Heat Effects on Mortality in 15 European Cities

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Background: Epidemiologic studies show that high temperatures are related to mortality, but little is known about the exposure-response function and the lagged effect of heat. We report the associations between daily maximum apparent temperature and daily deaths during the warm season in 15 European cities.

Methods: The city-specific analyses were based on generalized estimating equations and the city-specific results were combined in a Bayesian random effects meta-analysis. We specified distributed lag models in studying the delayed effect of exposure. Time-varying coefficient models were used to check the assumption of a constant heat effect over the warm season.

Results: The city-specific exposure-response functions have a V shape, with a change-point that varied among cities. The meta-analytic estimate of the threshold was 29.4°C for Mediterranean cities and 23.3°C for north-continental cities. The estimated overall change in all natural mortality associated with a 1°C increase in maximum apparent temperature above the city-specific threshold was 3.12% (95% credibility interval = 0.60% to 5.72%) in the Mediterranean region and 1.84% (0.06% to 3.64%) in the north-continental region. Stronger associations were found between heat and mortality from respiratory diseases, and with mortality in the elderly.

Conclusions: There is an important mortality effect of heat across Europe. The effect is evident from June through August; it is limited to the first week following temperature excess, with evidence of mortality displacement. There is some suggestion of a higher effect of early season exposures. Acclimatization and individual susceptibility need further investigation as possible explanations for the observed heterogeneity among cities.

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The impact of weather on human health is a matter of increasing concern, especially in light of climate change and the 2003 heat wave in Western Europe.[1,2] Climatologists forecast that temperature across Europe will rise over coming decades and the frequency of periods characterized by extremely high temperatures will double.[3] Optimal health protection requires an understanding of the nature of the effect of weather conditions on health.

High temperatures have been examined in relation to natural (nonaccidental) mortality, to certain specific causes of death, and to other health effects such as hospitalizations.[1,4] Time-series studies of the effects of heat on mortality have been conducted for several cities in the United States and in various European areas.[5] The association between temperature and mortality has often been shown as a J- or V-shaped function, with the lowest mortality rates at moderate temperatures and rising progressively as temperatures increase or decrease.[6] Variations in the temperature at which minimum mortality occurs may reflect population differences in acclimatization.[6,7]

In epidemiologic studies of the effects of heat, temperature has been generally used as the exposure of interest, sometimes with adjustment for humidity. More recently, several studies have considered the effect on mortality of apparent temperature, which is a thermal discomfort index that combines air temperature and humidity.[7–9]

The present work was developed within the PHEWE project (Assessment and Prevention of acute Health Effects of Weather conditions in Europe).[10] In this project, separate analyses have been performed on the health effects of meteorologic conditions during warm and cold seasons. In the present paper, we report findings concerning the association between maximum apparent temperature and mortality during the warm season, defined as the period from 1 April to 30 September. The choice of a 6-month season was made with

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the aim of being able to detect the effect of early and late warm-season exposures. Our primary purpose was to investigate the relationship between heat and mortality across Europe, with particular attention to a comparison among cities. We also explored the delayed effect of heat and the assumption of a constant heat effect over the summer period.

METHODS

The effect of weather on mortality during the warm season was explored in 15 cities: Athens, Barcelona, Budapest, Dublin, Helsinki, Ljubljana, London, Milan, Paris, Prague, Rome, Stockholm, Turin, Valencia, and Zurich. Data were collected for the period 1990–2000. Population size, percentage of elderly (≤75 years) and study period are reported in Table 1. The total population studied was about 30 million. The number of study years ranged from 5 in Athens to 11 in Dublin, Helsinki, Milan, and Stockholm.

Mortality Data

All cities provided daily counts of deaths for all causes excluding external causes (natural mortality, ICD-9: 1–799), cardiovascular diseases (ICD-9: 390–459) and respiratory diseases (ICD-9: 460–519). Mortality counts were subdivided by age groups (15–64 yrs, 65–74 yrs, 75+ yrs). The daily average number of deaths for all natural causes during the warm season (April-September) ranges from 6.3 in Ljubljana (263,290 inhabitants) to 149 in London (6,796,900 inhabitants). Daily averages range from 2.6 to 61.0 per day for deaths from cardiovascular causes and from 0.4 to 23.7 for mortality due to respiratory diseases (Table 1).

Meteorologic and Air Pollution Data

All enrolled cities provided 3-hour meteorologic data (air temperature and dew point temperature, wind speed, and barometric pressure at sea level). We retrieved this information from the nearest airport weather station.

We focused on the effect of apparent temperature on mortality. Apparent temperature is a measure of relative discomfort due to combined heat and high humidity. It was developed by Steadman[11] on the basis of physiologic studies on evaporative skin cooling. It can be calculated as a combination of air temperature (temp) and dew point (dew), according to the following formula[12]:

$$AT = -2.653 + 0.994 \text{ temp} + 0.0153\,(dew)^2.$$

Daily values of apparent temperature, barometric pressure, and wind speed were computed for each city from 3-hour measurements. For all cities except Barcelona, we used daily maximum apparent temperature defined as the maximum of 3-hour values. On Barcelona, we calculated the daily average apparent temperature from the daily mean values of temperature and dew point, given the lack of 3-hour data. Sensitivity analyses using daily minimum apparent temperature as exposure variable were performed.

