Temperature and Mortality Among the Elderly in the United States

A Comparison of Epidemiologic Methods

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Background: Time-series analyses have been used for decades to investigate time-varying environmental exposures. Recently, the case-crossover design has been applied to assess acute effects of air pollution. Our objective was to compare time-series and case-crossover analyses using varying referent periods (ie, unidirectional, ambidirectional, and time-stratified).

Methods: We examined the association between temperature and cardiorespiratory mortality among the elderly population in the 20 largest metropolitan areas of the United States. Risks were estimated by season and geographic region in 1992. We obtained weather data from the National Climatic Data Center and mortality data from the Division of Vital Statistics. Conditional logistic regression (case-crossover) and Poisson regression (time-series) were used to estimate the increased risk of cardiorespiratory mortality associated with a 10°F increase in daily temperature, accounting for dew-point temperature and other potential confounding factors.

Results: In the time-stratified case-crossover analysis, the strongest associations were found in the summer; in the Southwest, Southeast, Northwest, Northeast, and Midwest, the odds ratios were 1.15 (95% confidence interval = 1.07–1.24), 1.10 (0.96–1.27), 1.08 (0.92–1.26), 1.08 (1.02–1.15), and 1.01 (0.92–1.11), respectively. Mostly null or negative associations were found in the winter, spring, and fall. The ambidirectional case-crossover and the time-series analyses produced quantitatively similar results to those from the time-stratified analysis. The unidirectional analysis produced conflicting results.

Conclusions: Inferences from studies of weather and mortality using the ambidirectional or time-stratified case-crossover approaches and the time-series analyses are comparable and provide consistent findings in this study.

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Excessive ambient heat exposures may result in considerable mortality to vulnerable populations.[1] Every year in the United States, an average of 400 deaths are classified as being directly the result of heat-related causes.[2] The actual number of deaths may be notably greater, however, because heat-related deaths may be classified as the result of another underlying cause.[3] The elderly are particularly vulnerable to mortality from ambient heat exposures because of their impaired heat-adaptation abilities.[4,5] Persons with chronic diseases of the heart or lungs may be more susceptible to the effects of high ambient temperatures, because their physiological adaptations to heat are compromised or they may take medications that reduce adaptive responses.[6] Heat-related mortality may assume greater public health significance in the near future because of the projected consequences of global warming.[7] Characterization of the association between temperature and heat-related mortality in the elderly population is needed as a basis for developing preventive strategies.

Several epidemiologic methods may be applied to assess the effects of air pollution and temperature on health outcomes. Time-series analyses have been[8]used for this purpose.[9] The more recently developed case-crossover design has also been applied to studies of air pollution and health.[10,11] The case-crossover analysis is generally used to examine an association between a brief exposure and the acute onset of disease, and it allows adjustment for known and unknown time-stable confounders by study design; therefore, it is an ideal method for estimating mortality associated with temperature exposure. Since being introduced in 1991,[12] the case-crossover methodology has been refined, including the incorporation of varying referent periods for comparison to the case periods. Initially, designs were unidirectional with the referent period designated by specific time period(s)

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before the case period; subsequent ambidirectional designs incorporated referent periods both before and after the case period[10,11]; and more recently, the time-stratified design has been proposed with multiple referent periods designated throughout the same month as the case period.[8,13–15]

The primary goal of our study was to examine the results obtained using various epidemiologic approaches: the unidirectional, ambidirectional, and time-stratified case-crossover analyses and the time-series analysis. To compare these methods, we characterized the relationship between temperature and mortality (specifically from cardiovascular and respiratory diseases) among the elderly U.S. population. Potential confounding by particulate matter and ozone was also examined, because levels of both of these pollutants have been previously found to be associated with weather and mortality.[9,16,17]

METHODS

We investigated associations between temperature and cardiorespiratory mortality among persons at least 65 years of age in the 20 largest metropolitan areas in the United States in 1992. The metropolitan areas were selected based on overall population size according to the 1990 census[18] and defined as listed in the table available with the electronic version of this article.

Since 1988, the date of death for each individual is no longer provided on national databases for public use. However, we were able to obtain data including dates of death that were required for the case-crossover analysis with special permission from the Division of Vital Statistics for research purposes; 1992 represents the most recent year of data available in our dataset.

