Heat Waves and Cause-specific Mortality at all Ages

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Background: Mortality has been shown to increase with extremely hot ambient temperatures. Details on the specific cause of mortality can be useful for improving preventive policies. Infants are often identified as a population that is vulnerable to extreme heat conditions; however, information on heat and infant mortality is scarce, with no studies reporting on cause-specific mortality.

Methods: The study includes all deaths in the Catalonia region of Spain during the warm seasons of 1983–2006 (503,389 deaths). We used the case-crossover design to evaluate the association between the occurrence of extremely hot days (days with maximum temperature above the 95th percentile) and mortality. Total mortality and infant mortality were stratified into 66 and 8 causes of death, respectively.

Results: Three consecutive hot days increased total daily mortality by 19%. We calculated that 1.6% of all deaths were attributable to heat. About 40% of attributable deaths did not occur during heat-wave periods. The causes of death that were increased included cardiovascular and respiratory diseases, mental and nervous system disorders, infectious and digestive system diseases, diabetes, and some external causes such as suicide. In infants, the effect of heat was observed on the same day and was detected only for conditions originating in the perinatal period (relative risk = 1.53 [95% confidence interval = 1.16–2.02]). Within the perinatal causes, cardiovascular, respiratory, digestive system, and hemorrhagic and hematologic disorders were the causes of death with stronger effects.

Conclusions: Heat contributes to an increase in mortality from several causes. In infants, the first week of life is the most critical window of vulnerability.

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The relationship between extreme heat and total mortality has been recognized for many years,[1] and is of increasing concern with global warming.[2] Two reviews, covering the period 1970–2008, include 84 studies that consistently found increases on total mortality during periods of extreme heat. However, less is known about the specific causes of death, especially in infants, for whom little information is available.[3,4]

An increase in mortality with heat has been reported for some specific causes, namely cardiovascular disease,[3–5] respiratory disease,[3,4,6] mental, and nervous systems disorders[6–8]; diabetes[6,9,10]; and kidney and urinary system diseases.[8,11,12] Plausible biologic mechanisms have been described. However, an analysis of the remaining causes of death is still of interest for several reasons. First, extreme heat can have a deleterious effect on the health of persons who are already sick from other causes, which will then be assigned as the cause of death. Heat may affect these frail individuals differently depending on the disease. Knowing which patients are more vulnerable could help improve preparedness of the health system for primary and secondary prevention during heat waves. Second, even conditions directly attributed to heat, such as hyperthermia, are difficult to diagnose with certainty,[13] and therefore such deaths due to these conditions could be misclassified as due to other causes. An investigation of specific causes of death can help identify causes that are likely to contain some misclassified heat-related deaths. Finally, a comprehensive analysis of causes of death might lead to the discovery of conditions truly affected by heat that are not yet suspected as heat-susceptible.

Infants and children are regarded as populations that are especially vulnerable to the effects of heat and heat waves.[14] There are several physiologic differences between children and adults (eg, higher surface-area-to-mass ratio, lower sweating rate, and smaller blood volume) that could explain a higher vulnerability to extreme temperatures in children and infants.[15] This may be particularly important for neonates during the first few days after birth, when thermoregulatory

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mechanisms are not yet mature,[16] and for whom the thermal environment must be regulated by others. Only a few studies have considered the association of heat and mortality among infants and young children.[17–20]

We used a long mortality series (24 years) in a large geographic area of Spain to assess the effect of extremely hot days on mortality using a fine classification of the cause of death, including external causes and causes of infant mortality.

METHODS

Setting and Data

The study included all persons who died in Catalonia during the warm season (defined as May 15–October 15, which included the half-months with an average maximum temperature greater than 20°C) of the 24-year period from 1983 to 2006. Catalonia is an autonomous community in the north-east of Spain with an area of about 32,000 km^2 and a population of 7.1 million in 2006 (Statistical Institute of Catalonia, IDESCAT), and with Barcelona as its capital. Although the climate is predominantly Mediterranean, the presence of several mountain ranges gives Catalonia a complex mosaic of climates. The Meteorological Service of Catalonia divides the territory into 14 climatic zones according to temperature and rainfall (eFig. 1, http://links.lww.com/EDE/A517).

Mortality data were obtained from the Mortality Registry of Catalonia, and included the date of death, the main cause of death according to the International Classification of Diseases (ninth revision, ICD-9, from 1983 to 1998; and 10th revision, ICD-10 from 1999 to 2006), age, and sex. We used 2 lists of condensed mortality causes defined by the Mortality Registry of Catalonia: the D-65 list, based on ICD-9 and including 65 causes, and the D-73 list, based on ICD-10 and including 73 causes.[21] These 2 lists were combined into a single list with 66 causes. The resulting categories and their corresponding ICD codes are defined in eTable 1, http://links.lww.com/EDE/A517.

