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The impact of heat waves on mortality

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Abstract

Background—Heat waves have been linked with an increase in mortality, but the associated risk has been only partly characterized.

Methods—We examined this association by decomposing the risk for temperature into a “main effect” due to independent effects of daily high temperatures, and an “added” effect due to sustained duration of heat during waves, using data from 108 communities in USA during 1987-2000. We adopted different definitions of heat-wave days based on combinations of temperature thresholds and days of duration. The main effect was estimated through distributed lag non-linear functions of temperature, which account for non-linear delayed effects and short-time harvesting. We defined the main effect as the relative risk between the median city-specific temperature during heat-wave days and the 75th percentile of the year-round distribution. The added effect was defined first using a simple indicator, and then a function of consecutive heat-wave days. City-specific main and added effects were pooled through univariate and multivariate meta-analytic techniques.

Results—The added wave effect was small (0.2%-2.8% excess relative risk, depending on wave definition) compared with the main effect (4.9%-8.0%), and was apparent only after 4 consecutive heat wave days.

Conclusions—Most of the excess risk with heat waves in the USA can be simply summarized as the independent effects of individual days' temperatures. A smaller added effect arises in heat waves lasting more than 4 days.

Heat is a well-known public health hazard.¹ The relationship between high temperatures and a number of health outcomes, in particular mortality, has been documented in many epidemiologic studies.²⁻⁵ Extended periods of extreme heat, usually defined as heat waves, have been linked with a substantial increase in mortality,⁶ and specific events have been reported as public health disasters—such as in Chicago during July 1995⁷ and in France during August 2003.⁸⁻⁹ The characterization of the relationship of heat and heat waves with health assumes a particular importance given the predicted increase in their frequency and intensity based on climate change scenarios.¹⁰⁻¹¹

Past approaches to investigate the health effects of heat are of 2 types—episode analysis and continuous-temperature time-series analyses.¹² In episode analysis a heat wave is considered as a distinct event (episode), and excess risk associated with it is estimated by comparison with not-heat wave periods.¹³⁻¹⁵ A time-series analysis usually considers temperature as a continuous risk factor, using linear threshold parameterization,¹⁶⁻¹⁷ or smooth functions¹⁸⁻¹⁹ to specify its exposure-response relationship, sometimes allowing for lagged effects.

A few studies have recently brought these two approaches together, investigating the increase in risk during heat waves in a time-series regression model that also includes daily temperature as a numeric explanatory variable, possibly allowing for lagged effects. This method has been used to quantify harvesting during single events, as in August 2003 in Europe^{8,20} and July 1995 in Chicago,²¹ and also extended in studies with multiple heat wave periods.^{2,22} The rationale under this methodology assumes that the effect of heat may be described as the sum of two contributions: an increased risk due to the independent effects of daily temperature levels, and an additional risk due to duration of heat sustained for several consecutive days. The former is predicted by the usual exposure-response function for the temperature-health relationship, characterizing both heat wave and non-heat wave days, while the latter is commonly estimated by an indicator, usually defined as two or more consecutive days above a specified temperature. Here we refer to these contributions as main and added effect of heat, respectively.

This approach entails a more developed definition of heat-wave effects, identified as that not merely due to a series of days with extremely hot temperature, but due to periods when sustained heat produces an excess mortality beyond that predicted by independent contributions of daily temperature occurrences. In consequence, this method allows a more accurate prediction of the effect of heat on health by distinguishing between impacts from isolated days of heat and from sustained days of heat in waves. A substantial added effect implies the presence of additional patho-physiologic mechanisms that arise when the exposure to hot temperatures is protracted for several days, not occurring in single sporadic days of extreme heat. In contrast, a weak (if any) added effect would suggest that the increased risk during waves may be explained by the sole main effect, estimated by simpler models based on temperature-mortality exposure-response functions. Such evidence has a clear implication in order to plan public health interventions or to estimate the future burden of heat-related deaths under predicted climate change scenarios.

Studies on multiple heat-wave periods have indeed shown a substantial added effect.^{2,22} However, the extent of the wave effect appears to be sensitive to model features, in particular the specific function used to model the main exposure-response relationship.²² In this paper we seek to characterize more clearly the relationship between heat and mortality, analyzing the excess risks in heat-wave periods, by comparing the contributions of main and added effects, as defined above, under different wave definitions. In addition, we propose a new, more flexible model to describe the added effect in terms of duration, allowing the risk to vary smoothly by the number of consecutive heat wave days.