Outcome Definition

The Division of Vital Statistics of the National Center for Health Statistics supplied mortality information according to the International Classification of Diseases (ICD), 9th Revision.[19] We extracted data on the underlying cause of death, place of death, date of death, and age of every individual. Persons over 65 years of age who died of cardiovascular (ICD-9 codes 390–459) or respiratory (ICD-9 codes 460–519) diseases comprised our study population. In the case-crossover studies, individual deaths constituted the unit of analysis, whereas a daily aggregate of number of deaths was used in the time-series study. A total of 170,407 cardiorespiratory deaths were available for analysis.

Exposure Definition

Daily mean temperature and daily dew-point temperature in 1992 were provided by the National Climatic Data Center Earthinfo CD2 database for each metropolitan area in the analysis. We abstracted daily air pollution data corresponding to the mean temperature data from the Environmen-

TABLE 1. Environmental Exposures by Metropolitan Area (area abbreviations in parentheses)

	Temperature (°F) Mean (range)	Dew Point Temperature (°F) Mean (range)	Particulate Matter (μg/m^3) Mean (range)	Ozone (ppb) Mean (range)
Atlanta (atla)	62.8 (13.7 to 87.8)	50.3 (−2.9 to 75.2)	34.4 (4.4 to 107.9)	24.5 (2.3 to 71.7)
Chicago (chic)	50.4 (−15.6 to 88.6)	39.9 (−27.8 to 75.5)	35.6 (−7.3 to 362.8)	18.6 (−2.5 to 60.9)
Cleveland (clev)	51.0 (−10.9 to 89.3)	41.2 (−21.5 to 73.6)	45.1 (0.7 to 192.7)	27.5 (1.5 to 74.0)
Detroit (det)	50.5 (−10.6 to 88.2)	39.8 (−20.0 to 74.3)	40.9 (−6.6 to 154.4)	22.6 (0.3 to 76.1)
Dallas–Ft. Worth (dlft)	65.8 (9.7 to 94.7)	52.0 (−10.3 to 75.5)	23.8 (1.3 to 100.4)	25.3 (−0.2 to 62.6)
Houston (hous)	68.6 (16.1 to 89.0)	58.9 (−2.0 to 78.3)	30.0 (−3.5 to 278.5)	20.5 (−0.2 to 64.5)
Los Angeles (la)	63.9 (42.8 to 88.5)	51.3 (−2.1 to 68.2)	46.0 (5.2 to 129.4)	22.8 (−0.7 to 71.7)
Miami (miam)	76.8 (36.8 to 87.5)	66.8 (22.8 to 76.9)	25.7 (7.6 to 92.3)	25.9 (5.6 to 71.9)
Minneapolis (minn)	46.3 (−22.6 to 88.9)	35.0 (−31.5 to 75.2)	26.9 (−5.4 to 172.6)	Not measured
New York (ny)	54.7 (3.8 to 90.2)	42.5 (−8.9 to 75.8)	28.8 (3.9 to 78.9)	19.6 (−1.4 to 84.2)
Oakland (oakl)	58.3 (33.3 to 87.8)	49.8 (7.2 to 62.8)	26.3 (2.3 to 132.3)	17.2 (0.2 to 49.3)
Philadelphia (phil)	56.0 (0.1 to 90.8)	44.0 (−11.5 to 76.6)	35.4 (9.7 to 102.7)	20.5 (−5.8 to 81.5)
Phoenix (phoe)	75.0 (36.7 to 106.8)	41.0 (2.7, 72.2)	39.7 (0 to 120.7)	22.9 (0.6 to 50.1)
Pittsburgh (pitt)	52.0 (−12.0 to 87.6)	41.1 (−23.3, 71.8)	31.6 (−6.4 to 373.0)	20.7 (0.1 to 73.6)
San Antonio (sana)	69.1 (17.8 to 90.1)	55.8 (−11.3, 76.6)	23.8 (2.8 to 99.3)	22.2 (−0.8 to 61.7)
San Bernardino (sanb)	67.4 (22.5 to 101.0)	34.6 (−12.0, 70.5)	37.0 (−7.7 to 127.5)	35.9 (5.4 to 90.2)
San Diego (sand)	63.2 (49.9 to 84.0)	52.6 (13.8, 70.4)	33.6 (−3.3 to 115.1)	31.6 (6.7 to 70.4)
San Jose (sanj)	59.9 (31.7 to 84.6)	45.3 (9.2, 63.1)	30.4 (1.3 to 159.3)	17.9 (0.1 to 51.6)
Seattle (seat)	52.5 (13.8 to 81.7)	43.9 (−8.2, 60.8)	25.3 (2.1 to 134.0)	19.4 (−2.8 to 57.4)
Santa Ana (staa)	63.4 (40.6 to 92.1)	48.8 (6.6, 67.0)	37.4 (4.9 to 115.1)	23.0 (−1.1 to 71.0)

tal Protection Agency's Aerometric Information Retrieval System,[20] including PM_{10} (per 10 $\mu g/m^3$), available approximately every sixth day, and mean daily ozone (per 10 parts per billion). If multiple monitoring sites were available for weather or air pollution data in a metropolitan area, an average of the measurements from all monitors was taken to produce an overall estimate.