Maximum daily temperatures were obtained for 66 weather stations covering Catalonia, with at least one station in each of the 14 climatic regions (eFigure 1, http://links.lww.com/EDE/A517). (Results for daily minimum temperatures were very similar and are not reported.) Humidity data were also obtained for 50 stations. Because not all stations covered the entire period, missing values were imputed using other stations' values. Details on the imputation process can be found in eAppendix 1 (http://links.lww.com/EDE/A517). Validation R^2 statistics for the imputations were higher than 85% for all stations for temperature and higher than 64% for humidity. Exposures to temperature and to humidity were assigned to each deceased person based on the values registered in the nearest weather station within the climatic zone of the town of death.

Data on daily levels of particulate matter (PM) concentrations with a diameter of <10 μm (PM_{10}), <2.5 μm ($PM_{2.5}$), and <1 μm (PM_1) were obtained from a single monitoring station in the city of Barcelona for the period 2003–2005. Information on ozone (O_3) levels was obtained from 4 monitoring stations in Barcelona for the period 2003–2006. We used these data to perform sensitivity analyses restricted to the city of Barcelona during the years of data availability. The study was approved by the Ethics Committee of the Municipal Institute of Medical Research.

Statistical Analyses

Maximum temperature was dichotomized according to the 95th percentile of the historical distribution of each weather station during the warm seasons. We considered days over the 95th percentile as extremely hot days. Using a weather station-specific percentile, rather than a common cut-off at a given temperature, takes into account the fact that individuals adapt to their local weather conditions.[22] The choice of the 95th percentile was based on the finding that the temperature threshold above which effects are observed in the city of Barcelona coincided with the 95th percentile.[23]

A time-stratified case-crossover design was used in which, for every individual, the same days of the week of the same month and year were selected as the set of control referent periods.[24] We then compared cases with their set of controls using conditional logistic regression. This analysis is mathematically equivalent to a Poisson time-series analysis of mortality with indicator variables defining the strata.[24] Therefore, the odds ratios from the conditional-logistic-regression model can be interpreted as mortality ratios comparing a hot day with a non-hot day, restricting the comparison to days that are otherwise expected to be very similar (similarity indicated by the strata). We report these results as relative risks (RRs). By design, the analyses are adjusted for long-term seasonality, for the day of the week, and for all characteristics of the population that remain stable over a 1-month period (eg, the percent of smokers).

Temperature lags 0–6 days were included in a lag-stratified distributed lag model, where the coefficients for lags 0–2 days were constrained to be equal, and likewise for the coefficients for lags 3–6. We report the cumulative effect of each of the 2 lag intervals.[25] The first estimate (lag 0–2) represents the increase in mortality risk after 3 consecutive hot days, whereas the second (lag 3–6) represents the effect of having had 4 consecutive hot days followed by 3 days that may not have been as hot. We used the latter to investigate both delayed heat effects and short-term mortality displacement or harvesting.[4] Note that the lag 0–2 effect obtained from this model is different from the lag 0–2 effect one would obtain if the model did not include lags 3–6.

Analyses were first conducted separately for each climatic region, and the cumulative effects were combined using meta-analysis. Because there was no heterogeneity of

effect by climatic region, we present the results obtained after pooling the data and analyzing them jointly. Analyses were stratified by age, sex, and mortality causes. To assess the effect of multiple comparisons, we applied a false-discovery-rate correction.[26] Most analyses included people of all ages; infant mortality was also examined separately.

We computed the attributable fraction, ie, the percent of deaths attributable to heat. This was calculated by first predicting the RR of each day of study for each weather station (RR_{is} for day i and station s), using our lag-stratified distributed lag model, and then computing the weighted average of the quantity $(RR_{is} - 1)/RR_{is}$, weighting by the number of deaths on each day.[25] To test for a temporal trend in the relative risks over the years of study, we calculated relative risks separately for each year and tested for a linear trend over time using meta-regression.

We performed several sensitivity analyses. Humidity was tested as a possible confounder or effect modifier (for the latter, dichotomized at the 75th percentile); the confounding effect of air pollution was assessed by restricting the analysis to the city of Barcelona for the period with available air pollution data and then individually including the lag 0 of each pollutant in the model; the interaction of heat and ozone was also tested in the same city and period. In addition, to facilitate the comparison of our results with other studies, some analyses were repeated using linear threshold models (eAppendix 2, http://links.lww.com/EDE/A517). Analyses were performed with Stata 10 (code available in eAppendix 3, http://links.lww.com/EDE/A517).

RESULTS

A total of 503,389 deaths occurred in Catalonia during the warm seasons of the 24-year period. Table 1 reports the number of deaths by main causes, while a finer stratification can be found in eTable 1, http://links.lww.com/EDE/A517. Because of the population distribution in Catalonia, most of the deaths (52%) occurred in the Central Coastal Mediterranean climatic region, which includes the city of Barcelona.