A large variability in climate characteristics was observed among cities. Daily average of maximum apparent temperature during April-September ranged from 14.3°C in Helsinki to 27.9°C and 29.5°C in Athens and Valencia, respectively (Table 1).

TABLE 1. Population Size, Study Period and Number of Valid Days in the Period; Daily Average of Deaths for All Natural, Cardiovascular, and Respiratory Causes; Descriptive Statistics (Mean, Minimum, and Maximum) of Daily Maximum Apparent Temperature During the Warm Season (April–September)

				Average Daily Deaths by Cause During the Warm Season			Maximum Apparent Temperature; °C		
City	Population	Study Period	Valid Days	Natural	Cardiovascular	Respiratory	Mean	Min	Max
Athens	3,188,305	1992–1996	914	67.5	32.6	4.2	27.9	7.9	41.6
Barcelona	1,512,971	1992–2000	1182	35.9	13.0	3.1	23.3	6.5	36.9
Budapest	1,797,222	1992–2001	1822	71.0	34.9	2.2	21.9	0.2	38.8
Dublin	481,854	1990–2000	2013	11.4	4.9	1.4	14.7	1.5	28.5
Helsinki	955,143	1990–2000	2013	17.1	8.2	1.4	14.3	−3.7	32.8
Ljubljana	263,290	1992–1999	1302	6.3	2.6	0.4	20.1	−1.7	35.4
London	6,796,900	1992–2000	1485	149.0	61.0	23.7	18.1	1.5	35.2
Milan	1,304,942	1990–2000	1769	26.3	9.9	1.7	25.4	2.7	40.8
Paris	6,161,393	1991–1998	1458	115.7	34.8	7.7	19.7	1.5	39.4
Prague	1,183,900	1992–2000	1628	34.9	20.3	1.1	17.8	−3.3	36.3
Rome	2,812,573	1992–2000	1638	52.8	20.9	2.6	26.1	5.9	40.5
Stockholm	1,173,183	1990–2000	1997	27.9	13.5	2.2	15.4	−2.1	34.0
Turin	901,010	1991–1999	1519	19.1	7.9	1.0	23.4	4.2	45.8
Valencia	739,004	1995–2000	1094	14.6	5.3	1.4	29.5	10.6	44.9
Zurich	990,000	1990–1996	1272	11.6	5.2	0.6	19.0	0.7	35.2

PHEWE Study, 1990–2000.

Air pollution data coming from the urban monitoring network were collected for each city. We used the maximum hourly value of nitrogen dioxide (NO_2) as an indicator of the overall daily air pollution level for all the cities, except in Dublin, where we considered the daily average level of black smoke.

A negligible percentage of isolated missing values (less than 1% for most cities, with a maximum of 4% for Turin) characterized meteorologic and air pollution data. We imputed these through the average of values observed in the same month. For a few cities (Barcelona, Turin, and London), meteorologic information was lacking for series of consecutive days (1 or even 2 months). In this case, the missing periods were not included in the analysis (Table 1). Sensitivity analyses excluding years with higher number of missing measurements produced similar results (results not reported).

Rationale for the City-Specific Modeling Approach

In the larger project, we have investigated the effect of cold and heat separately. Restriction to 6-month seasons permitted us to reduce the complexity of controlling for temporal confounding and enabled us to use different model specifications by season. A common a priori definition of warm season, from 1 April to 30 September, was adopted for all the cities.

As data from each city were represented by several disjoint 6-month daily time series (clusters), we used a generalized estimating equations (GEE) approach, which extends generalized linear models to the analysis of longitudinal data, when the observations on different clusters can be assumed to be independent and the observations within clusters are correlated.[13] For each city, the data consisted of an outcome variable (number of deaths) and several covariates (confounders and apparent temperature), observed day by day for each available summer. We assumed that observations during a single summer were correlated, while observations from different summer periods were independent. A similar approach has been suggested by Schwartz and Dockery[14] in the context of the analysis of short-term effects of air pollution on health and recently by Hajat et al[15] in studying the health effect of heat waves in 3 major European cities. Other examples are in the papers by Fouillet et al[16] and by Gorjanc et al.[17]

Since the number of clusters is mostly lower than the number of observations within clusters, specifying the appropriate autocorrelation structure is a relevant point to assure consistency of the standard error estimates.[18] We established the correct specification of the error structure taking advantage of an exploratory analysis based on dynamic models.[19] The dynamic models are linear regression models with lagged regressors and correlated errors. To highlight a common autocorrelation structure, we defined dynamic models with different correlations between errors and, for each season and for each city, we employed an automatic method for the best model selection. The results suggested that we should use a first order autocorrelation structure. We then used the model-based variance estimator, as recommended in the presence of few large clusters.[13]

City-Specific Model Specification

For each city, we specified a GEE model, assuming the dependent variable was Poisson distributed. Confounders included in the models were dummy variables for holidays, day of the week and calendar month; linear and quadratic terms to pick up long-term time trend; linear terms for barometric pressure (lag 0–1) and wind speed. Air pollution was found to confound the effect of high temperature.[20,21] We adjusted for maximum hourly NO_2 concentrations (lag 0–1). The choice of NO_2 as the air pollution indicator was based on comparability, availability, and completeness of daily measurements among cities.