The mortality, temperature, and air pollution databases were merged by date of death and county listed on each death certificate. The place of death served as the index for assessing temperature exposure for each individual, so that persons who died in each metropolitan area were assigned the same exposures. Nonresidents were not excluded because temperature was expected to have an acute response.

Overview of the Modeling Approach

Because temperature ranges and mortality rates vary by season, all analyses were stratified by meteorologic season in 1992 (winter: December, January, and February; spring: March–May; summer: June–August; fall: September–November) to account for possible effect modification. Dew-point temperature was also included in the model, because it incorporates the effect of humidity on cardiorespiratory mortality. High relative humidity results when the air and dew-point temperatures are very close to each other. SAS software (SAS Institute, Cary, NC) was used for the analysis, whereas the estimates were graphically depicted using S-PLUS software (Insightful Corp., Seattle, WA).

Because seasonal effects may vary by latitude, regional variations of cardiorespiratory mortality risk associated with temperature were explored. We obtained regional estimates by pooling the metropolitan area estimates produced from models containing temperature and dew-point temperature. The regions consisted of Southwest (SW), Northwest (NW), Midwest (MW), Northeast (NE), and Southeast (SE); for a list of cities in each region, see the table available with the electronic version of this article. To account for possible heterogeneity among metropolitan areas in each region, a random-effects model was applied.[21] The random-effects model estimated the regional effect by taking a weighted average of the metropolitan area estimates weighted by the inverse of the variance. STATA (Stata Corp., College Station, TX) was used to pool the metropolitan area estimates into regional estimates.

Case-Crossover Study: Design and Analysis

The case-crossover design is a modification of the matched case-control design in which each case acts as his or her own control, and the distribution of exposure is compared between cases and controls. The distinction between this study design and the case-control study is that here the exposure at the time just before the event (the case period) is compared with a set of referent sets (control periods) that represent the expected distribution of exposure for nonevent follow-up times.[22] In our study, the case period was defined as the date of death, because high ambient temperatures were hypothesized to trigger cardiorespiratory deaths within a short time interval.[23–25] We conducted 3 separate case-crossover analyses with varying referent period selection for comparison: the unidirectional, ambidirectional, and time-stratified analyses (Fig. 1).

The unidirectional approach had 1 referent period equivalent to the temperature exposure 7 days before the mortality date. By choosing only 7 days between case and referent periods, we accounted for activities that vary by day of the week while keeping almost all cases and referent periods in the same season (except when death occurs in the first 7 days of the season). Each individual also had a similar risk profile in the case and referent periods (ie, no changes in individual physiological or health behavior would have occurred).

Using the ambidirectional approach, referent periods were chosen as the exposure 7 days before the mortality date and 7 days after the mortality date for each individual. Symmetric referent periods were selected to account for potential biases from linear time trends of temperature exposure that could have been present if we had selected a referent period in the past.[26] Furthermore, the bidirectional case-crossover study with referent days far apart removes local autocorrelation.[13] There could, however, be some bias as a result of designating the selection of referents with respect to the case period, and the value of the first referent period could influence the value of the second referent period (ie, the

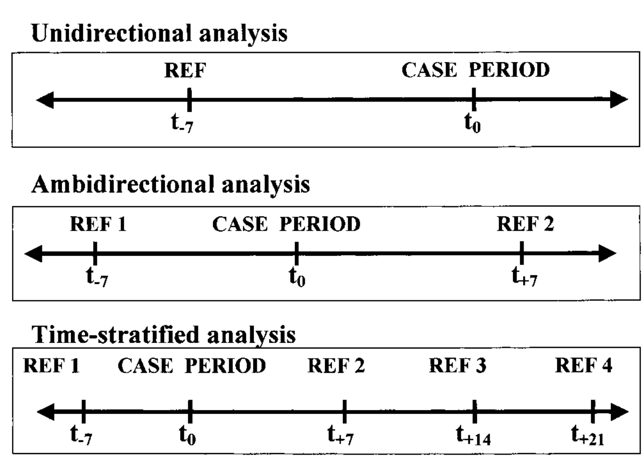

FIGURE 1. Schematic diagram of case-crossover study designs. "Ref" is referent period; t_0 is date of death; t_{-7} is 7 days before date of death; t_{+7} is 7 days after date of death; t_{+14} is 14 days after date of death; and t_{+21} is 21 days after date of death. Time-stratified analysis diagram is based on example in text; referent periods can also be t_{-14}, t_{-21}, t_{-28}, or t_{+28} depending on when the death occurs during the month.

overlap bias). If the referent periods are determined by the case period and are not disjointed, then the independent sampling inherent in the conditional likelihood approach may be invalidated.