The average maximum daily temperature in the 14 climatic regions during the warm season ranged from 19.9°C to 27.4°C. eFigure 2 (http://links.lww.com/EDE/A517) shows the historic 95th percentile of maximum temperature during the warm season by climatic region, which ranged between 27.3°C and 38°C. The hotter regions were found in the west inland territory. eFigure 3 (http://links.lww.com/EDE/A517) shows the distribution of duration of heat waves. Overall in the 14 regions, 57% of hot days occurred as isolated hot days, and only 2% of the heat waves lasted for >6 days.

The cumulative effect of lags 0–2 was a 19% increase in mortality, and the cumulative effect of lags 3–6 was a 13% increase in mortality. Overall, 7 consecutive days of heat increased mortality by 35%. We did not detect a linear temporal trend of relative risks over the years of study (change in lag 0–2, RRs per year = 0.3% [95% CI = −0.7% to 0.02%]; change in lag 3–6, RRs per year = 0% [95% CI = −0.5% to 0.5%]). Table 1 shows the results stratified by main mortality causes. We observed an effect for all main causes at lags 0–2, with the effect remaining after longer lags for some of the causes.

Figure 1 shows the cumulative heat-related mortality risk at lags 0–2 using a finer stratification by 66 causes of death. A Q test for heterogeneity of the effect by cause did not reach statistical significance ($P = 0.28$). Only 9 of the 66 causes examined presented a relative risk below 1.0. The highest risk estimate was observed for "other infectious diseases" (RR = 2.6), although this was based on small numbers. We observed the most consistent increases in risk for diseases within the main categories of "mental and nervous system disorders," "cardiovascular diseases," "respira-

TABLE 1. Number of Deaths Among People of All Ages by Main Causes and Association Between Extremely Hot Days and Mortality From a Lag-Stratified Distributed Lag Model

Main Causes[a]	No. (%)	Cumulative Lag 0–2 RR (95% CI)	Cumulative Lag 3–6 RR (95% CI)
Cardiovascular diseases	176,830 (35)	1.22 (1.18–1.27)	1.13 (1.09–1.18)
Neoplasms	143,282 (29)	1.12 (1.08–1.17)	1.00 (0.95–1.04)
Respiratory diseases	38,843 (8)	1.21 (1.12–1.30)	1.29 (1.19–1.40)
Mental and nervous system disorders	32,586 (7)	1.30 (1.21–1.40)	1.40 (1.30–1.52)
External causes	30,050 (6)	1.23 (1.13–1.35)	1.07 (0.97–1.18)
Other internal diseases	27,892 (6)	1.19 (1.09–1.30)	1.39 (1.26–1.52)
Digestive system diseases	27,664 (6)	1.12 (1.02–1.24)	1.01 (0.91–1.12)
Endocrine diseases	19,716 (4)	1.19 (1.07–1.33)	1.14 (1.01–1.28)
Infectious diseases	6526 (1)	1.22 (1.02–1.46)	1.25 (1.04–1.51)
Total	503,389 (100)	1.19 (1.17–1.22)	1.13 (1.11–1.16)

Extremely hot days were those that exceeded the weather station-specific 95th percentile of maximum temperature.
[a]ICD codes to define the categories can be found in eTable 1 (http://links.lww.com/EDE/A517).

