Temperature, Myocardial Infarction, and Mortality

Effect Modification by Individual- and Area-level Characteristics

Jaime Madrigano,[a,b] *Murray A. Mittleman,*[a,c] *Andrea Baccarelli,*[b] *Robert Goldberg,*[d] *Steven Melly,*[b] *Stephanie von Klot,*[e] *and Joel Schwartz*[a,b]

Background: Although several studies have examined associations between temperature and cardiovascular-disease-related mortality, fewer have investigated the association between temperature and the development of acute myocardial infarction (MI). Moreover, little is known about who is most susceptible to the effects of temperature.

Methods: We analyzed data from the Worcester Heart Attack Study, a community-wide investigation of acute MI in residents of the Worcester (MA) metropolitan area. We used a case-crossover approach to examine the association of apparent temperature with acute MI occurrence and with all-cause in-hospital and postdischarge mortality. We examined effect modification by sociodemographic characteristics, medical history, clinical complications, and physical environment.

Results: A decrease in an interquartile range in apparent temperature was associated with an increased risk of acute MI on the same day (hazard ratio = 1.15 [95% confidence interval = 1.01–1.31]). Extreme cold during the 2 days prior was associated with an increased risk of acute MI (1.36 [1.07–1.74]). Extreme heat during the 2 days prior was also associated with an increased risk of mortality (1.44 [1.06–1.96]). Persons living in areas with greater poverty were more susceptible to heat.

Conclusions: Exposure to cold increased the risk of acute MI, and exposure to heat increased the risk of dying after an acute MI. Local area vulnerability should be accounted for as cities prepare to adapt to weather fluctuations as a result of climate change.

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From the [a]Department of Epidemiology, Harvard School of Public Health, Boston, MA; [b]Department of Environmental Health, Harvard School of Public Health, Boston, MA; [c]Cardiovascular Epidemiology Research Unit, Beth Israel Deaconess Medical Center, Boston, MA; [d]Department of Quantitative Health Sciences, University of Massachusetts Medical School, Worcester, MA; and [e]Institute of Epidemiology II, Helmholtz Zentrum München-German Research Center for Environmental Health, Neuherberg, Germany and Boehringer Ingelheim GmbH.

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Correspondence: Jaime Madrigano, Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, 722 West 168th Street, 11th Floor, New York, NY 10032. E-mail: jm3731@columbia.edu.

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Human activity is expected to result in a global increase in temperature as well as differential changes by season and location. In addition, the frequency of extreme temperature episodes is projected to increase.[1] Many studies have linked increased mortality to changes in or extremes of temperature.[2–5]

Although the association between temperature and cardiovascular mortality is important,[6] fewer studies have investigated the association between the incidence of cardiovascular disease and ambient temperature. Many of the studies that have examined the association between temperature and myocardial infarction (MI) have used MI mortality as an outcome rather than nonfatal events. Moreover, few of these studies have adjusted for potentially important confounders, including air pollution.[7]

The Interagency Working Group on Climate Change and Health recently highlighted vulnerability to the human health effects of climate change as a research priority.[8] Although there is some evidence that sociodemographic characteristics including advanced age, race, and lower educational attainment can increase the risk of mortality because of temperature,[6,9] little is known about susceptibility in the relationship between temperature and occurrence of MI.[7]

We examined the association between temperature and occurrence of acute MI as well as subsequent mortality. In addition to the main effects of temperature, we examined effect modification of the association between temperature and acute MI as well as subsequent mortality, by individual- and area-level characteristics.

METHODS

The data for this investigation are from the Worcester Heart Attack Study, an ongoing community-wide investigation examining changes over time in the incidence and case-fatality rates of confirmed episodes of acute MI in residents of the greater Worcester area who were hospitalized with acute MI at all area medical centers. The details of this study have been described previously.[10–12] In brief, during the 5 study years of 1995, 1997, 1999, 2001, and 2003, the medical records of the 11 acute care general hospitals serving residents of the Worcester metropolitan area were searched for patients with a possible discharge diagnosis of acute MI. The records were individually reviewed and validated according to diagnostic criteria described previously.[10] These