To overcome this limitation, Lumley and Levy[14] have proposed the time-stratified sampling for selecting the referent periods. They suggested dividing the time periods into fixed strata and using the remaining days in a stratum as referents for a case that falls in that stratum. For example, days of the week within calendar months could define strata so that the exposure for a case occurring on Monday, 8 July, would be compared with exposure occurring on all other Mondays in July (ie, 1 July, 15 July, 22 July, and 29 July). Because the prespecified strata are fixed and disjointed, the time-stratified referent sampling scheme is not subject to overlap bias, and it therefore preserves the validity of the conditional logistic regression model. By allowing the referent periods to be chosen throughout the month in our time-stratified analysis (using 7 days to control for day-of-the-week effects while also controlling for month), we allowed the control periods to be selected at random with respect to the time the case occurred; this strategy ensured that the estimate for mortality risk would not be biased by case and referent period sampling.

The case-crossover study analysis is analogous to a matched case-control study design[27]; in a matched case-control study, conditional logistic regression models ensure that each case-control pair is individually matched by the specified variable(s) for the analysis. In our study, each individual contributed up to 5 observations to the analysis, 1 for the case period and 1 to 4 for the referent periods. Conditional logistic regression models were used to estimate the risk by metropolitan area and by season with varying referent selection depending on the analysis method used: unidirectional, ambidirectional, or time-stratified (Fig. 1). Specifically, odds ratios (ORs) of risk for cardiorespiratory mortality associated with a 10°F increase in mean daily temperature, adjusted for mean daily dew-point temperature, and corresponding 95% confidence intervals (CIs) were calculated, using the PHREG procedure in SAS software.[28]

Effect modification by age group (65–74, 75–84, and 85+ years) was also assessed by region for the summer and winter seasons. Lag times of zero (same day), 1 day, 2 days, and 3 days temperature exposure before mortality were evaluated to determine the temperature exposure with the strongest association. We could not examine confounding by air pollutants in the case-crossover analyses, because PM_{10} is not monitored daily, and thus sufficient data for the referent periods would not be available.

Time-Series Study: Design and Analysis

Using the time-series study design, we compared the results produced by the case-crossover approaches. An exploratory analysis was conducted to compare the effect of mean daily temperature (per 1°F) on daily cardiorespiratory mortality counts for each metropolitan area using an ecologic times-series approach with the Loess smoothing function in S-PLUS.[29] Relative rates (RRs), measuring the increase in mortality per 10°F increase in mean daily temperature (adjusted for mean daily dew-point temperature and day of the week), and corresponding 95% CIs were produced for the time-series analysis using an overdispersed Poisson regression model for each season. The GENMOD procedure using an unstructured covariance in SAS software[28] was applied for this portion of the data analysis. We adjusted for temporal confounding by adding a function of time and by incorporating season into the models. In addition, confounding by air pollutants was evaluated in the summer and winter seasons in the time-series analysis by adding PM_{10} and ozone separately as continuous variables.

RESULTS

Table 1 summarizes temperature, dew-point temperature, PM_{10}, and ozone by metropolitan area. The mean case period temperature for all metropolitan areas was 58.4°F (range, 28.6–83.7°F), with similar means and ranges for the referent periods (results not shown).