Exposure-Response Relationship

We studied the effect of lag 0–3 exposure (the average of the current and the previous 3 days maximum apparent temperature).

First, we used a flexible parametric approach to describe the exposure-response curve, including in the model a cubic regression spline for apparent temperature with 1 knot every 8°C.[22] Second, to summarize and to address heterogeneity, we further described the relationship between apparent temperature and mortality during the warm season by 2 linear terms constrained to join at a common point, which we call the threshold. The threshold is the value of apparent temperature, which corresponds to a change in the effect estimate. For a V-shaped curve, this is the value of apparent temperature associated with the minimum mortality rate. The city-specific thresholds were obtained by the maximum likelihood approach proposed by Muggeo.[23] The slopes above the breakpoint were used as effect estimates.

A drawback of this method is that threshold estimation can be strongly dependent on the algorithm starting point.[23] We used the same starting point for all the cities to avoid post hoc data dredging, but a sensitivity analysis showed that in our data the threshold estimate is substantially independent of the starting point.

Delayed Effect of Exposure

The lagged effect of daily maximum apparent temperatures above the city-specific threshold was investigated up to 40 days using a constrained distributed-lag model.[24] We assumed that all coefficients from lag 0 to lag 40 fell on a curve of a 5th-order polynomial, to obtain a reasonably flexible distribution of lags and parsimony in the number of parameters estimated. We considered alternative constraint definitions and performed analyses leaving the current day effect unconstrained to check the robustness of estimates to outlying immediate effects. The various approaches produced negligible differences (results not shown).

Time-Varying Effect of Maximum Apparent Temperature

We relaxed the season definition extending our GEE model to allow a time-varying effect of lag 0–3 maximum apparent temperature during the warm season. We assumed that the effect of exposure above the threshold was smooth over time. We used sine and cosine terms to describe this pattern[25]:

$$\beta_t = \alpha_0 + \sum_{k=0}^{1} \alpha_{1k} \sin\left(\frac{2\pi t}{183} 2^k\right) + \sum_{k=0}^{1} \alpha_{2k} \cos\left(\frac{2\pi t}{183} 2^k\right)$$

where t indexes time, from 1 April to 30 September ($t = 1, 2, \ldots, 183$), β_t is the effect of maximum apparent temperature and (α_0, α_{10}, α_{11}, α_{20}, α_{21}) are unknown coefficients to be estimated. This analysis provided a way for checking whether the slope above the threshold is constant over the warm season. At the same time, it gave information about the effective period when the effect is significant.

All city-specific analyses were conducted using STATA/SE 9.0 (StataCorp, College Station, TX) and R Software 1.2.1 (Team R Development Core).

Combined Analysis

City-specific results were pooled into 2 groups defined on the basis of meteorologic and geographic criteria[10]:

1. "Mediterranean" cities: Athens, Rome, Barcelona, Valencia, Turin, Milan, and Ljubljana.
2. "north-continental" cities: Prague, Budapest, Zurich, Paris, Helsinki, Stockholm, London, and Dublin.

The aim was to control part of the heterogeneity among cities and to compare the 2 regions. The definition of the geographic subgroups was done a priori.