criteria included a suggestive clinical history, increased serum biomarker levels above each hospital's normal range, and serial electrocardiographic findings indicative of acute MI. At least two of these three criteria were necessary for study inclusion. The present investigation was limited to patients age 25 years and older who were hospitalized with independently confirmed acute MI. Patients' residential addresses at the time of acute MI were collected from information contained in hospital medical records and geocoded. Date of death was ascertained for any patient who died after hospital admission for acute MI. This included patients who died in the hospital and those who were discharged from the participating medical centers. Long-term survival status was ascertained through the end of calendar year 2005 by reviewing records for additional hospitalizations and by searching state and national death certificates for residents of greater Worcester. The study was approved by the Committee for the Protection of Human Subjects at the University of Massachusetts Medical School and the Human Subjects Committee at the Harvard School of Public Health.

Exposure

We used daily mean apparent temperature, calculated from air and dew-point temperature,[2] as the exposure metric in our analysis because it is a combined index of temperature and humidity that captures the physiologic experience better than temperature alone and has been used in other studies assessing morbidity and mortality.[13,14] Air and dew-point temperatures at the Worcester Airport were obtained from the National Climatic Data Center. Although we used only one temperature measurement site for our exposure, the intraclass correlation between ambient temperatures during the study period at Worcester Regional Airport and Boston Logan Airport, which is 80 km away, was 0.934. This suggests that day-to-day variation in temperature at Worcester Regional Airport is a good surrogate for day-to-day variation at the participants' residential locations within the Worcester metropolitan area. The median distance between subjects' homes and the Worcester Regional Airport was 9.3 kilometers (standard deviation = 7.0 km; range = 1.3–35.4 km).

Covariates and Effect Modifiers

Ozone and $PM_{2.5}$ measurements were obtained from a stationary monitoring source located in Boston, MA. Absolute humidity was calculated from the dew-point temperature (www.gorhamschaffler.com/humidity_formulas.htm).

A number of individual- and area-level characteristics were available to examine effect measure modification (Table 1). Individual-level data were abstracted from hospital medical records for each patient and included demographic characteristics, medical history (angina, diabetes, hypertension, family history of coronary heart disease), smoking status (current vs. non), acute MI order (initial vs. prior), acute MI type (Q-wave vs. non-Q-wave), and hospital complications of acute MI (heart failure, atrial fibrillation, and cardiogenic shock).

Year 2000 census data were obtained from the US Bureau of the Census Summary File (III) at both the tract and block group level (for 101 census tracts and 375 block groups). Census tracts have an average population of ~4,000, and census block groups have a population of ~1,500. Both are designed to have relatively homogeneous socioeconomic characteristics. Census block group data on economic poverty have been shown to be a relatively sensitive measure of socioeconomic inequalities in health outcomes.[15] We used the proportion of the population with year 1999 income below the federally defined poverty level and median household income within a census block group as area-based measures of socioeconomic position. To get a sense of area-level building characteristics, we obtained census-tract-level data on the median year of building construction, housing density, and percent of housing units that have more than four units. Data on open space, bodies of water, and elevation at patient's residence were downloaded from the MassGIS website.[16] The Normalized Difference Vegetation Index was obtained as an additional measure of greenness. We chose a summer measurement from the year 2000 to match the census data in our analysis and assumed no change in the mean vegetation index in the same season by year.[17] We used 250-m resolution 16-day composite vegetation index data downloaded from the Global Land Cover Facility (http://glcf.umiacs.umd.edu/) and averaged it over 3×3 neighboring cells (750 m^2) to capture conditions around subjects' homes.

Statistical Analysis

We used case-crossover analyses to compare temperature on the day of hospital presentation for acute MI and control days for each patient. To minimize potential biases because of season and long-term time trends,[18] we selected control periods according to the time-stratified approach proposed by Lumley and Levy.[19] Exposure during the 24 hours immediately preceding an event (and other corresponding moving averages) was compared with exposure within the same month of the same year by using every third day of that month as control days to reduce serial correlation (when compared with using adjacent days) in the exposure variable. We used conditional logistic regression models in which the individual patient was the conditioning factor. We also controlled our models for day of the week with indicator variables, regional daily average $PM_{2.5}$ and ozone on the day of presentation, and absolute humidity. Because we used up to 6-day-moving-average windows of exposure, and some of the control periods would overlap with our exposure periods, we also performed a sensitivity analysis, in which we used as control days the same day in the other weeks within the same month of the same year.

