm). The analysis was conducted in 14 U.S. cities that have daily PM_{10} monitoring. After matching, there were about 400,000 deaths in each analysis. Results were combined across cities using a maximum likelihood method. PM_{10} was a significant predictor of mortality when controlling for gaseous air pollutants, with effect sizes ranging from a 0.45% increase per 10 μg/m^3 increment of PM_{10} [95% confidence interval (CI), 0.12–0.79%] when matched on maximum hourly ozone levels, to a 0.81% increase per 10 μg/m^3 increment of PM_{10} (95% CI, 0.47–1.16%) when matched on 24-hr average SO_2. *Key words:* air pollution, case–crossover, confounding, matching, particles. *Environ Health Perspect* 112:557–561 (2004). doi:10.1289/ehp.6431 available via *http://dx.doi.org/* [Online 9 December 2003]

Particulate air pollution has been associated with daily deaths in numerous studies (Katsouyanni et al. 1997; Schwartz and Dockery 1992). Still, questions remain, including the potential for confounding by gaseous air pollutants. Several methods have been used to address this concern. For example, the National Morbidity, Mortality, and Air Pollution Study (NMMAPS; Samet et al. 2000) fit two pollutant models in multiple cities to estimate whether there were significant associations independent of the gases, and found that the association with particles was unchanged by control for gases. Another approach used a two-stage hierarchical model to examine confounding by gaseous air pollutants (Schwartz 2000b; Zanobetti et al. 2000), an approach that has been more resistant to measurement error (Schwartz and Coull 2003). Although reassuring, such model-based approaches are susceptible to failures in the model assumptions. For example, if the association between a gaseous air pollutant and daily deaths is nonlinear, and a two-pollutant model is fit assuming a linear association with the gas, confounding may not have been adequately controlled. This suggests that an approach that is less sensitive to assumptions about the relation between the copollutant and the outcome would be useful.

Matching is a traditional approach to control for potential confounding in epidemiology. If, in a case–control study, the cases and controls are matched on a potential confounder, the conclusions are not sensitive to the shape of the association between the confounder and outcome, or between the confounder and the exposure of interest. To date, such an approach has not been applied to the question of confounding by gaseous pollutants.

The case–crossover design, introduced by Maclure (1991) in 1991, is a method for investigating the acute effects of an exposure. In the case–crossover approach, a case–control study is conducted whereby each person who had an event is matched with him/herself on a nearby time period where s/he did not have the event. The subject's characteristics and exposures at the time of the case event are compared with those of control periods in which the event did not occur. Each risk set consists of one individual as that individual crosses over between different exposure levels in the case and control time periods. These matched pairs may be analyzed using conditional logistic regression. Multiple control periods may be used.

In recent years, this approach has been applied to the analysis of the acute effects of environmental exposures, especially air pollution (Lee and Schwartz 1999; Levy et al. 2001b; Neas et al. 1999; Sunyer et al. 2000). Applied to the association of air pollution with risk of death, the approach has several advantages. Because in this analysis each subject serves as his or her own control, the use of a nearby day as the control period means that all covariates that change slowly over time, such as smoking history, age, body mass index, usual diet, diabetes, and so forth, are controlled for by matching.

The method also allows a more straightforward approach to seasonal control. Traditional methods involve Poisson regressions with smooth functions or regression splines to control for season. The case–crossover design controls for seasonal variation, time trends, and confounders that vary slowly by time because the case and control periods in each risk set are separated by a relatively small interval of time. That is, season and time trends are controlled by matching. Bateson and Schwartz (1999, 2001) demonstrated that by choosing control days close to event days, even very strong confounding of exposure by seasonal patterns could be controlled by design in the case–control approach. This makes the approach an attractive alternative to the Poisson models. Although Bateson and Schwartz (2001) have shown that the power is lower in the case–crossover approach, this is less of a concern in a large multicity study.

Although it is straightforward to sample control days in a manner that removes seasonal confounding, there can be a subtle selection bias in these analyses. Several approaches have been shown to address this problem, and in this study I use the time-stratified approach of Levy et al. (2001a).

Once one has adopted the framework of choosing control days close to the event day for each subject, it is straightforward to extend this to control for a gaseous air pollutant. One can examine all of the potential control days that are close enough in time to each event day to control for seasonal confounding, and select the subset that also matches on the level of a gaseous copollutant. This approach limits the number of control days for each event, often substantially, and the reduced power limits the applicability for studies in single cities. However, by applying the approach in multiple cities, it is possible to recover the needed power.