Based on regional analyses using the time-stratified case-crossover method, the greatest risk for temperature-related cardiorespiratory mortality occurred in the summer (Fig. 2). The association was strongest in the Southwest, where the ORs for cardiorespiratory mortality per 10°F temperature increase in the summer was 1.15 (95% CI = 1.07–1.24). Elevated risks were also found in the Northeast (1.08;

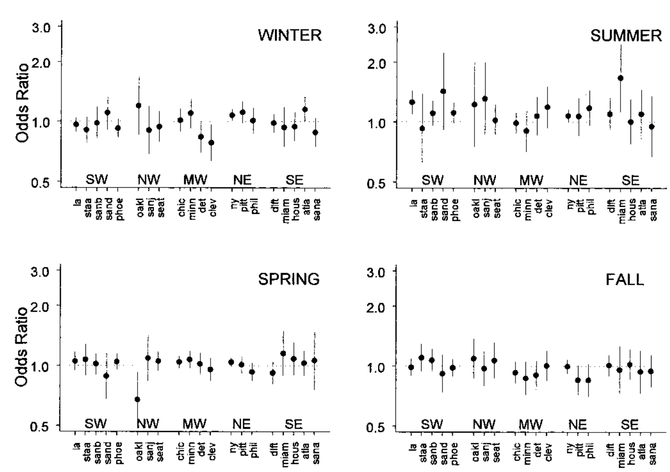

FIGURE 2. The odds ratio for cardiorespiratory mortality associated with a 10°F increase in temperature, adjusted for dew-point temperature. These estimates were obtained using conditional logistic regression in a time-stratified case-crossover analysis. Circles represent odds ratios, and vertical lines indicate 95% confidence intervals.

1.02–1.15), the Southeast (1.10; 0.96–1.27), and the Northwest (1.08; 0.92–1.26). We found a negligible effect in the Midwest, with an OR of 1.01 (0.92–1.11). In the winter, all regional estimates showed no effect using the time-stratified design. Null or negative associations were also found in the spring and fall seasons, with few exceptions: for the Northwest in the fall (1.04, 0.92–1.17), for the Southwest in the spring (1.04; 0.98–1.09), and for the Midwest in the spring (1.03; 0.98–1.08).

The ambidirectional case-crossover study (Table 2) produced results very similar to those found in the time-stratified analysis. In general, the estimates in the summer were elevated, with the exception of the Midwest, which demonstrated a negative association (0.88; 0.79–0.99). Like in the time-stratified analysis, the strongest associations were found in the summer in the Southwest and Northeast. The estimates in the fall, winter, and spring consistently showed null or negative associations, with the exception of the fall in the Southwest.

In both the time-stratified and ambidirectional analyses, lag-zero and lag-1 day exposures had similar estimates, and both had stronger associations between temperature and cardiorespiratory mortality than lag-2 or -3 days (results not shown). Stratifying by age group gave no consistent evidence for effect modification by age for all regions (results not shown).

The time-series analysis produced results similar to those found in the time-stratified and ambidirectional case-crossover analyses (Figs. 3 and 4). The regional time-series results are presented in Table 2 for comparison with the results of the ambidirectional and time-stratified case-crossover approaches. Figure 4 compares the results produced from each metropolitan area using the time-stratified case-crossover and time-series methods. In both study designs, temperature-associated mortality was generally elevated in the summer, whereas there was little or no evidence for an effect in the winter. In the regional analyses, the correlations (r^2) between the 2 methods on the log scale were as follows:

TABLE 2. Region-Specific Estimates of Increase in Mortality per 10°F* in Temperature Using Conditional Logistic Regression for the Case-Crossover Studies and Poisson Regression for the Time-Series Study

