How Sensitive Is the Association between Ozone and Daily Deaths to Control for Temperature?

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***Rationale*: Air pollution has been associated with changes in daily mortality. *Objectives*: Generally, studies use Poisson regression, with complicated modeling strategies, to control for season and weather, raising concerns that the results may be sensitive to these modeling protocols. For studies of ozone, weather control is a particular problem because high ozone days are generally quite hot. *Methods*: The case-crossover approach converts this problem into a case-control study, where the control for each person is the same person on a day near in time, when he or she did not die. This method controls for season and individual risk factors by matching. One can also choose the control day to have the same temperature as the event day. *Measurements*: I have applied this approach to a study of more than 1 million deaths in 14 U.S. cities. *Main results*: I found that, with matching on temperature, a 10-ppb increase in maximum hourly ozone concentrations was associated with a 0.23% (95% confidence interval [CI] 0.01%, 0.44%) increase in the risk of dying. This finding was indistinguishable from the risk when only matching on season and controlling for temperature with regression splines (0.19%; 95% CI 03%, 0.35%). Control for suspended particulate matter with an aerodynamic diameter of 10 μm or less (PM_{10}) did not change this risk. However, the association was restricted to the warm months (0.37% increase; 95% CI 0.11%, 0.62%), with no effect in the cold months. *Conclusions*: The association between ozone and mortality risk is unlikely to be caused by confounding by temperature.**

Keywords: air pollution; case-crossover; deaths; ozone; temperature

Air pollution has been associated with changes in daily death counts in cities all over the world. The most common and consistent association has been with airborne particulate matter (1–3). However, gaseous pollutant associations have been reported as well (4, 5). Strong associations have been reported with SO_2 in Europe, for example. However, in a study of the 90 largest U.S. cities, no association was seen with SO_2 (6). This finding suggests that day-to-day changes in SO_2 in Europe may be a surrogate for daily changes in some other, unmeasured factor. Diesel vehicles are much more common in Europe, for example, and have much higher concentrations of sulfur in fuel than gasoline. Although a wide range of results have been reported for ozone, including protective associations (7–9), large multicenter studies in Europe (10) and the United States (3) have reported that ozone was associated with daily deaths, particularly in the summer. Negative associations in the winter have also been reported, although a meta-analysis has found an overall risk (11). This consistency makes ozone the best candidate for an independent effect of another air pollutant on daily deaths.

However, although the correlation between airborne particulate matter and temperature is usually moderate, and of different signs in different cities, the correlation between temperature and ozone is high, and always positive. This is because the chemistry of tropospheric ozone formation is complex and nonlinear, with temperature affecting the reaction rates of several key chemical reactions, which makes the question of control for temperature a difficult one. Thurston and Ito (12) have argued that studies that include nonlinear temperature terms tend to have higher ozone estimates. Nonlinear methods of modeling weather, such as regression splines or nonparametric smoothing, have been standard since the mid-1990s. However, controversy still exists over whether enough flexibility has been allowed to capture the highly nonlinear effects of temperature. This has generally been in the context of whether the results are sensitive to how many degrees of freedom are used to control for temperature.

Even high-degree-of-freedom splines can fit poorly at the extremes of the temperature range, but that is precisely where much of the effect of temperature on mortality is seen. This situation may be important for confounding. In general, such model-based approaches are susceptible to failures in the model assumptions, which suggests that an approach that is less sensitive to assumptions about the relation between the covariate 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 of the ozone effect by temperature.

The case-crossover design, introduced by Maclure (13) 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- or herself on a nearby time period in which that individual did not have the event. The subject's characteristics and exposures at the time of the case event are compared with 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 to increase power.

In recent years, this approach has been applied to the analysis of the acute effects of environmental exposures, especially air pollution (14–17). Because 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. The case-crossover design controls for seasonal

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variation, time trends, and slowly time-varying confounders by design 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 (18, 19) 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.

Although this choice of control sampling removes seasonal confounding, there can be a subtle selection bias in these analyses. Several approaches have been shown to address this problem (18, 20). This article uses the time-stratified approach of Levy and coworkers (21).

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 temperature. 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 is also matched on temperature. 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 ozone and deaths in 14 U.S. cities, and I specifically contrast the results using a three-degree-of-freedom curve to control for temperature to results where control days are matched on temperature (and month).

METHODS

I examined the counties containing the following 14 U.S. cities: Birmingham, AL; Boulder, CO; Canton, OH; Chicago, IL; Cincinnati, OH; Colorado Springs, CO; Columbus, OH; Detroit, MI; Houston TX; New Haven, CT; Pittsburgh, PA; Provo-Orem, UT; Seattle, WA; and Spokane, WA.