I have applied this approach to a multicity study of particulate air pollution and daily deaths in 14 U.S. cities.

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Materials and Methods

Most cities in the United States monitored particulate matter with an aerodynamic diameter ≤ 10 μm (PM_{10}) only once every 6 days. I focused on 14 U.S. cities with daily data to obtain adequate power, and because most studies have found that 2-day averages of air pollution were more strongly associated with risk of death. They were Birmingham, Alabama; Boulder and Colorado Springs, Colorado; Canton, Columbus, and Cincinnati, Ohio; Chicago, Illinois; Detroit, Michigan; Minneapolis/St. Paul, Minnesota; New Haven, Connecticut; Pittsburgh, Pennsylvania; Provo–Orem, Utah; and Seattle and Spokane, Washington. I chose the metropolitan county containing each city, except for Minneapolis and St. Paul, which were combined and analyzed as one city.

Daily mortality. Daily deaths in the metropolitan county containing each city were extracted from tapes prepared by the National Center for Health Statistics for the calendar years 1986 through 1993. Deaths from accidental causes (*International Classification of Diseases*, 9th Revision, classification categories > 799) were excluded, as were all deaths that occurred outside of the city. Daily measurements of mean temperature and relative humidity were obtained from the nearest National Weather Service surface station for each county (EarthInfo CD NCDC Surface Airways; EarthInfo Inc., Boulder, CO).

Air pollution data for PM_{10} were obtained from the U.S. Environmental Protection Agency's Aerometric Retrieval System (Nehls and Akland 1973). Many of the cities have more than one monitoring location, requiring a method to average over multiple locations. In this study I use an algorithm previously reported (Schwartz 2000a). To ensure that our exposure measure represented general population exposure and not local conditions affecting only the immediate vicinity of a given monitor, monitors within the lowest 10th percentile of the correlation among monitors across all counties were excluded. Some monitors measure PM_{10} only 1 day in 6, and different monitors have different means and standard deviations. I did not want the daily pollution value to change from day to day because of changes in which monitors reported, as opposed to differences in actual ambient levels. In each city, the daily mean among monitors for each pollutant was calculated using an algorithm that accounted for differences in the annual mean and the standardized deviations of each monitor as follows. For each monitor for each year, the daily mean was computed and subtracted from the values for that monitor and year. The resulting values were divided by the standard deviation of PM_{10} for that monitor and year. These daily standardized deviations for each monitor on each day were averaged; these were then multiplied by the standard deviation of all of the monitor readings for the entire year and added back in the annual average of all of the monitors. I examined the association with PM_{10} on the day of death and the day before death.

Analytic strategy. I started with the time-stratified control sampling scheme recommended by Levy et al. (2001a), where control days for an event are all of the other days of the same month of the same year. I then restricted those to a subset that was also matched on concentration of a gaseous air pollutant. I defined a day to be matched for sulfur dioxide if the 24-hr average concentration was within 1 ppb, matched for ozone if the daily maximum concentration was within 2 ppb, matched for nitrogen dioxide if the 24-hr average concentration was within 1 ppb, and matched for carbon monoxide if the daily 24-hr concentration was within 0.03 ppm of the concentration on the event day. Matched strata were constructed for each subject, consisting of the event day (day of death) and the matched control days. Control days were chosen before and after the event day because Bateson and Schwartz (1999) demonstrated using simulation studies that unidirectional sampling gives biased results due to confounding by long-term time trends, whereas bidirectional sampling gives unbiased results. Navidi et al. (1999) pointed out that bidirectional sampling is needed to avoid some biases in the case–control study and does not present any conceptual difficulties as long as the inactivity of the subject after death does not affect the air pollution concentrations. Further, as noted by Lumley and Levy (2000), a unidirectional sampling approach violates the sampling principle of matched case–control studies because we always know which observation in matched strata is the case (the one with the last date). They show that the time-stratified approach, used here, avoids that problem. A simulation study by Schwartz et al. (2003) has shown that the Lumley approach also has unbiased coefficients and standard errors in the face of a wide variety of seasonal confounding.