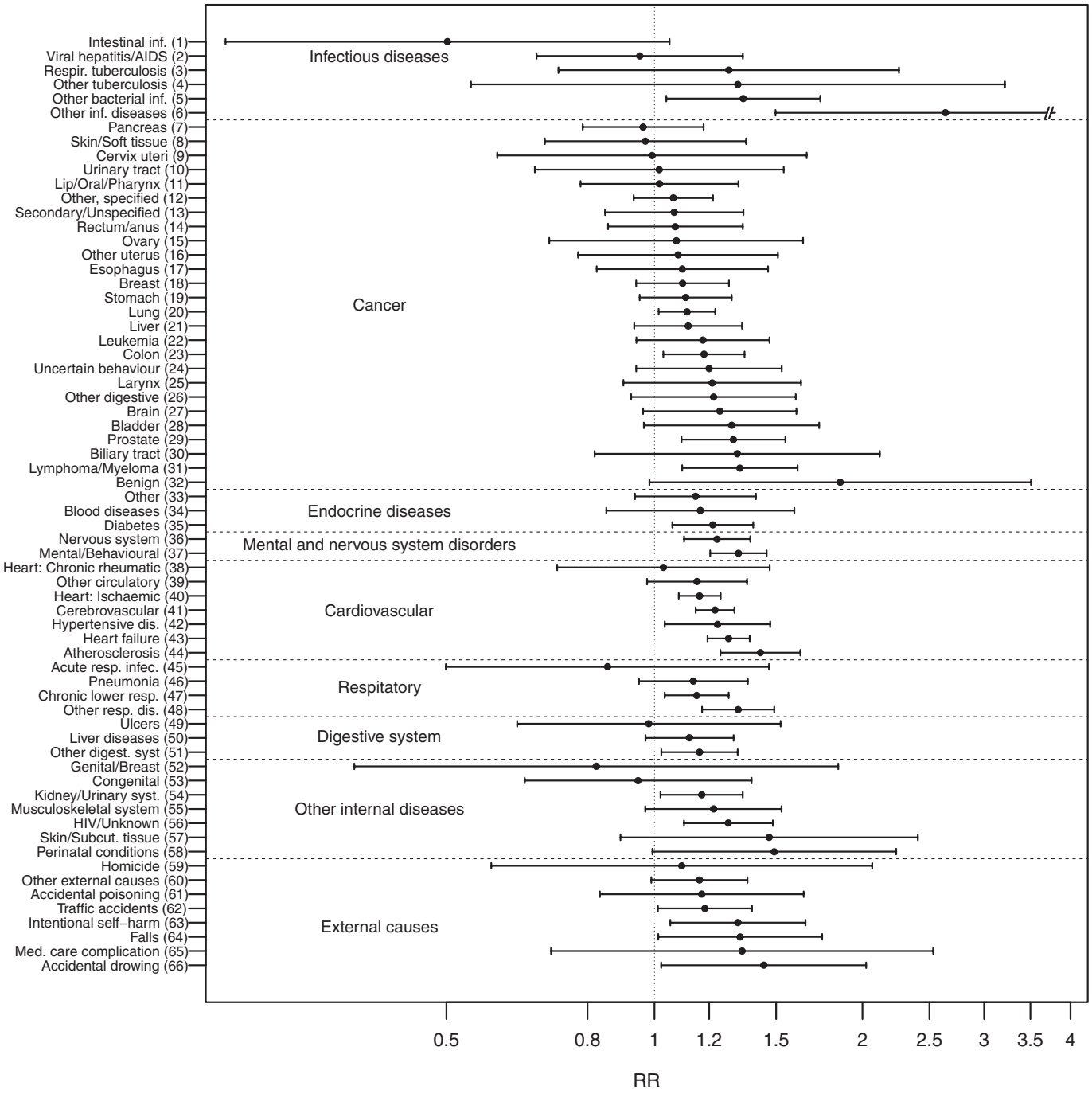

FIGURE 1. Relative risk (RR) and 95% confidence intervals of mortality and extremely hot days by 66 causes of death. Estimations are cumulative lags 0–2 relative risk from a lag-stratified distributed lag model including lags 0–6. X-axis is on logarithmic scale. Details on the 66 categories of cause of death can be found in eTable 1.

tory diseases," and "external causes." Within cardiovascular diseases, atherosclerosis showed the highest risk (RR = 1.4); within respiratory diseases, risks from all causes except acute respiratory infections were elevated; and within the external causes, suicide (intentional self-harm) (RR = 1.3), falls (1.3), and drowning (1.4) were most important. Elevated mortality risks were observed for diabetes (1.2), kidney and urinary system diseases (1.2), other bacterial infections (1.3), other digestive system diseases (1.2), and a few neoplasms.

When the false-discovery-rate correction was applied to control for multiple comparisons, a number of the associa-

tions became statistically nonsignificant: other bacterial infections, lung and colon cancer, hypertensive disease, other digestive system, kidney and urinary system, and all external causes. Several mortality causes showed increased risks at both lags 0–2 and lags 3–6 (eFigure 4, http://links.lww.com/EDE/A517). These included: all mental and nervous system disorders, the respiratory diseases mentioned above, other bacterial infections, ischemic heart disease, hypertensive disease, cerebrovascular disease, heart failure, diabetes, kidney and urinary system diseases, and HIV. There was a protective RR at lags 3–6 for several neoplasms, suggesting short-term mortality displacement (eFigure 4, http://links.lww.com/EDE/A517). Similarly, other infectious diseases, suicide, and falls presented a significant risk at lags 0–2 but a protective association at lags 3–6.

Although stratification by sex showed a higher heat-associated risk for girls and women (cumulative lags 0–2, RR = 1.23 [CI = 1.19 to 1.27] versus 1.16 [1.13 to 1.19] for boys and men), this difference became less evident when analyses were further stratified by age (Fig. 2). This was done to take into account the fact that more women reached older ages (average age of death 77.5 vs. 69.3 years for men), at which time people become more susceptible to death due to heat. By using narrower age categories than those presented in the figure, the sex differences among older adults nearly vanished.