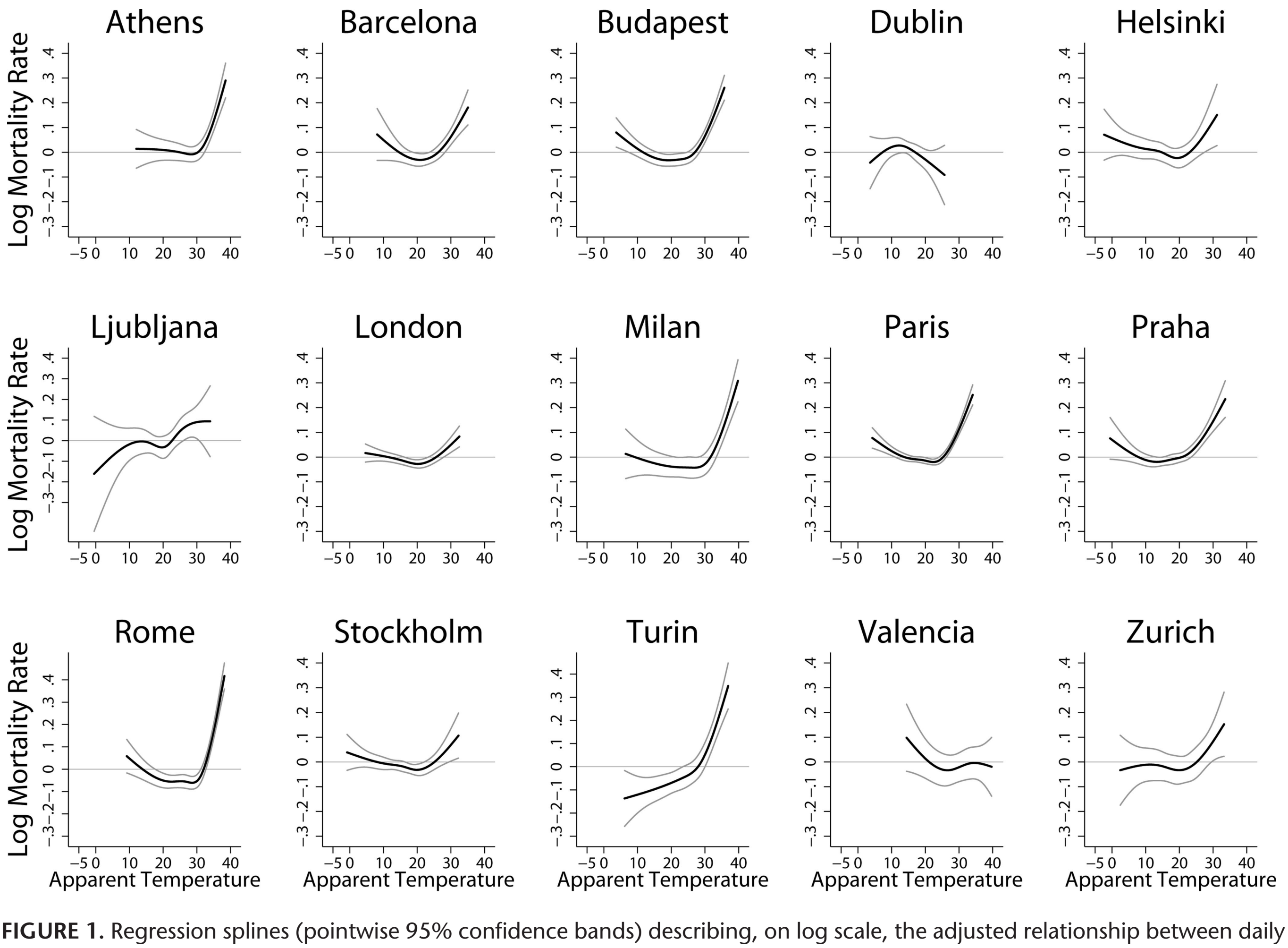

FIGURE 1. Regression splines (pointwise 95% confidence bands) describing, on log scale, the adjusted relationship between daily maximum apparent temperature (lag 0–3) and natural mortality in 15 European cities: Athens, Barcelona (mean apparent temperature), Budapest, Dublin, Helsinki, Ljubljana, London, Milan, Paris, Prague, Rome, Stockholm, Turin, Valencia and Zurich.

We obtained overall exposure-response curves fitting GEE regression models with a cubic regression spline for maximum apparent temperature (with one knot every 8°C) on the pooled data sets.[22] We did the analysis separately for Mediterranean and north-continental cities. Fixed city-specific intercepts and interaction terms between confounders and city indicators were introduced in the model. We assumed independence among years and first-order autocorrelation structure within season.

To produce regional averages of city-specific estimates of the effect parameters, we specified Bayesian hierarchical models.[26] Let $\hat{\lambda}_1, \ldots, \hat{\lambda}_c, \ldots, \hat{\lambda}_C$ be the vectors of the city-specific estimates of interest and $V_1, \ldots, V_c, \ldots, V_C$ the corresponding variance-covariance matrix estimates. In combining results from the distributed lag models and from the time-varying models, $\hat{\lambda}_c$ is a vector of model parameters. In pooling estimates of threshold or slope, $\hat{\lambda}_c$ is a scalar. A multivariate Gaussian distribution with unknown mean vector λ_c and variance-covariance matrix V_c was assumed for each $\hat{\lambda}_c$:

$$\hat{\lambda}_c \mid \lambda_c \overset{ind}{\sim} N(\lambda_c, V_c)$$

and a multivariate normal distribution with common mean vector and unknown variance-covariance matrix Σ was assumed on λ_c:

$$\lambda_c \mid \alpha, \sum \overset{ind}{\sim} N\left(\lambda_c, \sum\right)$$

Σ models the intercity variability. Vague proper priors were elicited on hyper-parameters. Inference was based on an algorithm proposed by Everson and Morris, implemented in the TLNise library of R software or on MCMC methods with WinBUGS 14.[27]

RESULTS

The relationship between maximum apparent temperature (lag 0–3) and log mortality rates were *V* or *J* shaped for most cities. This indicated an excess of risk for exposures to apparent temperature above a threshold that varies among cities (Fig. 1).

We combined the city-specific curves except Barcelona, where the exposure was defined in terms of daily mean apparent temperature. The curves in Figure 2 represent the overall estimate of the exposure-response relationship, separately for Mediterranean and north-continental cities. The pooled curves had a minimum around higher apparent temperatures and the effect of heat appeared slightly stronger in Mediterranean cities than in north-continental cities. When we used minimum apparent temperature as the exposure indicator, the combined curve was similar in shape, but, as expected, with a minimum around lower apparent temperature values (Fig. 2).