In all analyses, I controlled for day of the week and weather. Day of the week was controlled using six dummy variables. Most studies of air pollution and daily deaths have controlled for temperature and relative humidity. However, humidity per se is likely less important as a predictor of mortality risk than humidity is as a modifier of the effect of temperature. A considerable literature in biometeorology has examined how meteorologic variables affect human physiology, and several measures have been developed that try to integrate the effect of temperature and humidity to develop a composite index. This is similar to the use of the wind chill index to combine the effects of temperature and wind speed. I used apparent temperature (Kalkstein and Valamont 1986) as the composite index in this study. Temperature may be nonlinearly related to deaths, and so I used regression splines to control for apparent temperature on the day of death and the day before death. These splines used 3 degrees of freedom each. Because the control days are chosen close to the event day in the case–crossover analysis, the range of variation of temperature and therefore the range of variation in its effects are lower than in other study designs.

A city-specific regression was fit using the matched strata from each city. The log odds ratios from those 14 analyses were then combined using the iterative maximum likelihood algorithm of Berkey et al. (1995). In this analysis, heterogeneity in the response to PM_{10} was allowed across city by fitting a random variance component.

Results

Table 1 shows the 25th, 50th, and 75th percentiles of the main environmental variables in each of the 14 locations. The use of apparent temperature results in a broadened distribution of perceived temperature compared with air temperature. In some locations, such as Birmingham, the impact is predominantly for warm weather, where the third quartile increased from 24°C for air temperature to 28°C for apparent temperature. In other locations, such as Pittsburgh, the first quartile dropped from 3°C for air temperature to 0°C for apparent temperature. All pollutants were not measured in every city, with no CO data available in Canton, only a small number of days with O_3 in Minneapolis, and so on. Table 2 shows the numbers of deaths that were successfully matched in each city, when matching for CO, O_3, NO_2, and SO_2. I confirmed that, after matching for a gaseous pollutant, the mean of the control dates equaled the exposure date in each analysis, assuring that long-term time trends were controlled.

In the second-stage analysis, I found a significant association between PM_{10} and daily deaths (Table 3). The magnitude of the association ranged from a 0.45% increase per 10-μg/m^3 increment of PM_{10} [95% confidence interval (CI), 0.12–0.79%] when I matched on maximum hourly O_3 levels, to a 0.81% increase per 10-μg/m^3 increment of PM_{10} (95% CI, 0.47–1.16%) when I matched on 24-hr average SO_2. The individual city results are also shown in Table 3.

Discussion

I found a significant association between airborne particles and the risk of deaths in a multicity study. This association was seen after control, by matching, for season and level of

gaseous copollutants; and although there was some variation in the PM_{10} effect depending on the copollutant that was matched, it was neither dramatic nor statistically significant.

When one controls by matching on two covariates, in this case season and the copollutant, one controls for interactions between the two covariates as well as the covariates themselves. Because the control days were all within a few weeks of the event day, this analysis controlled for confounding by gaseous copollutants whose impact on mortality might vary by month. This plus the insensitivity of this method of control to the shape of the relation between PM_{10} and the covariate, or between the gaseous pollutant and the risk of death, indicates that the observed associations are unlikely to derive from such confounding. This adds to the considerable evidence developing from epidemiology, toxicology, and controlled human exposure studies indicating a causal relationship.

For example, recent controlled human exposure studies have demonstrated that exposure to particles produces increases in clotting factors in the blood and decreases in heart rate variability (Ghio et al. 2000). These are known risk factors for cardiovascular deaths. Inhalation of fine particles has also been associated with vasoconstriction in a controlled exposure study (Brook et al. 2002).

Toxicologic studies also support the cardiotoxicity of urban particles. For example, Wellenius et al. (2003) exposed dogs to either filtered air or concentrated air particles, followed by a temporary occlusion of the coronary artery. The animals exposed to particles experienced greater ischemia than those exposed to filtered air. Suwa et al. (2002) have demonstrated that exposure to particles increases plaque formation and decreases plaque stability. Increased fibrinogen has also been demonstrated in an animal model of particle exposure (Gardner et al. 2000).

Other recent epidemiology studies are also informative about the potential for confounding. For example, a panel study of elderly subjects in Boston during the summer found associations between airborne particles and heart rate variability (Gold et al. 2000). SO_2 was not associated with heart rate variability, and levels during the summer are very low, so this can be ruled out as a confounder. The association persisted when controlling for O_3. Another similar panel study was done in the winter, when O_3 is basically not present, and also found associations between particle exposure and heart rate variability (Liao et al. 1999).

The recent report of Sarnat et al. (2001) in Baltimore is also informative on the question of confounding. They used personal multipollutant samplers in cohorts of adults and children in the summer and winter and found that day-to-day variations in ambient gaseous air pollutants were not associated with day-to-day changes in personal exposures to those gases.