Mortality under one year of age increased 25% on hot days, with an effect observed only at lag 0 (Table 2). When stratifying by sex, we found a 64% increase in mortality among girls, not observed in boys. This increase was observed mainly for causes originating in the perinatal period, with baby girls having twice the mortality risk during extremely hot days. When we examined specific perinatal mortality causes, we found that the contribution to the high risk was mainly driven by digestive system disorders, hemorrhagic and hematologic disorders, infections, and cardiovascular and respiratory causes (although all these estimates were based on small numbers).

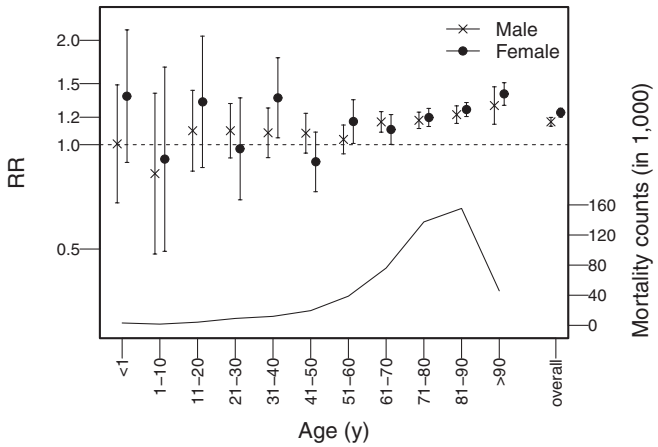

FIGURE 2. Association (cumulative lags 0–2 relative risk (RR) estimate and 95% confidence interval (CI) from a lag-stratified distributed lag model with lags 0–6) between total mortality and extremely hot days stratified by age and sex. Extremely hot days were those that exceeded the weather station-specific 95th percentile of maximum temperature.

We estimated that 1.6% of the total mortality in the warm season was attributable to extreme heat, which would correspond to an average of 333 annual deaths in the whole Catalonia region. Twenty-four percent of the mortality attributable to extreme heat was due to scenarios in which, on the day of death or the previous 6 days, only a single hot day occurred. An additional 16% was due to scenarios in which only 2 or 3 nonconsecutive hot days occurred during the same period. Overall, 40% of deaths attributable to heat occurred in periods that would not usually be considered heat waves.

In sensitivity analyses, humidity did not confound the associations (eTable 3, http://links.lww.com/EDE/A517), and we found no evidence of interaction with days of high humidity (lags 0–2, cumulative RR for extremely hot days was 1.20 for days with humidity $\leq$80% and 1.21 for days with humidity $>$80%). In addition, in an analysis restricted to the city of Barcelona for the periods with air pollution availability, adjustment for PM produced no changes, while adjusting for ozone only slightly reduced the point estimates (eFigure 5, http://links.lww.com/EDE/A517). There was no statistically significant interaction of heat and ozone, although the effect of extreme heat was higher for days with higher ozone levels (eFigure 5).

DISCUSSION

In a large case-crossover study, we found an effect of heat on daily total mortality, with mortality increases being as large as 19% when 3 consecutive hot days occurred. Extreme heat accounted for 1.6% of all deaths in the warm seasons, and about 40% of these deaths occurred in periods that would not be classified as heat waves, ie, on isolated hot days. The heat effect on mortality was concentrated among the elderly, with no sex differences after age was taken into account.

Our study investigated a total of 66 mortality causes and identified several causes that increased with heat, some of which have rarely been studied in heat-mortality investigations. In infants, the effect of heat was particularly strong, with mortality increases of 25% when considering only the first hot day. This effect was most noticeable in girls, resulting in mortality increases as large as 64%. An effect was observed only for conditions originating in the perinatal period, pinpointing the first week of life as the most critical window of susceptibility to heat in young children.

In line with many previous studies,[4] we found larger mortality risks in the elderly, with increasingly higher risks as age increased above 60 years. We found no sex differences after stratifying by age. Although different studies have used different temperature metrics (which makes comparisons dif-

TABLE 2. Infant Mortality[a] Associations (Lag 0) Between Extremely Hot Days and Mortality