We report the heat effect as percent change in mortality associated with a 1°C increase in maximum apparent temperature above the city-specific threshold. City-specific and overall meta-analytic estimates of thresholds and percent change are reported in Table 2. For Ljubljana, Stockholm, and Zurich estimated thresholds were just below 22°C whereas for Athens, Milan, and Rome estimates were over 30°C. The overall meta-analytic value of the threshold was 29.4°C (95% credibility interval [CrI] = 25.7 to 32.4) for Mediterranean cities (excluding Barcelona) and about 6 degrees lower for North-continental

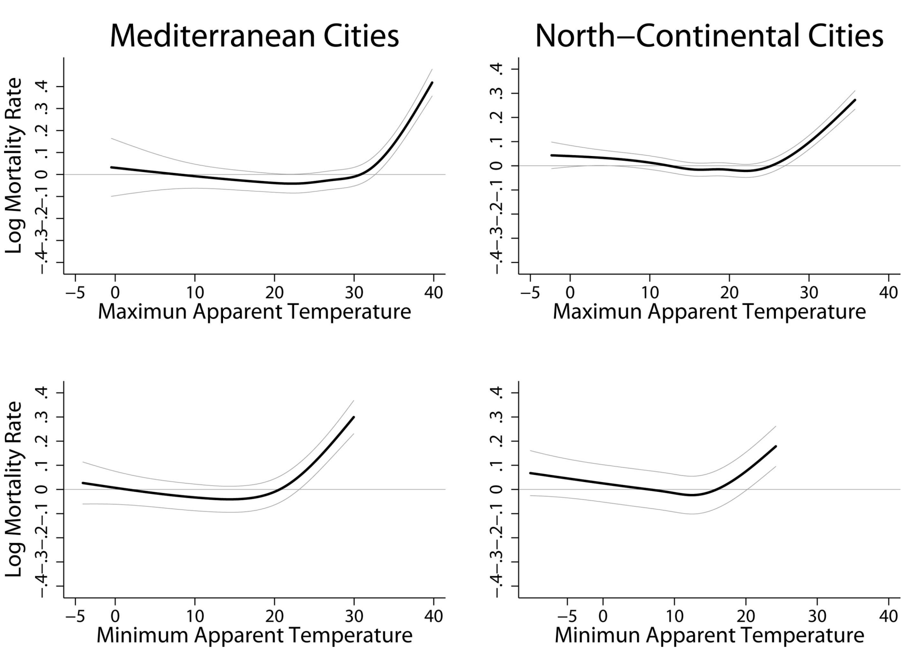

FIGURE 2. Fixed effects meta-analytic curves (pointwise 95% confidence bands) describing, on log scale, the adjusted effect of daily maximum (top) and daily minimum (bottom) apparent temperature at lag 0–3 on natural mortality. The left panel illustrates meta-analytic curves for Mediterranean cities (excluding Barcelona). The right panel shows the same curves for north-continental cities.

TABLE 2. Regional Meta-Analytic Estimates and City-Specific Estimates of Threshold and Percent Change in Natural Mortality Associated With a 1°C Increase in Maximum Apparent Temperature Above the City-Specific Threshold

	Threshold (°C) (95% CrI/CI)[a]	% Change (95% CrI/CI)[a]
Region		
North-continental	23.3 (22.5 to 24.0)	1.84 (0.06 to 3.64)
Mediterranean	29.4[b] (25.7 to 32.4)	3.12 (0.60 to 5.72)
City		
Athens	32.7 (32.1 to 33.3)	5.54 (4.30 to 6.80)
Barcelona	22.4[c] (20.7 to 24.2)	1.56 (1.04 to 2.08)
Budapest	22.8 (21.9 to 23.7)	1.74 (1.47 to 2.02)
Dublin	23.9 (20.7 to 27.1)	−0.02 (−5.38 to 5.65)
Helsinki	23.6 (21.7 to 25.5)	3.72 (1.68 to 5.81)
Ljubljana	21.5 (15.0 to 28.0)	1.34 (0.32 to 2.37)
London	23.9 (22.6 to 25.1)	1.54 (1.01 to 2.08)
Milan	31.8 (30.8 to 32.8)	4.29 (3.35 to 5.24)
Paris	24.1 (23.4 to 24.8)	2.44 (2.08 to 2.80)
Praha	22.0 (20.4 to 23.6)	1.91 (1.39 to 2.44)
Rome	30.3 (29.8 to 30.8)	5.25 (4.57 to 5.93)
Stockholm	21.7 (18.2 to 25.3)	1.17 (0.41 to 1.94)
Turin	27.0 (25.2 to 28.9)	3.32 (2.53 to 4.13)
Valencia	28.2 (23.7 to 32.7)	0.56 (−0.35 to 1.47)
Zurich	21.8 (16.5 to 27.0)	1.37 (0.49 to 2.25)