Table 1. 25th, 50th, and 75th percentiles of environmental variables in 14 U.S. cities.

City	Apparent temperature (°C)	Temperature (°C)	PM_{10} ($\mu g/m^3$)	CO (ppm)	SO_2 (ppb)	NO_2 (ppb)	O_3 (ppb)
Birmingham, AL	8	10	20	0.76	10.7	6.8	39
	17	18	31	1.06	15.9	10.4	51
	28	24	46	1.48	24.0	13.9	64
Boulder, CO	1	3	19	0.55	—	—	36
	9	11	26	0.74	—	—	48
	17	19	38	1.05	—	—	62
Canton, OH	–1	2	19	0.39	14.8	—	42
	8	10	26	0.54	24.6	—	54
	19	19	34	0.74	37.7	—	69
Chicago, IL	–1	2	23	0.67	8.2	19.8	26.5
	8	10	33	0.84	12.7	24.6	35.1
	20	19	46	1.08	19.7	30.0	47.0
Cincinnati, OH	2	4	24	0.78	16.1	22	38.8
	11	13	32	0.98	28.0	26.6	51.7
	22	21	43	1.21	48.1	51.7	65
Colorado Springs, CO	0	2	18	0.72	—	—	35.8
	8	11	23	1.02	—	—	44.2
	16	18	31	1.47	—	—	53.1
Columbus, OH	1	3	22	—	8.6	—	35
	10	12	29	—	15.2	—	49
	21	21	40	—	26.5	—	64
Detroit, MI	0	2	21	0.51	12.8	15.9	28.8
	8	11	32	0.68	20.3	21.2	40
	20	19	49	0.94	30.1	26.9	55.1
Minneapolis/St. Paul, MN	–3	–1	17	1.11	4.6	13.1	29
	6	8	24	1.39	9.5	18.3	36
	19	19	35	1.70	17	24	44
New Haven, CT	1	3	17	1.21	12.8	21.4	35.6
	9	11	26	1.58	20.6	27	47
	20	19	38	2.01	36.7	33.2	62.9
Pittsburgh, PA	0	3	19	0.80	25.4	21	29.1
	10	12	30	1.06	39.4	26.2	40.1
	20	20	47	1.47	59.3	32.1	55.1
Provo, UT	0	3	22	1.08	—	16.1	52
	10	12	31	1.49	—	21.2	60
	19	21	45	2.10	—	28.0	68
Seattle, WA	5	7	18	1.37	2.4	—	27.8
	9	11	27	1.71	6.6	—	35.8
	15	16	39	2.20	13.1	—	46.3
Spokane, WA	–1	2	23	1.72	0	—	37
	6	9	36	2.27	2.2	—	44
	14	16	57	2.92	7.6	—	51

—, Pollutant not measured.

However, they were associated with day-to-day changes in personal exposure to $PM_{2.5}$. Hence, in cities such as Baltimore, ambient gases may be alternative surrogates for exposures to particles and not measurements of confounders at all. This raises serious questions about the appropriateness of control for other pollutants at all. Another recent personal exposure study examined the association between ambient measurements of temperature, personal exposure to temperature, and skin temperature in Baltimore (Basu and Samet 2002). In this case, as well, ambient temperature was not correlated with either personal exposure to temperature or with skin temperature, indicating little potential for confounding.

Although the size of the effect varied somewhat from model to model in this study, it is generally similar to the results recently reported by Katsouyanni et al. (2001) in a study of 29 European cities. They also used the mean of PM_{10} on the day of and day before the event, and reported a coefficient of 0.6 (Katsouyanni et al. 2002). Hence, these results are consistent with other large multicity studies. It is intriguing that the effect sizes within some cities, such as Chicago and Detroit, remained quite stable to which copollutant was being controlled, whereas the effect sizes in other cities, such as Birmingham and Canton, were much more variable. Whether this represents random fluctuation or is telling us something about particle sources, composition, or patterns of confounding is unclear. In general, although there were some negative associations in each analysis, there was no consistency across confounders in which city produced a negative association, suggesting most of this variation is random.

Across cities in analyses matched by specific other pollutants, the evidence for heterogeneity varied, with $p = 0.89$ for heterogeneity in the SO_2 models to $p = 0.10$ for heterogeneity in the CO models. Given the modest power of tests for heterogeneity, the evidence from the CO models is most suggestive. Because CO may be serving as a marker for traffic particles (Sarnat et al. 2001), this may suggest greater variability in the toxicity of nontraffic particles across cities.