	Case-Crossover			
	Unidirectional OR (95% CI)	Ambidirectional OR (95% CI)	Time-stratified OR (95% CI)	Time-series RR (95% CI)
Winter				
Southwest	2.82 (2.44–3.26)	1.01 (0.94–1.09)	0.96 (0.91–1.01)	0.97 (0.92–1.02)
Northwest	2.27 (1.85–2.79)	1.09 (0.90–1.31)	0.97 (0.85–1.11)	0.91 (0.79–1.04)
Midwest	1.95 (0.92–4.13)	1.00 (0.77–1.29)	0.93 (0.81–1.08)	0.86 (0.69–1.06)
Northeast	1.35 (0.96–1.91)	1.02 (0.82–1.27)	1.00 (0.89–1.12)	0.95 (0.84–1.07)
Southeast	1.58 (1.23–2.02)	1.02 (0.91–1.14)	0.98 (0.90–1.07)	0.95 (0.90–1.00)
Spring				
Southwest	3.31 (2.44–4.49)	1.01 (0.94–1.08)	1.04 (0.98–1.09)	1.00 (0.97–1.04)
Northwest	1.83 (1.13–2.97)	0.93 (0.82–1.05)	0.95 (0.75–1.21)	0.92 (0.78–1.09)
Midwest	1.21 (1.09–1.35)	1.03 (0.97–1.09)	1.03 (0.98–1.08)	0.99 (0.95–1.03)
Northeast	1.28 (1.12–1.45)	0.98 (0.89–1.08)	1.00 (0.94–1.07)	0.99 (0.92–1.06)
Southeast	2.26 (1.41–3.62)	1.10 (0.96–1.27)	1.01 (0.93–1.09)	1.02 (0.96–1.08)
Summer				
Southwest	1.11 (0.75–1.63)	1.26 (1.06–1.50)	1.15 (1.07–1.24)	1.10 (0.98–1.23)
Northwest	0.51 (0.17–1.55)	1.06 (0.81–1.40)	1.08 (0.92–1.26)	1.08 (0.96–1.21)
Midwest	0.61 (0.52–0.71)	0.88 (0.79–0.99)	1.01 (0.92–1.11)	1.02 (0.94–1.10)
Northeast	1.06 (0.72–1.56)	1.12 (1.01–1.24)	1.08 (1.02–1.15)	1.06 (1.00–1.12)
Southeast	0.74 (0.48–1.12)	1.05 (0.94–1.18)	1.10 (0.96–1.27)	1.09 (1.00–1.20)
Fall				
Southwest	0.15 (0.12–0.20)	0.74 (0.67–0.83)	1.01 (0.95–1.06)	0.91 (0.87–0.95)
Northwest	0.22 (0.12–0.42)	0.91 (0.78–1.05)	1.04 (0.92–1.17)	0.90 (0.76–1.06)
Midwest	0.35 (0.27–0.45)	0.98 (0.89–1.08)	0.92 (0.85–1.00)	0.92 (0.86–0.97)
Northeast	0.34 (0.22–0.53)	1.03 (0.93–1.15)	0.92 (0.81–1.03)	0.89 (0.82–0.96)
Southeast	0.46 (0.39–0.55)	1.01 (0.92–1.11)	0.98 (0.91–1.07)	0.97 (0.92–1.02)

*Results from models containing mean daily temperature adjusted for mean daily dew-point temperature.

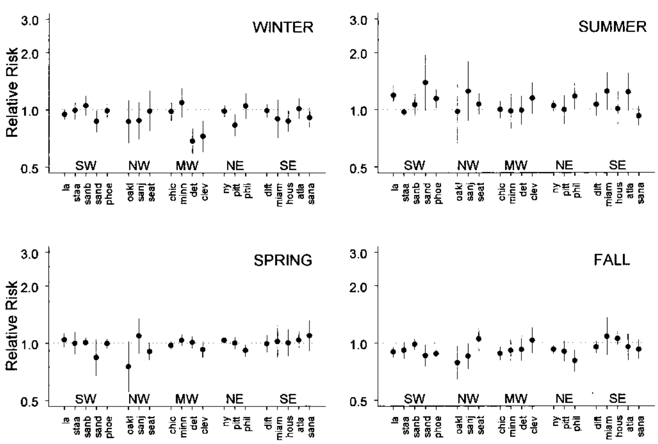

FIGURE 3. The relative rate for cardiorespiratory mortality associated with a 10°F increase in temperature, adjusted for dew-point temperature. These estimates were obtained by using an overdispersed Poisson regression model in a time-series study. Circles represent relative rate, and vertical lines indicate 95% confidence intervals.

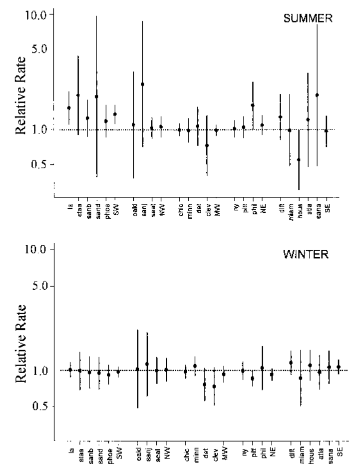

FIGURE 5. Relative rate estimates of cardiorespiratory mortality associated with a 10°F increase in temperature, adjusted for dew-point temperature and particulate matter. These estimates (RR) were obtained by using an overdispersed Poisson regression model in a time-series study.