Methods

Data

The analysis includes the data for 108 urban communities in the U.S.A. during the period 1987-2000. The series for mortality, weather and pollution data were assembled from publicly available data sources as part of the National Morbidity, Mortality, and Air Pollution Study.²³⁻²⁴ Daily overall mortality consists of death counts among residents, excluding injuries and external causes (International Classification of Diseases, 9th revision (ICD-9) codes 800 and above, ICD-10 codes S and above). Maximum and minimum temperatures are computed as the highest and lowest hourly measurements registered within each day, with mean temperature as the average between them. General information about how the data were collected and assembled have been previously reported, together with a detailed summary of descriptive statistics for each community (<http://www.ihapss.jhsph.edu>). For the current analyses we restrict the period to summer months (June-September), to avoid the complexities of having to model cold as well as heat effects.^{3,22,25}

Statistical analysis

The analytic strategy follows a scheme already proposed for multi-city studies, with a common model applied to each community and then the use of meta-analytic procedures to derive the pooled estimates.²⁶ Here the effect of heat is decomposed into the main and added effects introduced above, by including two terms for mean temperature in the city-specific model. An algebraic representation is given by:

$$\log [E (Y_i)] = \alpha + \sum_{j=1}^P g_j (x_{ij}) + m (t_i) + w (t_i)$$

where Y_i is the mortality count, assumed to follow an overdispersed Poisson distribution for each day i . The covariates x_j , with effects expressed by the functions g_j , include an indicator for day of the week and spline functions for dew point temperature, day of the year and time. These last two terms describe a regular seasonal trend, forced to be identical each year, and a smooth long-time trend, using 5 and 3 degrees of freedom (df), respectively, following a parsimonious approach previously applied for analyses restricted to summer months.^{3,22,25}

The main effect of heat on day i is described by the function m of the series of lagged temperatures $t_{i-\ell}$, with $\ell = 0, \dots, L_m$ and L_m as maximum lag. To allow flexibility, m is specified as a two-dimensional spline function, defining a distributed lag non-linear model that allows the main effect to vary smoothly along both dimensions of temperature and lags.^{18,27} The relationship in the temperature space is modelled by a cubic spline with 6 degrees of freedom (df). Changes in the shape along lags is modelled by a natural cubic spline with 5 df, up to a maximum lag $L_m = 10$. This flexible model accounts simultaneously for non-linear and lagged effects and short-time harvesting. In spite of this flexibility, the relationship specified by the term m still assumes that effects of temperature at each lag are independent. We summarize the main effect from each city-specific model from the term $m(t)$, predicting the relative risk between the median temperature among heat wave days versus the 75th percentile of annual temperature distribution. This reference was chosen as a temperature at which little if any adverse effect of temperature on mortality is expected.¹⁹

The pooled main effect across cities is computed through a random effect meta-analysis based on restricted maximum likelihood.²⁸

The additional risk of sustained heat is left to the added effect described by the function w . The choices for this function are introduced below.

Heat wave indicator

In a first analysis, we specify $w(t_i)$ with:

$$w(t_i) = \prod_{\ell=0}^{L_w} I(t_{i-\ell} > \tau)$$

where I is an indicator which assumes value 1 if $t_{i-\ell}$ is higher than a threshold level τ . In practice, in this first analysis $w(t)$ is the usual indicator defining heat wave days as those with temperature above an intensity criterion τ for at least $L_w + 1$ days of duration. Following the definitions already proposed in literature,^{2,22} we set τ equal to the 97th, 98th or 99th percentiles of the year-round city-specific distribution, and L_w equal to 1 or 3 (2 or 4

days of duration). The city-specific added effect is estimated as the exponential of the coefficient for the indicator variable.

The same meta-analytic techniques used for the main effect were applied to estimate the pooled added effect across cities.