We first examined acute MI as the outcome of interest and next examined subsequent all-cause mortality after acute MI as an outcome. Importantly, the all-cause mortality

TABLE 1. Individual- and Area-level Characteristics of Patients in the Worcester Heart Attack Study Cohort

	AMI Occurrence Analysis (n = 4,765)	Mortality Analysis (n = 2,427)
Age (years); mean (SD)	70.3 (13.9)	76.7 (11.4)
Sex; no. (%)		
Male	2,736 (57)	1,213 (50)
Female	2,029 (43)	1,214 (50)
Race; no. (%)		
White	4,296 (90)	2,230 (92)
Black	53 (1)	19 (1)
Other	254 (5)	103 (4)
Unknown	162 (3)	75 (3)
Medical history[a]; no. (%)		
Angina	1,046 (22)	594 (25)
Diabetes mellitus	1,429 (30)	901 (37)
Hypertension	3,052 (64)	1,671 (69)
Stroke	515 (11)	411 (17)
Family history of CHD[b]	1,437 (30)	441 (18)
Current smoker[b]; no. (%)	860 (18)	276 (11)
Type of MI; no. (%)		
Q-wave	1,429 (30)	585 (24)
Non-Q-wave	3,336 (70)	1,842 (76)
Initial	3,356 (70)	1,522 (63)
Prior	1,409 (30)	905 (37)
Clinical complications; no. (%)		
Atrial fibrillation	822 (17)	538 (22)
Cardiogenic shock[a]	299 (6)	234 (10)
Heart failure	1,701 (36)	1,220 (50)
Elevation at residence, meters[c]; mean (SD)	172.0 (51.8)	172.2 (49.7)
Lives within 400 m of large (>100,000 m^2) water body[c]; no. (%)	664 (14)	336 (14)
Census block group median household income in 1999[c] ($); mean (SD)	48,465 (19,258)	46,299 (18,654)
Census block group % of persons below the federally defined poverty line[c]; mean (SD)	10.4 (11.6)	11.2 (12.3)
% of census tract conservation/recreation[c]; mean (SD)	11.0 (10.7)	10.5 (10.8)
Normalized Difference Vegetation Index[c]; mean (SD)	191.2 (29.1)	189.4 (29.0)
Census tract year of building construction[c]; median	1958	1957
Census tract housing density (units/km^2)[c]; mean (SD)	638 (768)	698 (798)
Census tract % of buildings containing >4 units[c]; mean (SD)	17.9 (15.4)	19.3 (16.0)

[a]Missing data for one patient.
[b]Missing data for 896 patients in MI occurrence analysis and 554 patients in mortality analysis.
[c]Address could not be geocoded for 103 patients included in the MI occurrence analysis and 52 patients in the mortality analysis.

analysis is on a subset of this population (all of whom previously had an acute MI), who died within the study period. We ran separate models for warmer (April to October) and colder (November to March) months. We examined apparent temperature as a continuous variable and as a binary indicator for extreme weather. To determine if an exposure period was "extreme," the mean temperature was assessed against the 5th or 95th percentile during that season. For example, for a 2-day mean exposure, the mean of both days was calculated. If this mean value was greater than the 95th percentile of temperature during the warm season, it was considered an extreme period of heat.

We next examined effect modification between individual- and area-level characteristics and both continuous apparent temperature and temperature extremes. When residential address could not be geocoded at the street level, patients (n = 103) were excluded from the effect-modification analysis of area-level characteristics. We calculated stratum-specific estimates for all modifying characteristics.

In sensitivity analysis, we examined daily mean temperature and ran models that included both continuous apparent temperature and binary temperature extremes in the same model. All statistical analyses were performed using SAS version 9.2 software (SAS Institute, Inc., Cary, NC).