Data

Nonaccidental deaths in each county were extracted from National Center for Health Statistics tapes for 1986–1993. Daily mean temperature and relative humidity were obtained from the nearest National Weather Service surface station for each county (EarthInfo, Inc., Boulder, CO).

Air pollution data for ozone were obtained from the U.S. Environmental Protection Agency's Aerometric Retrieval System (22). The average over all monitors reporting on a given day of the maximum hourly ozone concentration (on the event day or control day) was used as the exposure.

Methods. I chose control days for an event to be all other days of the same month of the same year. I repeated the analyses examining separate effects for ozone in May through September, and in the rest of the year. The comparison analyses restricted the control days to a subset that was also matched on temperature (same rounded °C).

I also examined whether the observed associations were confounded by suspended particulate matter with an aerodynamic diameter of 10 μm or less (PM_{10}) by adding PM_{10} as a covariate to the full-year model.

In all analyses, I controlled for day of the week and weather. Humidity *per se* is likely less important as a predictor of mortality risk than as a modifier of the effect of temperature. Biometeorology has examined how meteorologic variables affect human physiology, and several measures have been developed to integrate the effect of temperature and humidity in a composite index. I used apparent temperature (23) as the composite index in this study. This approach has been used previously in examining the effects of weather (24), and as a method of control in air pollution studies (25). 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. A spline divides the range of temperature into sections and fits separate polynomials to each section, allowing different curves for the low and high temperature ranges. These splines (one for the day of death, one for the previous day) used three degrees of freedom each, and the spline for same-day temperature was kept in the temperature-matching analysis. 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, is 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 and coworkers (26). In this analysis, heterogeneity in the response to ozone 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 Houston, the impact is predominantly for warm weather, where the third quartile increased from 27°C for air temperature to 32°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.

Over 1 million deaths were available for analysis in the baseline model. After matching control days to event days by temperature, the number of deaths that could be analyzed fell to 847,406. The remaining deaths could not be matched to any control days with the same temperature in the same month of the same year.

Table 2 shows the results of the baseline analysis, matching on month and year, and controlling for today's and yesterday's temperature with regression splines. Ozone was associated with an increased risk of death, with a 0.19% increase associated with a 10-ppb increase in ozone concentrations (95% confidence interval [CI] 0.03%, 0.35%) in a full-year analysis. When PM_{10} was also controlled for in the regression, a similar result was found (0.19% increase; 95% CI 0.03%, 0.36%). When analyzed separately in the warm and cold seasons, the effect was confined to the warm season (0.26% increase for 10 ppb of ozone [95% CI 0.07%, 0.44%]) compared with 0% (95% CI −0.27%, 0.27%) in the cold months.

When I chose control days matched on temperature of the day of death and controlled in the regression for the temperature the day before the event or control day using a regression spline, similar results were found (Table 2). With matching, the effect estimate did increase for the warm season but became negative for the cold season, with a similar full-year effect.

Although only the same-day temperature was controlled directly by matching, choosing control days in the same month of the same year, with the same temperature, results in considerable indirect matching by the previous day's temperature. The mean of the absolute value of the difference between the previous day's temperature on case days versus control days was only 3°C, with a standard deviation of 2.8°C.

There was considerable variation from city to city in the results, as shown in Figures 1 and 2, for the full-year data. However, the standard errors within individual cities were generally quite high as well, and a test for whether this was more variation than could be expected by chance was not significant.

DISCUSSION

Ozone concentrations were associated with daily deaths, when analyzed over the full year in these 14 cities. This association, however, appeared to be caused entirely by an association in the warm months. This finding could reflect a threshold at lower concentrations. However, there was considerable overlap between warm season and cold season ozone concentrations,

TABLE 1. DISTRIBUTION OF VARIABLES IN 14 U.S. CITIES

City	Apparent Temperature (°C)	Temperature (°C)	Deaths Analyzed (No Matching)	Deaths Analyzed (Temperature Matching)	O_3, 1-h max (*ppb*)
Birmingham	8	10	55,877	45,021	39
	17	18			51
	28	24			64
Boulder	1	3	8,714	6,989	36
	9	11			48
	17	19			62
Canton	−1	2	18,583	14,353	42
	8	10			54
	19	19			69
Chicago	−1	2	292,058	232,296	26.5
	8	10			35.1
	20	19			47.0
Cincinnati	2	4	45,149	34,361	38.8
	11	13			51.7
	22	21			65
Colorado Springs	0	2	14,054	11,543	35.8
	8	11			44.2
	16	18			53.1
Columbus	1	3	57,597	44,744	35
	10	12			49
	21	21			64
Detroit	0	2	173,531	135,752	28.8
	8	11			40
	20	19			55.1
Houston	14	15	121,790	96,858	30.9
	23	22			42.7
	32	27			61.7
New Haven	1	3	29,861	23,997	35.6
	9	11			47
	20	19			62.9
Pittsburgh	0	3	123,841	96,814	29.1
	10	12			40.1
	20	20			55.1
Provo	0	3	7,697	6,498	52
	10	12			60
	19	21			68
Seattle	5	7	85,502	76,204	27.8
	9	11			35.8
	15	16			46.3
Spokane	−1	2	25,286	21,976	37
	6	9			44
	14	16			51