Numeric measure of heat wave duration

The second approach to characterize the added effect retains the temperature dichotomy (at the 97th percentile), but replaces the duration dichotomy by allowing risk to depend on how many consecutive days there have been above the threshold. In this case, $w(t) = f(d)$, where:

$$d_i = \sum_{\ell=1}^{L_w} \left[I(t_{i-\ell} > \tau) \prod_{j=0}^{\ell-1} I(t_{i-j} > \tau) \right]$$

Here d_i is defined as the consecutive day the temperature has by date i exceeded the threshold τ . The product term in the equation above ensures that all the preceding days show a temperature above τ . Note that, d is 0 for non-heat wave days and for the first day above the threshold τ , then 1 for the second day and so on, up to the day the temperature comes back below the limit, with a maximum of L_w days. Here we set τ equal to the 97th city-specific percentile and a maximum duration L_w of 10 days. The function f describing the added effects in terms of consecutive heat wave days d is specified in two ways: through a step function (strata: 1, 2-3, 4-5, 6-7, 8-10), or through quadratic splines with 5 df (without natural constraints, 3 knots at 2, 5, 8 days).

The estimates and variance-covariance matrix for the 5 parameters of the function $f(d)$ are then included in a multivariate meta-analysis,²⁹ in order to obtain the pooled added effect along consecutive heat-wave days. The maximum heat-wave length is different in each city, and those with maximum duration less than 10 days may contribute only to a subset of parameters. This is handled by the meta-analytic procedure allocating very large variances to the missing parameters, so that they will receive very small weight and not contribute to the average estimate.²⁹⁻³⁰ The limit of 10 consecutive days was set in order to retain enough cities in the analysis actually contributing to the estimates.

Sensitivity analysis

Given the complex statistical approaches adopted in the analyses above, involving several assumptions and a-priori choices, a sensitivity analysis was carried out on the parameters for the city-specific model for functions g_j and m . Specifically, we modified the degree of smoothing for seasonality and the complexity of the distributed lag functions, varying the df and type for the splines for day of the year, temperature and lag dimensions in the models with the mildest (97th percentile, 2 days of duration) and strictest (99th percentile, 4 days of duration) wave definitions.

We also carried out some analyses to elucidate whether the main and added terms are too correlated for their effects to be disentangled. First we computed the simple correlations between mean temperature and both indicators and continuous measure of consecutive heat wave days. Then, we more generally assessed the multi-collinearity between the full set of main effect terms and the added wave term. Specifically, we computed the R^2 of a model regressing each heat-wave term on the cross-basis variables: a high R^2 indicates that the heat-wave term is almost perfectly predicted by the variables for the main effect, potentially inducing problems of multi-collinearity in our regression model.

Further information on modelling choices and residual, correlation and additional sensitivity analyses are provided in eAppendix (<http://links.lww.com>), Sections S1-S3.

Software

The main analyses and graphical representation are performed in the statistical environment R version 2.11.1.³¹ Distributed lag non-linear models are specified through the package *dlnm* (version 1.2.3), while univariate meta-analyses are carried out through the package *metafor* (version 1.1-0). Multivariate meta-analytical estimates are obtained by Stata 11,³² using the command *mvmeta*.

The main results included in the paper are entirely reproducible.³³ The data are freely available using the R package *NMMAPlite* (version 0.3-2). The R code to run the main analysis, plus the Stata code for multivariate meta-analysis are available in eAppendix (<http://links.lww.com>), Sections S4.

Results

Mean summer temperature shows a high variability in the 108 communities, ranging from 12.8°C in Anchorage to 33.0°C in Phoenix, with an average of 23.5°C. The number of heat-wave days during the 14-year period, defined by the indicator variable used in the first analysis, varies depending on wave definitions. The average number of heat-wave days in each community is 90.0 (range: 38-129) when using the 97th percentile and 2 days duration, and 7.2 (range: 0-21) using the 99th percentiles and 4 days.

Table 1 shows the estimated increase in risk due to main and added effects in those days matching the 6 definitions. The average main effect is similar between definitions based on 2 or 4 days of duration, and increases proportionally to the intensity criterion (97th, 98th, and 99th percentiles), being computed on the median temperature among heat-wave days, which increases accordingly. In contrast, the duration criterion plays an important role for the added effect: the models using 2 days of minimum duration show very small increases in risk; if the minimum duration period is extended to 4 days, the average added effect increases proportionally to the selected percentile. Only the strictest definition of days showing a temperature above the 99th percentile for at least 4 past days provides an increase of 2.8% (95% confidence interval [CI]: 0.4% to 5.3%) in mortality. The contribution of the main effect substantially exceeds the added effect during heat wave days in all the 6 definitions.