TABLE 2. 24-Hour Averages of Meteorologic Data for Worcester, MA, 1 November 1994 to 31 December 2003

	Overall Study Period					Cold Months[a]					Warm Months[b]				
				Percentile					Percentile					Percentile	
	Mean	Median	IQR	5th	95th	Mean	Median	IQR	5th	95th	Mean	Median	IQR	5th	95th
Apparent temperature (°C)	7.9	6.6	18.1	−6.9	25.5	−1.3	−1.8	6.6	−8.6	8.2	14.7	15.3	12.3	2.0	26.9
Temperature (°C)	8.8	9.2	16.4	−7.2	23.1	0.02	0.0	8.1	−10.0	10.3	15.3	16.1	9.4	4.4	24.2
Absolute humidity (kg/m^3)	0.0072	0.0058	0.01	0.0016	0.0158	0.0037	0.0033	0.0022	0.0013	0.0076	0.0098	0.0097	0.0065	0.0035	0.0169
O_3 (ppm)[c]	0.02	0.02	0.02	0.01	0.05	0.02	0.02	0.01	0.004	0.03	0.03	0.03	0.02	0.01	0.05
$PM_{2.5}$ ($\mu g/m^3$)[c]	11.8	10.2	7.3	4.6	24.7	11.6	10.5	6.6	4.9	21.9	11.9	9.8	7.7	4.4	26.4

[a]January, February, March, November, and December.
[b]April, May, June, July, August, September, and October.
[c]Data from Boston, MA.
IQR, interquartile range.

RESULTS

Data were available for 4,774 persons presenting with acute MI during the study period. We excluded two patients living outside the Worcester metropolitan area and one patient without information on address. Another six patients were excluded because their admission dates were not available, leaving a total of 4,765 patients for our analysis of temperature and occurrence of acute MI. Of these, 2,427 died either in the hospital or over the follow-up period and were included in our analysis of mortality. Information on meteorologic variables for Worcester County during the study period is shown in Table 2. The mean apparent temperature in the study area was −1.3°C during the cold months and 14.7°C during the warm months.

Onset of Acute MI

A decrease in an interquartile range of apparent temperature on the same day of presentation was associated with an increased risk of acute MI during cold months (Table 3). Extreme cold during the 2-day moving average (average of mean apparent temperature for lag 0 and lag 1) was associated with an increased risk of acute MI during cold months (Table 4). We did not find any association between temperature and acute MI during the warm months.

All-cause Mortality

We found no associations with continuous apparent temperature in either cold or warm months for subsequent mortality in people who had previously had an acute MI (Table 3). However, we found that extreme hot temperatures in the 2- and 4-day moving averages preceding death were associated with mortality (Table 4) in this population of patients who had previously had an acute MI. We also found a marginally increased risk for mortality during extreme cold days, particularly during longer averaging periods (6-day moving average). Our results were not materially different when we used day of the week to select control days.

TABLE 3. Occurrence of Acute MI and All-cause Mortality with an IQR Change in Apparent Temperature

	Cold Months[a] HR[c] (95% CI)	Warm Months[b] HR[d] (95% CI)
Occurrence of acute MI		
Same day	1.15 (1.01–1.31)	1.04 (0.86–1.26)
2-day average (lag0 − lag1)	1.10 (0.97–1.25)	1.11 (0.92–1.35)
3-day average (lag0 − lag2)	1.08 (0.96–1.22)	1.13 (0.94–1.35)
4-day average (lag0 − lag3)	1.08 (0.95–1.23)	1.07 (0.90–1.27)
5-day average (lag0 − lag4)	1.10 (0.97–1.25)	1.00 (0.84–1.19)
6-day average (lag0 − lag5)	1.11 (0.98–1.27)	0.96 (0.80–1.15)
All-cause mortality		
Same day	0.93 (0.80–1.10)	0.92 (0.71–1.20)
2-day average (lag0 − lag1)	1.00 (0.85–1.17)	0.88 (0.67–1.16)
3-day average (lag0 − lag2)	1.03 (0.88–1.20)	0.88 (0.68–1.13)
4-day average (lag0 − lag3)	1.07 (0.92–1.25)	0.85 (0.66–1.08)
5-day average (lag0 − lag4)	1.12 (0.95–1.32)	0.84 (0.66–1.07)
6-day average (lag0 − lag5)	1.16 (0.98–1.37)	0.88 (0.68–1.12)

[a]January, February, March, November and December.
[b]April, May, June, July, August, September, and October.
[c]HR for an IQR decreases in apparent temperature. The IQR for cold months was 6.6°C. Models adjusted for day of week, $PM_{2.5}$, and absolute humidity.
[d]HR for an IQR increases in apparent temperature. The IQR for warm months was 12.3°C. Models adjusted for day of week, $PM_{2.5}$, ozone, and absolute humidity.
IQR, interquartile range; HR, hazard ratio; CI, confidence interval.