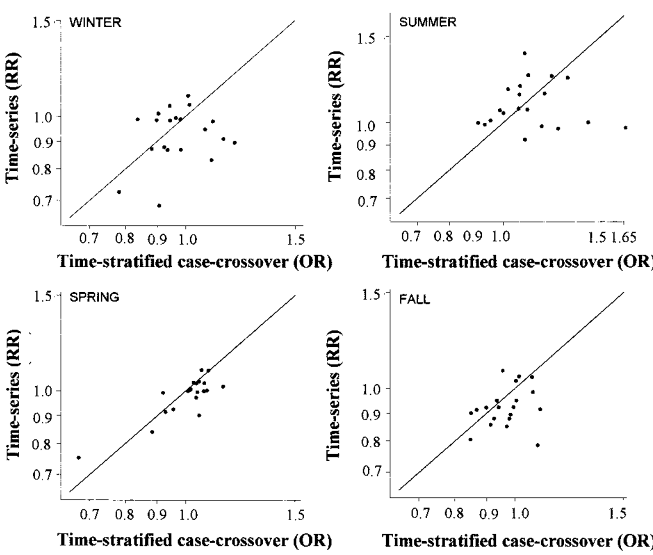

FIGURE 4. A comparison of the metropolitan area estimates between OR from time-stratified case-crossover analysis and RR from time-series analysis of cardiorespiratory mortality associated with a 10°F increase in temperature, adjusted for dew-point temperature.

0.70 in the winter, 0.83 in the spring, 0.94 in the summer, and 0.54 in the fall.

In the time-series analysis, PM_{10} appeared to be a confounder only in the summer months (Fig. 5). In the summer, the estimates for temperature When PM_{10} is included in the model, the estimates for summer temperature effects were slightly higher for some regions (Northeast and Southwest) and slightly lower for other regions (Southeast and Midwest) compared with the estimates for temperature effects shown in Figure 3. The estimates for temperature in the winter, however, were similar among the regions, and the confidence intervals were relatively narrow compared with those in the summer. Ozone did not appear to be a confounder in the summer or winter months (results not shown).

The unidirectional case-crossover analysis produced results that conflicted with the other approaches (Table 2). The risks were generally elevated in the winter; in the Southwest, the OR was 2.82 (CI = 2.44–3.26); in the Northwest, 2.27 (1.85–2.79); and in the Southeast, 1.58 (1.23–2.02). In the summer, negative associations were found in the Northwest, Midwest, and Southeast, and positive associations in the 2 other regions. Strong positive associations were found in the spring, and strong negative associations were found in the fall.

DISCUSSION

The primary goal of our study was to compare 3 approaches for referent period selection in the case-crossover study design (time-stratified, ambidirectional, and unidirectional) and the time-series analysis. The case-crossover and time-series study designs assumed ecologic temperature exposures and examined short-term effects. Some degree of misclassification results from using ambient temperature exposure provided by weather stations, depending on the extent to which ambient and microenvironmental temperatures are correlated.[30] The 2 designs should give valid estimates when examining large populations over a specified time period under varying exposure but constant or slowly varying confounders. The main difference among the approaches is that the case-crossover study inherently controls for known and unknown confounders, because each study participant serves as his or her own control. In the case-crossover studies, conditional logistic regression models provided OR estimates for mortality risk associated with a 10°F increase in temperature. In the time-series study, Poisson regression models provided RR estimates for mortality associated with a 10°F increase in temperature. Because mortality is a rare event, ORs and RRs produced from the 2 methods were directly comparable.

We found that the results of the time-stratified, ambidirectional, and time-series analyses were in strong agreement by season and geographic region: elevated cardiorespiratory mortality risk was associated with temperature exposure in the summer and negligible effects in the other seasons for all regions. The time-stratified analysis showed more agreement with the time series than the ambidirectional design. Of the 20 region-season pairs (from 5 regions and 4 seasons), 14 of the time-stratified and time-series pairs had the same magnitude and direction of effect ($r^2 = 0.83$ on the log scale); only 9 of the time-stratified estimates had the same magnitude and direction as the ambidirectional analyses ($r^2 = 0.35$ on the log scale). The ambidirectional case-crossover and time-series analyses had agreement in magnitude and direction for 10 of the 20 region-season pairs ($r^2 = 0.50$). The unidirectional case-crossover study produced inconsistent results by season and region; these estimates were based mostly on random-effects models, whereas the majority of the estimates from the other approaches showed homogeneity by region. Moreover, the results from the unidirectional analysis conflicted with the other 3 approaches. Thus, a bias in time trend may have resulted from choosing only 1 referent period before death, as well as from inadequately adjusting for season, resulting in residual confounding. Other reports on the case-crossover design have addressed this bias in greater detail.[14,22,31]