The three rows for each city show the 25th, 50th, and 75th percentile of the exposure variables.

suggesting that there may be more to this observation. Cold months are typified by low air exchange rates in buildings, where windows are generally closed. In such circumstances, indoor concentrations of ozone are close to zero. Because it is adult deaths that are associated with ozone in this analysis, and adults spend almost all of their time indoors in cold weather, this observation could reflect differences in exposure.

A key finding of this study is that essentially similar results were obtained when choosing control days matched to the same temperature of the day of each death, which provides considerable assurance that the ozone association is not caused by confounding by temperature on the day of death. Moreover, because matching on two covariates controls for all interactions between the covariates and any nonlinear associations, matching on month and temperature controlled for any changes over the course of the year in the association between temperature and daily deaths. This question has not been addressed before, but it is quite possible that the response to a given temperature does vary seasonally. In the event, any such variations did not confound the ozone effect. Because the effects of hot temperatures are greatest at lag 0,

TABLE 2. ASSOCIATION OF OZONE WITH MORTALITY RISK USING A CASE-CROSSOVER ANALYSIS IN MODELS CONTROLLING FOR TEMPERATURE AND MATCHING ON TEMPERATURE

Scenario	Full Year	Warm Season	Cold Season
Baseline	0.19% (0.03%, 0.35%)	0.26% (0.07%, 0.44%)	0% (−0.27%, 0.27%)
Temperature-matched controls	0.23% (0.01%, 0.44%)	0.37% (0.11%, 0.62%)	−0.13% (0.28%, −0.53%)

The results are the summary estimates for 14 U.S. cities and are shown as percentage of change per 10-ppb increase in daily maximum 1-hr ozone, with 95% confidence intervals of the estimate in parentheses.

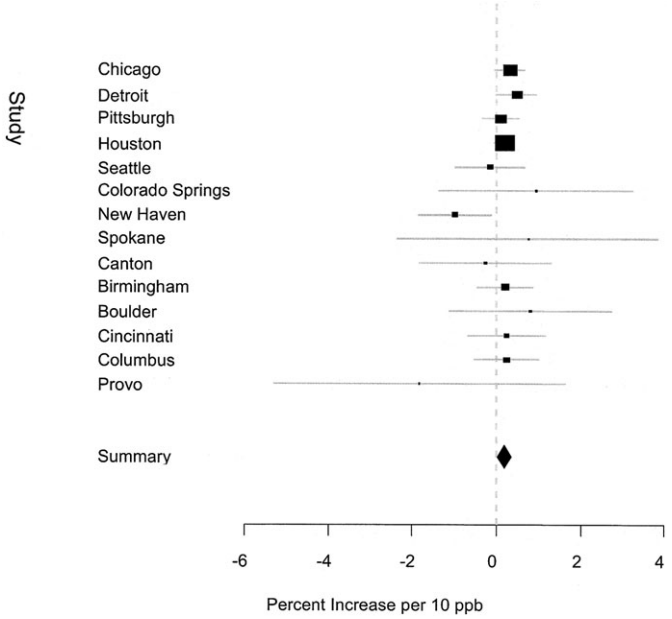

Figure 1. The city-specific effect estimates for ozone on mortality risk, with their 95% confidence intervals from a baseline case-crossover analysis, controlling for season and time trends by matching and temperature using regression splines. The size of the central estimate is inversely proportional to its estimated variance and therefore indicates the relative importance of that estimate in the summary analysis. The figure also shows the summary estimate, based on a random-effects model.