Effect Modification

We evaluated effect modification for all of the individual- and area-level characteristics described in Table 1 (eTables 1–4, http://links.lww.com/EDE/A658). Persons who had a prior acute MI were more susceptible to the effects of decreases in apparent temperature during cold months (hazard ratio = 1.46 [95% confidence interval] = 1.14–1.87) compared with those who had an initial acute MI (1.04 [0.89–1.22]); test for interaction, $P = 0.003$. We also found that subjects who had a large (>100,000 m^2) lake or reservoir within a

TABLE 4. Occurrence of Acute MI and All-cause Mortality with Extreme[a] Temperature

	Cold Months[b] HR[d] (95% CI)	Warm Months[c] HR[e] (95% CI)
Occurrence of acute MI		
Same day	1.23 (0.98–1.53)	1.07 (0.86–1.33)
2-day average (lag0 – lag1)	1.36 (1.07–1.74)	0.93 (0.73–1.19)
3-day average (lag0 – lag2)	1.10 (0.83–1.46)	1.11 (0.86–1.43)
4-day average (lag0 – lag3)	1.03 (0.77–1.36)	1.03 (0.78–1.36)
5-day average (lag0 – lag4)	1.01 (0.74–1.37)	1.20 (0.89–1.62)
6-day average (lag0 – lag5)	1.05 (0.77–1.44)	1.10 (0.78–1.54)
All-cause mortality		
Same day	1.01 (0.74–1.39)	1.29 (0.96–1.72)
2-day average (lag0 – lag1)	0.97 (0.68–1.37)	1.44 (1.06–1.96)
3-day average (lag0 – lag2)	1.11 (0.78–1.58)	1.34 (0.97–1.86)
4-day average (lag0 – lag3)	1.20 (0.84–1.72)	1.41 (1.00–1.98)
5-day average (lag0 – lag4)	1.19 (0.82–1.72)	1.22 (0.81–1.82)
6-day average (lag0 – lag5)	1.38 (0.95–1.99)	1.31 (0.85–2.01)

[a]Extreme temperature days were those when the apparent temperature for that averaging periods was in the upper fifth percentile of all temperatures during the warm season or in the lower fifth percentile of all temperatures during the cold season.
[b]January, February, March, November, and December.
[c]April, May, June, July, August, September, and October.
[d]HR comparing days when temperatures were in the lowest fifth percentile to other days. Models adjusted for day of week, $PM_{2.5}$, and absolute humidity.
[e]HR comparing days when temperatures were in the highest fifth percentile to other days. Models adjusted for day of week, $PM_{2.5}$, ozone and absolute humidity.
HR, hazard ratio; CI, confidence interval.

400-m radius of their home were less susceptible to the effects of a decrease in temperature (0.90 [0.63–1.28]) than those who did not (1.20 [1.04–1.39]); test for interaction, $P = 0.02$. Although we did not find any association between increases in temperature or extreme heat and acute MI in our main analysis, we did find that certain populations were more susceptible to the occurrence of acute MI from extreme heat. Persons living in census blocks with at least 14% of families below the poverty line (the median proportion in our cohort) had a stronger association between extreme heat and acute MI (1.39 [0.90–2.14]) than those living in census blocks with <14% of families below the poverty line (0.77 [0.57–1.04]); test for interaction, $P = 0.01$. In addition, those living in more urban areas (census tracts with a housing density ≥1000 units/km^2) were more likely to suffer from an acute MI on extremely hot days (hazard ratio = 1.48 [95% confidence interval = 0.88–2.49]) than those living in less dense census tracts (0.81 [0.61–1.08]); test for interaction, $P = 0.02$.