The NMMAPS study of U.S. cities has reported lower coefficients (Dominici et al. 2002). Although some of this may be explained by a different set of cities being studied, two factors likely also contribute to that difference. The first is that the NMMAPS study analyzed cities where PM_{10} was sampled only 1 day in 6 and was unable to use 2-day averages of exposure, as in this study or the Air Pollution and Health: A European Approach (APHEA; Katsouyanni et al. 2001) study. Many studies (Braga et al. 2001; Schwartz 2000c; Zanobetti et al. 2002) have reported that the association between PM_{10} and the risk of death persists for > 1 day and that analyses using only a single day will underestimate the effect. In general, the effect is largest at lags of 0 and 1 day and falls to near 0 by lag 3. Hence, the use of a 2-day mean in this and most other studies likely captures most of the immediate effect of airborne particles. Zanobetti et al. (2002) have reported that when the effects of exposure are accumulated during the 40 days after the exposure, the effect size is more than doubled compared with the results using the mean of lags 0 and 1 days. This question is not amenable to the case–crossover approach, because the long lags for exposure could interact with the control day sampling.

The other likely explanation is the large number of degrees of freedom used in the NMMAPS model, which seems to produce lower estimates than reported in other studies. Both of these factors likely play a role in the differences. Nevertheless, the overall pattern is one of consistent finding of roughly similar associations between particulate air pollution and daily deaths from all over the world. Other pollutants do not confound these associations, and the experimental exposure studies report findings that are consistent with these associations being causal.

Table 2. Number of deaths with matched controls when matching by level of copollutant.

City	CO	O_3	NO_2	SO_2
Birmingham, AL	21,740	24,539	2,894	19,597
Boulder, CO	3,990	4,745	—	—
Canton, OH	9,773	5,561	—	6,533
Chicago, IL	148,585	187,171	167,567	168,038
Cincinnati, OH	22,088	14,145	26,350	13,489
Colorado Springs, CO	5,504	9,901	—	—
Columbus, OH	—	20,031	—	27,075
Detroit, MI	89,585	73,555	75,605	91,463
Minneapolis/St. Paul, MN	38,402	—	51,237	16,609
New Haven, CT	9,961	8,050	15,146	12,969
Pittsburgh, PA	52,351	68,227	67,580	35,723
Provo, UT	2,496	1,742	3,374	—
Seattle, WA	30,026	27,229	—	4,845
Spokane, WA	7,337	4,082	—	—
Overall	441,839	448,978	409,753	396,341

—, Pollutant not measured.

Table 3. Estimated effect[a] ($\beta \times 1{,}000$, SE $\times$ 1,000) of PM_{10} (mean of lags 0 and 1) on daily deaths in 14 U.S. cities.

City	CO	O_3	NO_2	SO_2
Birmingham, AL	0.557 (0.909)	0.353 (0.735)	–3.30 (2.02)	–0.453 (0.809)
Boulder, CO	4.38 (2.09)	1.81 (1.31)	—	—
Canton, OH	–1.74 (1.54)	0.221 (2.14)	—	1.48 (2.20)
Chicago, IL	0.855 (0.286)	0.694 (0.239)	0.963 (0.274)	0.892 (0.254)
Cincinnati, OH	1.84 (0.911)	1.18 (1.13)	0.973 (0.820)	0.868 (1.20)
Colorado Springs, CO	–0.847 (2.01)	–0.460 (0.959)	—	—
Columbus, OH	—	1.74 (0.945)	—	0.803 (0.810)
Detroit, MI	0.634 (0.331)	0.828 (0.340)	0.436 (0.406)	0.751 (0.350)
Minneapolis/St. Paul, MN	–0.332 (0.684)	—	0.380 (0.627)	1.57 (0.874)
New Haven, CT	2.73 (1.18)	0.419 (1.58)	0.456 (1.01)	1.29 (1.19)
Pittsburgh, PA	0.247 (0.505)	–0.106 (0.365)	1.03 (0.420)	0.399 (0.679)
Provo, UT	1.15 (1.90)	3.98 (3.43)	2.65 (1.88)	—
Seattle, WA	–1.240 (1.02)	–0.534 (0.612)	—	1.56 (1.17)
Spokane, WA	–0.117 (0.870)	–0.134 (0.640)	—	—
Overall	0.527 (0.251)	0.451 (0.170)	0.784 (0.185)	0.811 (0.175)

—, Pollutant not measured.
[a]This is interpretable as the percent change in deaths for a 10-μg/m^3 increase in PM_{10}.

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