	Overall		Boys		Girls	
	No.	RR (95% CI)	No.	RR (95% CI)	No.	RR (95% CI)
Infant mortality[a]	3144	1.25 (1.02–1.53)	1767	0.99 (0.75–1.31)	1377	1.64 (1.22–2.19)
Conditions not originating in the perinatal[b] period	1664	1.02 (0.76–1.36)	924	0.83 (0.56–1.25)	740	1.30 (0.85–1.98)
Congenital malformations, deformations, and chromosomal abnormalities	995	1.19 (0.82–1.72)	551	0.98 (0.58–1.63)	444	1.50 (0.87–2.59)
Other	669	0.82 (0.51–1.30)	373	0.66 (0.34–1.27)	296	1.06 (0.54–2.07)
Conditions originating in the perinatal[b] period	1480	1.53 (1.16–2.02)	843	1.18 (0.80–1.76)	637	2.03 (1.36–3.04)
Conditions related to duration of gestation	252	1.25 (0.63–2.47)	154	1.51 (0.61–3.76)	98	0.98 (0.35–2.81)
Cardiovascular and respiratory diseases	495	1.56 (0.96–2.54)	283	1.43 (0.74–2.76)	212	1.74 (0.85–3.57)
Infections specific to the perinatal period	152	1.14 (0.44–3.02)	82	0.27 (0.03–2.19)	70	2.67 (0.81–8.86)
Hemorrhagic and hematologic disorders	207	2.00 (0.91–4.42)	117	1.10 (0.37–3.29)	90	4.62 (1.30–16.4)
Digestive system diseases	62	3.85 (1.02–14.5)	30	1.81 (0.16–20.1)	32	5.70 (1.02–31.8)
Other	312	1.41 (0.79–2.53)	177	1.09 (0.49–2.42)	135	1.97 (0.82–4.73)

Extremely hot days were those that exceeded the weather station-specific 95th percentile of maximum temperature.
[a]Mortality before 1 year of age. ICD codes to define the categories used in this table can be found in eTable2.
[b]The perinatal period commences at 22 completed weeks of gestation and ends 7 completed days after birth.

ficult), the magnitude of the effect is comparable with that observed in other Mediterranean cities.[27] We found that 1.6% of all deaths in the warm seasons can be attributed to heat. This figure is similar to 1.5% reported for Milan and 1.3% reported for Budapest, although higher than 0.4% reported for London.[28] Our data showed that 40% of the deaths attributable to heat did not occur with the usual definition of heat wave, based on periods of at least 2, 3, or 4 consecutive hot days.[27,29] This is consistent with the results of another study, which demonstrated that <50% of deaths attributable to heat occurred during heat-wave periods in London, and <20% in Milan and Budapest.[28] These results are important because most plans to prevent the consequences of extreme temperatures are based on surveillance systems that activate when a weather forecast predicts a series of consecutive days above a certain temperature.[14]

One of the main contributions of our study is the analysis of infant mortality associated with extreme heat. Although infants are known to be physiologically more vulnerable to heat, there is limited information on infant mortality during hot days. Using different age ranges, some studies have found an association,[17–19] whereas some others have not.[30,31] We found increased risks only for conditions originating in the perinatal period, which implies that the most critical window for heat-related infant deaths occurs within a few days after delivery. This finding is supported by previous reports on thermal instability of newborns due to immaturity of their thermoregulatory mechanisms.[16] Although examining specific perinatal mortality causes led to small numbers and imprecise estimates, cardiovascular, respiratory, hemorrhagic, and digestive system disorders seemed to be the most strongly associated with heat. The biologic mechanisms involved are expected to be the same as for adults, aggravated by the fact that infants have an increased ratio of body surface area to body mass that coexists with underdeveloped thermoregulatory mechanisms.[13] Girls seemed to be more susceptible to the heat effects after birth, although the biologic explanation for this difference is unclear. Differences could be due to small numbers, although our study included almost 1500 infant deaths.

Most mortality causes increased on extremely hot days, probably reflecting both the fact that heat can trigger some of these causes and the fact that extreme heat can advance the death of terminal cases of diseases not necessarily related to heat. We found associations for the more established causes (ie, cardiovascular diseases,[3–5] cerebrovascular diseases,[3,4] respiratory diseases,[3,4,6] mental and nervous system diseases,[6–8] diabetes,[6,9,10] and kidney and urinary system diseases[8,11,12]), but also for other that have been less commonly reported or have not been reported previously. They include mortality by cancer, bacterial infections, ill-defined conditions, and external causes, as well as infectious and digestive system diseases.

The physiologic mechanisms linking heat and cardiovascular, cerebrovascular, and respiratory mortality have been widely described elsewhere.[5,6,13,32] Briefly, these fatal events can be triggered when the thermoregulatory mechanisms of the body (ie, increased respiratory and heart rate, increased surface blood circulation, sweat, etc.) put an additional stress on the heart and lungs, particularly in the elderly or other frail individuals. The mechanisms underlying the higher heat-mortality risk among those with mental and nervous system diseases have also been extensively documented. These include not only the side effects of several psychotropic drugs (ie, impairment of the thermoregulation processes or direct increase of heat production[5–8,33]), but also impaired self-care,[6,7,33] inadequate medical care,[7] physio-

logic vulnerability,[7,33] and heat-triggered acute psychologic events.[33] As for patients with diabetes' higher susceptibility to heat, it has been suggested that this may be due to impairment of their autonomic control and endothelial function.[10] Persons with heat stroke usually present with acute renal failure, which can explain the association with kidney diseases.[13] Our category "other digestive system disorders" involves mainly acute vascular disorders of the intestine, intestinal obstruction without hernia, diseases of the pancreas, gastrointestinal hemorrhage, and other digestive system disorders that could not be classified. These results are consistent with studies in humans that found heat-related deaths presenting as acute pancreatitis,[13] and with experimental data showing that heat stress can lead to down-regulation of epithelial growth-factor signaling, intestinal epithelial injury, and impairment of the intestinal epithelial barrier function.[34,35] A previous study with a very small number of deaths also found an increase in heat-related mortality due to gastrointestinal hemorrhage.[11]