When examining vulnerability to all-cause mortality in these acute MI survivors, we found that younger patients (<65 years old) were more likely to die (1.32 [0.65–2.68]) on days with higher temperatures, compared with older patients (0.86 [0.64–1.14]); test for interaction, $P = 0.02$. We also found that patients who had a Q-wave acute MI were more likely to die on hotter days (1.61 [0.92–2.82]) than those who had had a non-Q-wave acute MI (0.79 [0.58–1.06]); test for interaction, $P = 0.02$. Consistent with our results in the acute MI occurrence analysis, we found that those living in census blocks with above-median percent of families below the poverty line had a stronger association between heat and mortality (1.22 [0.74–2.01]) than those living in census blocks with fewer families below the poverty line (0.79 [0.57–1.08]); test for interaction, $P = 0.03$. Finally, we found that people without previously diagnosed heart failure were more likely to die after periods of extreme heat (2.15 [1.41–3.26]) compared with those who had a history of heart failure (0.92 [0.58–1.47]); test for interaction, $P = 0.01$.

When we examined models that simultaneously included continuous change in apparent temperature and a binary variable for extreme temperature (eTable 5, http://links.lww.com/EDE/A658), we observed similar results, with some reduction in power for the continuous exposures. When using daily mean temperature as an exposure metric (eTable 6, http://links.lww.com/EDE/A658), we found no associations with acute MI occurrence and mortality.

DISCUSSION

We found that extreme cold and decreases in apparent temperature increased the risk of acute MI. We did not find any effects of heat on the risk of acute MI in the population as a whole, although certain susceptible groups had an increased risk of acute MI with heat. We also found that extreme heat was associated with an increased risk of dying in people with a prior acute MI.

The published literature on temperature and the development of MI is not as comprehensive as that on temperature and mortality. Findings from time-series studies have been inconsistent, with some reporting effects for cold, some for heat, and some for both.[7] These inconsistencies may be because of a number of factors including methodology and study-population differences. Few studies adjusted for air pollution, which can vary with season and temperature and has been associated with the development of acute coronary disease. Furthermore, a number of studies used MI-related mortality, which does not capture nonfatal events of MI and also may have poor specificity when the diagnosis is assumed. A recent systematic review and meta-analysis on ambient temperature and cardiorespiratory morbidity[20] found no effect of increasing temperature on cardiovascular morbidity (relative risk = 0.999 [95% posterior interval: 0.982–1.016] per 1°C increase in temperature). This is consistent with our finding of no effect of heat on acute MI in the overall study population. This same meta-analysis concluded that there were too few studies on effects of cold temperatures to draw conclusions, although a number of studies that examined validated MI as an outcome[21–23] found an association between cold weather and MI. A study of hospital admissions in England and Wales[24] found that a 1°C decrease in daily mean temperature was associated with a 2% increase in risk of MI over the current and after 28 days. Another population-based registry in Augsburg, Germany,[25] found that a 10°C decrease in 5-day average temperature was associated with a relative risk of MI of 1.10 (95%

confidence interval = 1.04–1.15), similar in magnitude to our results. These studies adjusted for both air pollution and level of influenza and also validated most cases of MI.

Both high and low temperatures have been associated with all-cause mortality in a wide range of populations.[26] Although some studies have found evidence for only a heat effect,[2] a comprehensive analysis of the effects of heat and cold on mortality found heat-related mortality for shorter lags and cold-related mortality for longer lags.[27] Studies in the United States have found evidence for an ~2% increase in mortality associated with a 10°F increase in apparent temperature.[28]In addition, the effects of temperature have been found to vary by latitude, with northern cities in the United States, such as Boston, experiencing more of an increase in mortality risk at higher temperatures than southern US cities.[3] Our analysis of short-term effects, as well as the location of our study, may explain why we observed the strongest associations with mortality for heat and saw trends toward associations for cold in longer lags. A number of mechanisms to explain how temperature affects morbidity and mortality have been proposed, including increases in blood pressure[29] and increases in fibrinogen[30] on cold days as well as increases in serum low-density lipoprotein levels with increasing ambient temperatures.[31] These different mechanisms may partially explain the differences in results in morbidity and mortality.