Recent investigations of the case-crossover design have suggested that conditional logistic regression may not be appropriate unless the referent periods are fixed and disjoint with respect to the time that the case occurred.[13] Thus, the time-stratified design was the only method in our study for which use of conditional logistic regression was appropriate. However, the bias in the ambidirectional analysis was not as severe as for the unidirectional analysis. In other words, the overlap bias that may have resulted from selecting 2 symmetric referent periods in the ambidirectional analysis appears to have been relatively small compared with the bias from time trend that was evident in the unidirectional analysis. Because 3 or 4 referent periods were selected in the time-stratified analysis (compared with only 2 referent periods in the ambidirectional analysis), the sample sizes and power were increased, resulting in generally narrower confidence intervals. Furthermore, the time-stratified analysis showed more consistency in the results; using the ambidirectional design, a few estimates in the winter were slightly elevated and one estimate in the fall showed a significant decrease—patterns that were not replicated in the time-stratified analysis.

Most previous studies evaluating the effects of extreme temperatures have analyzed deaths following heat waves.[32–35] These studies provided the initial indication of the harmful effects from extreme ambient temperature exposure while identifying key risk factors for vulnerability, including demographic factors and high-risk behaviors.[36–39] A few recent studies have examined temperature and mortality using modern statistical techniques such as the time-series analysis, which quantitatively estimated the effect of temperature on mortality in specific geographic areas.[8,23,40,41] For example, Hales et al.[8] reported a 1% increase in all-cause mortality and a 3% increase in respiratory mortality counts for each 1.8°F increase in temperature in Christchurch, New Zealand. We also quantified risk from temperature-associated mortality, and estimated 15% and 10% increased risk in cardiorespiratory mortality in the Southwestern and Southeastern regions, respectively, in the summer for every 10°F increase in temperature using the time-stratified case-crossover approach. Previous studies have demonstrated increased risk in these regions.[32,34] We did not, however, find increased mortality in the Midwest. Although many studies of heat waves focused on Midwestern cities (such as Chicago, St. Louis, and Milwaukee[33,39,42]), our study analyzed the temperature-mortality association in 1992, whereas the severe heat waves were reported in 1980, 1995, and 1999.

This study has several limitations that should be addressed in future research. We used 1 year of data, which was informative for accomplishing our main objective of comparing several case-crossover and time-series analyses. The resulting estimates, however, may not be generalizable to other time periods because of any unusual weather patterns. Another limitation of our study was the lack of some relevant data in national databases such as heat adaptations (eg, air conditioner use), socioeconomic status, or temperature exposure data for individuals. Although we consider persons with lower socioeconomic status and lack of access to air conditioning to be at higher risk for heat-related mortality, we could not assess variations among metropolitan areas or regions of the United States. A recent study of 12 U.S. cities, however, did not find poverty to confound the weather-mortality association.[43] Finally, all weather stations that provided temperature data in a county were averaged to obtain a mean county temperature, which may underestimate the effect of temperatures in urban areas where apparent temperatures have been reported to be greater than surrounding areas.[44] We were not able to separate urban and nonurban environments, because the data were aggregated before our analysis. We also could not account for dynamic populations, and therefore, assumed that all persons lived in the same metropolitan area throughout our study period, which is a limitation to an ecologic analysis.

Nonetheless, this study adds to the methodology of the case-crossover study design and expands the results of the previous literature examining temperature and mortality. We have introduced the use of the case-crossover study design to examine the health effects associated with ambient temperature. Our findings show that both the ambidirectional and time-stratified approaches are appropriate for analyzing these data, although the time-stratified approach may produce estimates with slightly less bias and more consistency throughout the seasons. Because the resulting inferences from the case-crossover and time-series analyses were comparable, both methods can be used to characterize temperature-associated mortality in further analyses.

Although not the main objective of our study, we were able to examine the relationship between temperature and cardiorespiratory mortality among persons 65 years of age and older. Consistent with a recent study conducted in the eastern United States,[23] we found that temperature on the same day (no lag) and the previous day (1-day lag) had the strongest associations with cardiorespiratory mortality, suggesting that the greatest mortality after temperature exposure occurs within 24 hours. This short time interval between temperature exposure and death may limit the scope of preventive efforts. Therefore, the identification of susceptibility factors, as well as better understanding the physiological mechanisms involved in heat-related mortality, are critical for preventing deaths before heatwaves occur. Among the key uses of the resulting evidence is to increase public awareness of the health hazards from ambient temperature and to create city- or county-specific programs to prevent heat-related deaths in the elderly. Evaluating risk factors for heat-related mortality will help focus community and individual education programs, as well as responses to heat emergencies, so that associated morbidity and mortality can be prevented for high-risk persons.

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