[a]95% credibility interval for regional meta-analytic estimates and 95% confidence interval for city-specific estimates.
[b]Excluding Barcelona.
[c]Mean apparent temperature.

cities (23.3°C; 22.5 to 24.0). The posterior distributions in Figure 3A indicate larger heterogeneity in thresholds among Mediterranean cities than among north-continental cities. Heterogeneity among Mediterranean cities remained high even if Ljubljana was removed, with the city-specific threshold estimates ranging in this case between 27.0°C (Turin) and 32.7°C (Athens). Overall meta-analytic percent change per degree of above-threshold apparent temperature equaled 3.1 (0.6 to 5.7) and 1.8 (0.1 to 3.6) for Mediterranean and north-continental cities, respectively. Heterogeneity was larger among Mediterranean cities (Fig. 3B).

Meta-analytic estimates of percent change in mortality per degree of above-threshold apparent temperature by cause and age class are reported in Table 3. We estimated different city-specific thresholds for each cause of death, which were close to those obtained for all natural mortality (not reported). The overall meta-analytic estimates of percent change in cardiovascular mortality per degree of above-threshold temperature were 3.7 (0.4 to 7.0) for Mediterranean cities and 2.4 (−0.1 to 5.3) for north-continental cities. Higher associations were found between heat and mortality due to respiratory diseases, with estimated percent changes equal to 6.7 (2.4 to

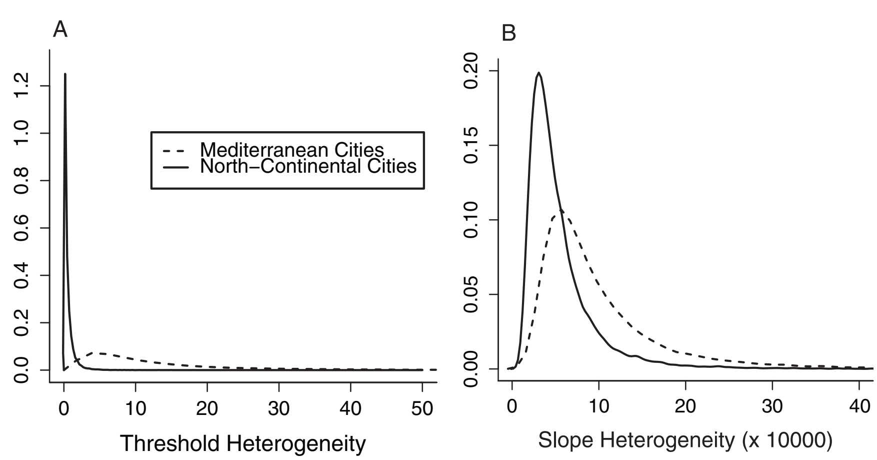

FIGURE 3. Posterior distribution of the heterogeneity variance for (A) threshold and (B) slope above the threshold among Mediterranean cities (excluding Barcelona) and north-continental cities. Values of the posterior density function on y-axis.

TABLE 3. Overall Meta-Analytic Percent Changes (95% Credibility Intervals) in Mortality for All Natural, Cardiovascular, and Respiratory Causes, in All Ages and by Age Group, Associated With a 1°C Increase in Maximum Apparent Temperature Above the City-Specific Threshold

	Mediterranean Cities		North-Continental Cities	
Age; yrs	% Change	(95% CrI)	% Change	(95% CrI)
Natural mortality				
All	3.12	(0.60 to 5.73)	1.84	(0.06 to 3.64)
15–64	0.92	(−1.29 to 3.13)	1.31	(−0.94 to 3.72)
65–74	2.13	(−0.42 to 4.74)	1.65	(−0.51 to 3.87)
75+	4.22	(1.33 to 7.20)	2.07	(0.24 to 3.89)
Cardiovascular mortality				
All	3.70	(0.36 to 7.04)	2.44	(−0.09 to 5.32)
15–64	0.57	(−2.47 to 3.83)	1.04	(−2.20 to 4.92)
65–74	1.92	(−1.49 to 5.35)	1.50	(−1.12 to 4.62)
75+	4.66	(1.13 to 8.18)	2.55	(−0.24 to 5.51)
Respiratory mortality				
All	6.71	(2.43 to 11.26)	6.10	(2.46 to 11.08)
15–64	1.54	(−3.68 to 7.22)	3.02	(−1.55 to 7.42)
65–74	3.37	(−1.46 to 8.22)	3.90	(−0.16 to 8.92)
75+	8.10	(3.24 to 13.37)	6.62	(3.04 to 11.42)