We found important heat-mortality risks associated with several external causes, a category that has frequently been excluded from time-series studies on the temperature-mortality association.[27,36] These causes may be of relevance and should be taken into account when assessing the total burden of heat-related deaths. We found an increase in deaths due to suicide, falls, traffic accidents, and drownings. The result for suicide has been found in other studies, and sociologic, biologic, and psychologic reasons have been suggested.[37]

The remaining causes for which we found an association have rarely been reported. Other studies have found increased cancer mortality after heat waves and, as in our study, this was attributed to short-term mortality displacement or harvesting.[38,39] The vast majority of deaths falling into the category "other bacterial infections" had septicaemia as the main cause of death, which has been associated with heat in other studies.[11,12] These deaths could be misclassifications of heat stroke, as septicaemia plays an important role in its pathology.[40] The results for "other infectious diseases," mainly driven by viral hepatitis, have not been reported previously, and a biologic explanation is not clear.

The strengths of our study include the large number of deaths, which allowed the exploration of a large number of causes of deaths, even in infants where an association with specific causes of death has not been previously investigated. This allowed the detection in a single population of many conditions that have been only reported occasionally. Some of these categories had small numbers of deaths, and therefore less precision. Finally, air pollution data were available only for Barcelona during a short period of time, which precluded the adjustment of our full analyses for air pollution. Nevertheless, an attempt to quantify possible confounding or effect modification by ozone was made in sensitivity analyses using a restricted dataset. Although having less statistical power, the analyses suggested that no major changes would be expected in the reported results.

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REFERENCES

1. Gover M. Mortality during periods of excessive temperature. *Public Health Rep*. 1938;53:1122–1143.
2. Solomon S, Qin D, Manning M, et al. Contribution of Working Group I to the Fourth Assessment Report of the Intergovernmental Panel on Climate Change. *Climate Change 2007: The Physical Science Basis*. Cambridge, UK and New York: Cambridge University Press; 2007.
3. Basu R. High ambient temperature and mortality: a review of epidemiologic studies from 2001 to 2008. *Environ Health*. 2009;8:40.
4. Basu R, Samet JM. Relation between elevated ambient temperature and mortality: a review of the epidemiologic evidence. *Epidemiol Rev*. 2002;24:190–202.
5. Donaldson GC, Keatinge WR, Saunders RD. Cardiovascular responses to heat stress and their adverse consequences in healthy and vulnerable human populations. *Int J Hyperthermia*. 2003;19:225–235.
6. Schifano P, Cappai G, De Sario M, et al. Susceptibility to heat wave-related mortality: a follow-up study of a cohort of elderly in Rome. *Environ Health*. 2009;8:50.
7. Bark N. Deaths of psychiatric patients during heat waves. *Psychiatr Serv*. 1998;49:1088–1090.
8. Stafoggia M, Forastiere F, Agostini D, et al. Vulnerability to heat-related mortality: a multicity, population-based, case-crossover analysis. *Epidemiology*. 2006;17:315–323.
9. Medina-Ramon M, Zanobetti A, Cavanagh DP, Schwartz J. Extreme temperatures and mortality: assessing effect modification by personal characteristics and specific cause of death in a multi-city case-only analysis. *Environ Health Perspect*. 2006;114:1331–1336.
10. Schwartz J. Who is sensitive to extremes of temperature?: A case-only analysis. *Epidemiology*. 2005;16:67–72.
11. Conti S, Masocco M, Meli P, et al. General and specific mortality among the elderly during the 2003 heat wave in Genoa (Italy). *Environ Res*. 2007;103:267–274.
12. Rey G, Jougla E, Fouillet A, et al. The impact of major heat waves on all-cause and cause-specific mortality in France from 1971 to 2003. *Int Arch Occup Environ Health*. 2007;80:615–626.
13. Nixdorf-Miller A, Hunsaker DM, Hunsaker JC III. Hypothermia and hyperthermia medicolegal investigation of morbidity and mortality from exposure to environmental temperature extremes. *Arch Pathol Lab Med*. 2006;130:1297–1304.
14. Koppe C, Kovats S, Jendritzky G, Menne B. Heat waves: risks and responses. *Health and Global Environmental Changes, Series No. 2*. Copenhagen: WHO Regional Office for Europe; 2004.
15. Falk B. Effects of thermal stress during rest and exercise in the paediatric population. *Sports Med*. 1998;25:221–240.
16. Adamson SKJr, Towell ME. Thermal homeostasis in the Fetus and Newborn. *Anesthesiology*. 1965;26:531–548.
17. Basu R, Ostro BD. A multicounty analysis identifying the populations vulnerable to mortality associated with high ambient temperature in California. *Am J Epidemiol*. 2008;168:632–637.
18. O'Neill MS, Hajat S, Zanobetti A, Ramirez-Aguilar M, Schwartz J. Impact of control for air pollution and respiratory epidemics on the estimated associations of temperature and daily mortality. *Int J Biometeorol*. 2005;50:121–129.
19. Wyndham CH, Fellingham SA. Climate and disease. *S Afr Med J*. 1978;53:1051–1061.
20. Shea KM. Global climate change and children's health. *Pediatrics*. 2007;120:e1359–e1367.