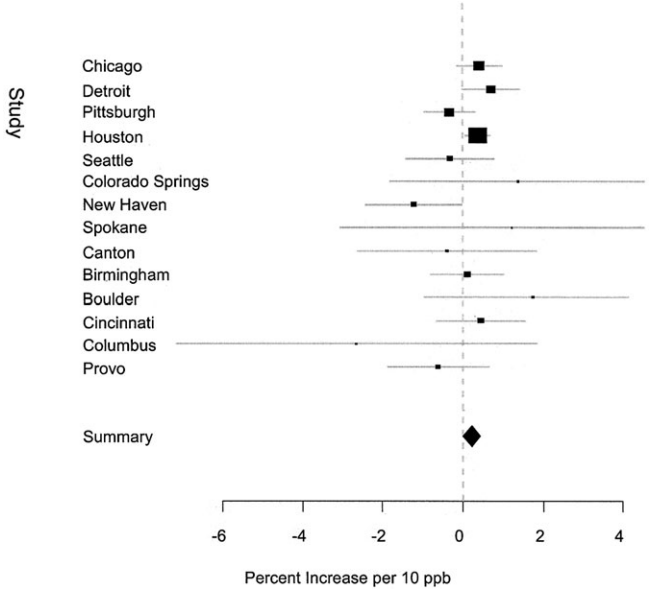

Figure 2. The city-specific effect estimates for ozone on mortality risk, with their 95% confidence intervals. These results are from a case-crossover analysis controlling for season and time trends, plus temperature, by matching. The size of the central estimate is inversely proportional to its estimated variance and therefore indicates the relative importance of that estimate in the summary analysis. The figure also shows the summary estimate, based on a random-effects model.

this analysis focused on the effects of ozone exposure at lag 0. This maximized the likelihood of confounding. Nevertheless, the analysis matching control days that had the same lag 0 temperature as event days showed no evidence for confounding. Control for PM_{10} likewise did not change the results.

Although the previous day's temperature was not also controlled by matching, the mean absolute value of the difference between the previous day's temperature on the case day and on the control days for each strata was only 3°C. Given such a small difference between event days and control days, the use of a three-degree-of-freedom spline to control the prior day's temperature by regression seems quite adequate to capture its effects. Of course, the effect of temperature may be spread over more than 2 days, which is a limitation of this analysis. However, ozone is a warm weather pollutant, and the physiologic effects of heat are quite immediate. Recent multicity studies by Braga and colleagues (27) and Curreiro and colleagues (28) have demonstrated that the increased mortality associated with temperature has a very short lag structure. Therefore, this limitation seems reasonable.

Matching on temperature reduced power for two reasons. First, with temperature matching, only 847,406 deaths were able to be matched to control days, and the number of control days for each event day was reduced, even when at least one match was found. Second, the matching reduced the range of variation of ozone. The average 10th to 90th percentile variation of ozone exposure was 45 ppb within city but was only 20 ppb within strata matched on temperature. Nevertheless, a significant association was found.

The finding of a negative, although insignificant, association in the winter requires some attention, as this has been reported before (3). This finding is generally believed to reflect the negative association between wintertime ozone and primary air pollutants, such as traffic particles, with well-established correlations with mortality. This explanation is plausible, and in some studies, control for PM_{10} reduced the negative association in the winter. However, if the negative association between ozone and daily deaths in the winter reflects confounding by traffic pollution, might not the positive association in the summer likewise reflect confounding with some other pollutant? An obvious candidate is sulfate particles because of the following reasons: these particles are produced by the same type of photochemical reactions that produce ozone; they are predominantly a long-range, transported pollutant; and they are highly correlated with ozone exposure. Unfortunately, sulfate monitoring is currently rare in the United States or Europe, and there are few data available to directly try to separate out these effects.

Personal exposure studies provide another tool for assessing this question. Ambient ozone concentrations in Baltimore (29) and Boston (30) have been shown to correlate better with temporal variations in sulfate *exposure* than with temporal variations in ozone *exposure*, which tends to support the possibility that the observed associations in this study are because of sulfate particles. Further research is required to resolve this question.

Ozone is a toxic substance, producing marked lung inflammation in controlled exposure studies (31, 32). In southern California, where exposure to ozone is likely larger and better correlated with ambient concentrations because of greater periods of open windows and outdoor activity, ozone has been associated with morbidity and mortality in adults (5, 33, 34). Similar results have been reported in Mexico City (35).

Different studies have used different exposure indices for ozone (highest hour of the day, highest 8 hours of the day, or 24-hour average), making quantitative comparisons of effect sizes difficult. Two studies that did report results for 1-hour maximum ozone were the other two large multicity studies. I found a 10-ppb increase in maximum hourly ozone associated with a 0.27 to 0.36% increase in mortality (depending on whether

I controlled for temperature by regression or matching) in the warm season. For comparison, warm-season results from Samet and coworkers (3) reported a 0.41% increase using data from the 20 largest U.S. cities, and Gryparis and coworkers (9), using data from 23 European cities, reported slightly greater results in the warm season (0.66% per 10 ppb). The low penetration of air conditioning and high ventilation rates in the summer may explain the higher slopes with ambient concentrations in Europe than in North America.

More remains to be learned about the ozone association, including resolving the question of sulfate confounding. However, relatively consistent associations are now being reported, and these do not appear to be confounded by inadequate control for temperature.

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