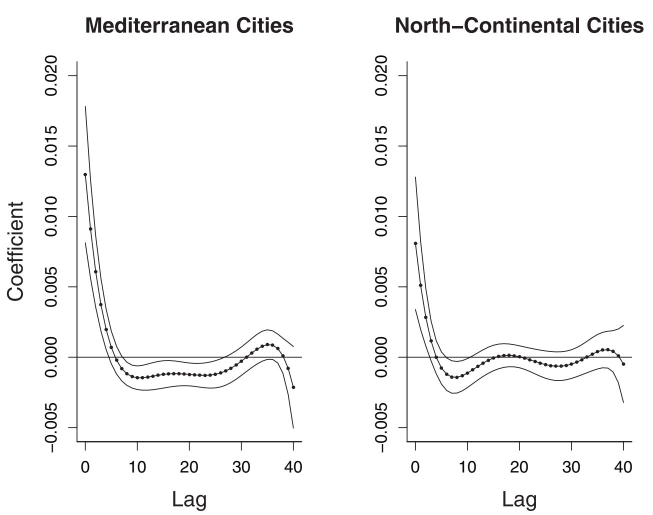

FIGURE 4. Meta-analytic curves (pointwise 95% credibility bands) describing the delayed effects of maximum apparent temperature above the threshold up to a lag of 40 days for Mediterranean and north-continental cities.

11.3) and 6.1 (2.6 to 11.1) for Mediterranean and north-continental cities, respectively.

The effect of heat was particularly large in the elderly. For people aged 75 and older, we estimated that a 1°C increase in maximum apparent temperature above the threshold was associated with an increase in mortality for all natural causes of 4.2% for the Mediterranean region and of 2.1% for the north-continental region. The same effect estimates were 8.1% and 6.6%, respectively, when only deaths for respiratory causes were considered.

TABLE 4. Meta-Analytic Cumulative Percent Changes (95% Credibility Intervals) in Natural Mortality Associated With a 1°C Increase in Maximum Apparent Temperature Above the City-Specific Threshold

	Mediterranean Cities		North-Continental Cities	
Lag Days	% Change	(95% CrI)	% Change	(95% CrI)
0	2.25	(0.07 to 4.49)	1.25	(−0.50 to 2.98)
3	3.12	(0.60 to 5.72)	1.84	(0.06 to 3.64)
5	3.00	(0.35 to 5.75)	1.28	(−0.71 to 3.17)
10	2.57	(0.12 to 5.10)	0.94	(−0.94 to 2.75)
15	1.88	(−0.36 to 4.16)	0.79	(−1.14 to 2.64)
20	1.38	(−0.72 to 3.51)	0.71	(−1.21 to 2.58)
25	1.01	(−1.06 to 3.09)	0.65	(−1.22 to 2.51)
30	1.26	(−0.78 to 3.36)	0.51	(−1.36 to 2.36)

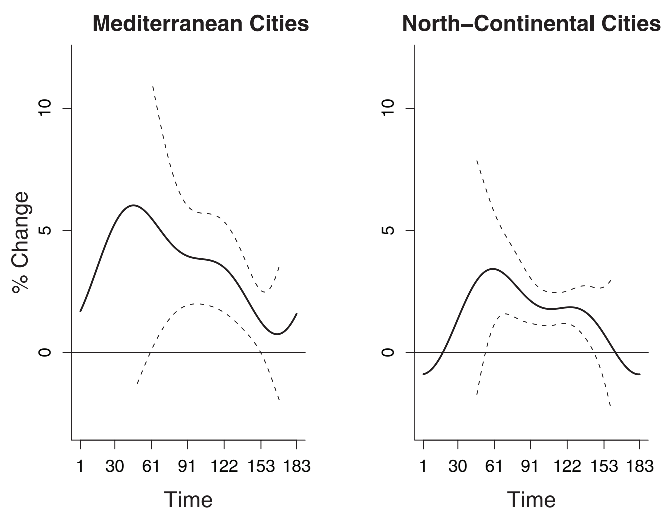

FIGURE 5. Mediterranean and north-continental meta-analytic time-varying effects (pointwise 95% credibility bands) of maximum apparent temperature above the threshold on natural mortality (lag 0–3).

Figure 4 shows the meta-analytic distributed lag curves by geographic region. A strong effect of high apparent temperatures was evident within the first week. The excess mortality declined in subsequent days, became negative, then returned to the level of baseline mortality-more slowly in the Mediterranean cities, faster in the north-continental cities. Table 4 summarizes the posterior distributions of the cumulative effects calculated at various lags from unrestricted models. Cumulative effects were larger for the Mediterranean cities than for the north-continental cities. They declined after the first 5 days from the day of above-threshold apparent temperature, becoming immediately not significant for north-continental cities and after 15 days for Mediterranean cities.

The results of the time-varying coefficients analysis indicated an effect of apparent temperature exposure above the threshold between June and August. Evidence of a stronger association between early above-threshold exposure and total mortality was found, although there were a small number of days during which maximum apparent temperature exceeded the threshold in April and May (Fig. 5).

DISCUSSION

Study Design and Modeling Issues

The exposure-response curves using daily maximum versus minimum apparent temperature were substantially similar in shape although (of course) shifted. The minimum apparent temperature curve was less precise and had a reduced slope above the threshold. This result could indicate a misclassification bias with the minimum apparent temperature: perhaps minimum (usually overnight) temperature is a less sensitive indicator of risk than the maximum apparent temperature.