Few studies have investigated susceptibility to the effects of temperature on acute MI occurrence. In one study of patients who had had a coronary event, there was no difference in the risk of MI because of temperature among those with and without a previous MI,[32] whereas a French registry-based study[21] found that recurrent cases of MI were more susceptible to decreases in temperature, similar to our results. Danet et al[21] suggested that this subgroup might be particularly vulnerable to weather because of their chronic cardiac disease and because analytic control of classic risk factors with secondary prevention might highlight the effort of less common risk factors such as weather.

We found that the effects of heat on both acute MI occurrence and mortality were greater in persons living in census blocks with a higher proportion of poverty. Little is known about how socioeconomic characteristics modify the effect of temperature on the occurrence of acute MI, but both individual and neighborhood characteristics related to lower socioeconomic position have been found to enhance the relationship between temperature and mortality.[3,33–35] This may partially be explained by air conditioning or other adaptive measures. Consistent with our results on acute MI occurrence, previous multicity studies have found that living in areas of higher population density enhances the temperature effect on mortality.[36,37]

We also found that persons living within 400 m of a large body of water were protected from the effects of decreasing temperature on MI incidence. Because it takes more energy to change the temperature of water than air, large water bodies moderate the local temperature. This finding suggests that the surrounding environment could be an important modifier in the relationship between temperature and morbidity. Although we did not observe modification by other built-environment attributes (eg, percentage recreation or conservation land), further studies should explore the potential public health impact of such modifiable environmental features.

To our knowledge, no previous studies of temperature and mortality have been able to examine vulnerability based on prior type of acute MI. In general, patients with a Q-wave MI have been found to have worse in-hospital survival than patients with a non-Q-wave MI, although this difference decreases over time.[38] Unexpectedly, we found that persons without previously diagnosed heart failure were more likely to die after periods of extreme heat than those who had a history of heart failure. This may be explained by the weakened condition of such patients, which may limit their mobility and confine them to indoors. A similar phenomenon was noted in a study of sudden cardiac death and seasonality among patients with and without prior CHD.[39] However, our explanation is speculative and in contrast to an increase in heat-related in-hospital mortality among those hospitalized for heart failure.[40] We also did not expect to find that younger persons would be more susceptible to the effects of heat, as this is in contrast with previous studies that have found increased age enhances vulnerability to heat.[9,28,37,41] Our mortality analysis is limited to a population of patients who had previously suffered from an acute MI, and therefore may represent a particularly vulnerable population.

Our study has several limitations. Ambient temperature was measured at only one monitoring station, which may have led to exposure error because of variability at individual residences and the amount of time spent indoors. However, the temporal correlation in ambient temperature is very high over wide spatial ranges in New England.[31] A recent study that used both airport monitoring data and a spatial model to predict temperature at residence found little difference in the results.[42] Given that temporal fluctuations in temperature are similar across this wide area, we do not expect error in our exposure metric to result in a large bias in this study of acute effects. Nonetheless, the inability to account for time spent in an environment with air conditioning or heating, which modify the relationship between temperature and mortality,[27,43] is a limitation of our study. We also note that microscale climatic differences may explain some of the results of our effect-modification analysis.

We used a case-crossover approach, a design that controls for time-invariant confounding.[44] We also controlled, through modeling, for such important time-varying confounders as absolute humidity and exposure to ozone and $PM_{2.5}$. Because daily measurements of ozone and $PM_{2.5}$ were not available for the Worcester metropolitan area, we used measurements from a monitoring site in Boston, MA, ~70 km away. Although concentrations of some pollutants have been shown to be homogeneous over a wide geographic region[45] and the ability to control for these pollutants to some degree

is a strength of our study, this may still be a source of residual confounding. Seasonal infection may be a source of unmeasured confounding in the relationship between temperature and development of acute MI during winter. In addition, our mortality analysis was performed on a cohort of patients who had already suffered from an acute MI and may be particularly vulnerable. Therefore, our mortality results are not necessarily generalizable to the general population.

Few studies have examined the short-term effect of hot and cold temperature on the occurrence of acute MI, and no other study, to our knowledge, has been able to examine such a broad set of individual- and area-level modifying characteristics. We found associations between cold and acute MI incidence as well as between heat and subsequent all-cause mortality. We also found that certain individual- and area-level factors modified these associations. These findings point to the importance of accounting for sociodemographic vulnerability as cities and towns prepare to adapt to weather fluctuations that result from climate change.

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