21. Generalitat de Catalunya. Noves agrupacions de malalties per a la nova classificació de causes de mort CIM-10. *Butlletí Epidemiològic de Catalunya*. 2001;22:1–8.
22. Medina-Ramon M, Schwartz J. Temperature, temperature extremes, and mortality: a study of acclimatization and effect modification in 50 United States cities. *Occup Environ Med.* 2007.
23. Tobias A, de Olalla PG, Linares C, Bleda MJ, Cayla JA, Diaz J. Short-term effects of extreme hot summer temperatures on total daily mortality in Barcelona, Spain. *Int J Biometeorol*. 2010;54:115–117.
24. Levy D, Lumley T, Sheppard L, Kaufman J, Checkoway H. Referent selection in case-crossover analyses of acute health effects of air pollution. *Epidemiology*. 2001;12:186–192.
25. Armstrong B. Models for the relationship between ambient temperature and daily mortality. *Epidemiology*. 2006;17:624–631.
26. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J Royal Stat Soc Series B*. 1995;57:289–300.
27. D'Ippoliti D, Michelozzi P, Marino C, et al. The impact of heat waves on mortality in 9 European cities: results from the EuroHEAT project. *Environ Health*. 2010;9:37.
28. Hajat S, Armstrong B, Baccini M, et al. Impact of high temperatures on mortality: is there an added heat wave effect? *Epidemiology*. 2006;17:632–638.
29. Anderson BG, Bell ML. Weather-related mortality: how heat, cold, and heat waves affect mortality in the United States. *Epidemiology*. 2009;20:205–213.
30. Diaz J, Linares C, Garcia-Herrera R, Lopez C, Trigo R. Impact of temperature and air pollution on the mortality of children in Madrid. *J Occup Environ Med*. 2004;46:768–774.
31. Hashizume M, Wagatsuma Y, Hayashi T, Saha SK, Streatfield K, Yunus M. The effect of temperature on mortality in rural Bangladesh–a population-based time-series study. *Int J Epidemiol*. 2009;38:1689–1697.
32. Keatinge WR, Coleshaw SR, Easton JC, Cotter F, Mattock MB, Chelliah R. Increased platelet and red cell counts, blood viscosity, and plasma cholesterol levels during heat stress, and mortality from coronary and cerebral thrombosis. *Am J Med*. 1986;81:795–800.
33. Hansen A, Bi P, Nitschke M, Ryan P, Pisaniello D, Tucker G. The effect of heat waves on mental health in a temperate Australian city. *Environ Health Perspect*. 2008;116:1369–1375.
34. Liu F, Yin J, Du M, et al. Heat-stress-induced damage to porcine small intestinal epithelium associated with downregulation of epithelial growth factor signaling. *J Anim Sci*. 2009;87:1941–1949.
35. Yang PC, He SH, Zheng PY. Investigation into the signal transduction pathway via which heat stress impairs intestinal epithelial barrier function. *J Gastroenterol Hepatol*. 2007;22:1823–1831.
36. Basu R, Feng WY, Ostro BD. Characterizing temperature and mortality in nine California counties. *Epidemiology*. 2008;19:138–145.
37. Page LA, Hajat S, Kovats RS. Relationship between daily suicide counts and temperature in England and Wales. *Br J Psychiatry*. 2007;191:106–112.
38. Hoffmann B, Hertel S, Boes T, Weiland D, Jockel KH. Increased cause-specific mortality associated with 2003 heat wave in Essen, Germany. *J Toxicol Environ Health A*. 2008;71:759–765.
39. Huynen MM, Martens P, Schram D, Weijenberg MP, Kunst AE. The impact of heat waves and cold spells on mortality rates in the Dutch population. *Environ Health Perspect*. 2001;109:463–470.
40. Lim CL, Mackinnon LT. The roles of exercise-induced immune system disturbances in the pathology of heat stroke: the dual pathway model of heat stroke. *Sports Med*. 2006;36:39–64.