We based our analysis on a GEE approach, assuming independence of the observations from different summer periods. This assumption implies the absence of long-term harvesting-like phenomena; ie, we are excluding the possibility that high mortality levels during one summer induce low mortality levels in the next summer, and vice versa, thus focusing on the effect of heat only within season.

For each city, the effect of heat was summarized by a minimum risk threshold and a linear term describing the effect of exposures exceeding the threshold. In principle, the algorithm for segmented regression would allow more than one threshold,[23] but the introduction of 2 cut-points would have made comparison among cities more difficult (despite a possible gain in terms of fitting).

The Muggeo algorithm for threshold estimation can be unstable, especially in small sample or when cut-points are not well defined.[23] In some studies, threshold estimation has been avoided and the effect of heat calculated by comparing the mortality rate at 2 different points over a flexible curve that describes the mortality-temperature association.[9] This approach provides effect estimates independent from the threshold, but dependent on the 2 points selected for comparison. This arbitrariness can be a drawback in comparing results from cities characterized by different ranges of exposure.

We did not make the strong assumption of a common threshold for all the cities, but instead obtained city-specific thresholds. In the same way, we estimated different thresholds for each cause of death, because in principle the minimum of the exposure-response curves can be different for different specific causes of death. In either situation, an incorrect assumption of common threshold could produce biased estimates of the slope. The same reasoning is in principle valid also for the age-specific analyses, but in this case estimating different thresholds for each age group is problematic due to the small number of daily events among younger people. This would worsen the performance of the estimation algorithm.

Epidemiologic Issues

We investigated the effect of heat on a large scale across a variety of climate conditions and socioeconomic and demographic characteristics. We applied a standardized methodology to data from 15 European cities, with a gain of power and assessment of variability across city-specific effect estimates.

We did not focus on heat wave episodes. Our results provide evidence of an effect of heat on daily mortality. Many investigators have reported V- or J-shaped associations between temperature and mortality.[6,7,9,15] We confirmed these findings.

Previous studies have shown that the temperature level corresponding to the minimum mortality rate (threshold) varies from city to city, and across different latitudes according to the local climate.[6,7,28] We found that the apparent temperature threshold in the Mediterranean cities was higher than in the north-continental cities, indicating that residents of north-continental cities are susceptible at lower values of apparent temperature.

As far as the effect of exposures that exceed the threshold is concerned, stronger percent changes in all natural mortality and in respiratory and cardiovascular mortality were observed in the Mediterranean region. Steeper slopes were found for mortality for respiratory causes, consistent with results of previous studies.[29]

The associations with mortality were stronger after 74 years of age than earlier in life, suggesting that the elderly are particularly vulnerable.[9,29,30]

Knowledge of the lag time between exposure to extreme weather conditions and negative health outcomes is important for public health authorities and health care providers in developing prevention plans. The effect of high apparent temperature is immediate both in Mediterranean and north-continental cities. This result is consistent with findings of previous studies indicating that the impact of heat on mortality reaches its maximum in less than a week.[31,32]

There is contradictory evidence as to whether the increase of mortality is followed by a deficit that partly compensates for the negative effect (harvesting). In some cases, a harvesting effect is found to fully balance the observed excess, whereas in others only part of the excess is compensated.[32,33] We found evidence of harvesting in both the Mediterranean and north-continental regions. The mortality displacement partially compensates for the effect of heat observed during the first week after exposure. In the Mediterranean cities, the harvesting phenomenon is more prolonged, but in both regions the cumulative effect at lag 25 is around 30% of the cumulative effect at lag 3.

The evidence of harvesting suggests the presence of subgroups of susceptible individuals for which heat precipitates deaths by a few days to weeks.

An overall heat effect was clearly present from June to August. However, the time-varying coefficients models suggested a greater effect of earlier exposures. This evidence was based on few observations (there were few days during the first months of the warm season with a maximum apparent temperature above the threshold), but was largely consistent among cities. The stronger effect of early exposure could have various explanations. From a physiologic point of view, the human organism may react better to later heat exposure due to acclimatization,[34] although this finding could also be explained by a changing composition of the population at risk over time, due to a harvesting-like phenomenon.

We adjusted for the confounding effect of air pollution. The discrepancy between adjusted and unadjusted effect estimates varied among cities. For example, in Athens, adjustment changed the percent increase in total mortality with 1°C rise in maximum apparent temperature from 6.2 to 5.5, while in Stockholm, adjustment had a negligible effect.

Future studies should investigate possible effect modifiers that could explain heterogeneity in threshold and slope estimates, both between and within regions. Varying acclimatization to weather changes could explain the observed heterogeneity.[35] However the observed differences among cities and between regions could also reflect demographic, cultural, socioeconomic, and technological circumstances that produce different proportions of susceptible persons in the enrolled cities.[21] In this sense, the estimated exposure-response curves can be considered a mixture of curves, each of which describes the relationship between apparent temperature and mortality in a subgroup of the population. Also meteorologic and geographic characteristics should be studied as possible contributors to heterogeneity among cities, insofar as they can modify mechanisms leading to acclimatization or interact with temperature, modifying the effect of heat.

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