Communities show some variability in the length of wave periods, when specified as 2 consecutive days with temperature above the 97th city-specific percentile, with an average maximum length of 9.5 days (range: 4-20 days). Heat waves of at least 10 and 7 days long, were experienced respectively, by 45.4% and 81.5% of communities. Heat wave periods are usually short, with 76.3% of days within the first 3 of heat wave. The average added effect, specified by increase in risk for consecutive heat wave days and modelled alternatively by both quadratic spline and a step functions, is depicted in the Figure. The analysis shows no effect during the beginning of a wave period, then an increase when the heat is sustained for longer than 4 uninterrupted days. The plot also displays a decrease after a peak at around 7 consecutive days, although wide confidence intervals.

The results of sensitivity analysis are illustrated in Table 2. The estimated added effect (0.3% and 2.8% in the original models, respectively) was robust to most of the changes. The most notable exceptions are the results reported in the last three rows of Table 2, which showed considerably higher wave effects (up to 3.7% and 7.0%). These models were characterized by either relatively inflexible splines for temperature, inflexible lag structure

or both. The 2 df spline with “natural” constraints is forced to be linear beyond the boundaries, further limiting its flexibility to model non-linear effects for extremely hot days. Because extremely hot days are also likely to be labelled as heat-wave days, this would produce an inflated added effect. The same happens when applying a very simple model with 1 df to describe lagged effect, corresponding approximately to a simple moving average of the temperatures in the lag period of ten days.

The correlation between mean temperature and heat-wave terms is not high: the average correlation coefficient r across cities is 0.40 (range, 0.29-0.51) for the indicator variable based on 97th percentile and 2 days of duration and 0.32 (range, 0.24-0.43) for continuous measure of consecutive heat wave days. The R^2 of the regression of wave terms on the cross-basis variables for the main effect, an index of multi-collinearity, shows an average of 0.63 (range, 0.43-0.76) for the same indicator and of 0.56 (range, 0.38-0.72) for the continuous variable. These results demonstrate that, although the main and added effects are correlated, the model and data still have power to separate these 2 effects.

Discussion

Our approach seeks to characterize the excess risk during heat-wave periods, quantifying how much of this additional burden is simply explained by the increase in temperature and how much is attributable to the heat continuing over several consecutive days. Furthermore, this additional risk during waves is described in terms of duration, proposing a new definition based on consecutive heat wave days.

This analysis addresses important epidemiologic and public health questions: the implementation of adequate preventive measures such as heat-wave plans (in the short-to-medium term) and the prediction of the burden of future events under the suggested climate change scenarios (in the long term) require a detailed characterization of the association between heat, heat-waves and mortality. The results suggest that most of the excess risk during waves is attributable to (and predictable by) the increase in daily temperatures whether isolated or occurring with other hot days, the effect of which is larger than any added effect. The latter is negligible for short heat-wave periods, although it does bring some additional risks after 4 days of uninterrupted heat.

Our analytic design offers several advantages. First, the choice of flexible distributed lag non-linear functions gives greater assurance than simpler models that the main effect is adequately accounted for, reducing the risk of confounding of the added effect by a residual main effect of heat. In addition, the analysis takes into account the adaptation of each population to its own climate,^{3,19} by allowing community-specific exposure-response functions for the main effect, and wave definitions based on community-specific percentiles. Finally, by modelling the heat-wave effect as a continuous function of duration, we avoid arbitrary duration criteria and allow direct estimation of the duration at which such effect become apparent.

Our findings from the first analysis using an indicator for heat-wave days, as described in Table 1, are rather different from some others previously reported in the literature. An analysis of London, Milan, and Budapest by Hajat and colleagues,²² with a wave definition based on the 99th percentile for at least 2 days and a natural cubic spline with 3 df to specify the un-lagged main exposure-response relationship, showed a percentage increase in mortality from 4.3% to 8.3%. Anderson and Bell,² analyzing the whole year data on the same dataset considered here and a natural cubic spline with 3 df for lag 0-1, found an average increase of 6.5% for a definition based on 99th percentile and 4 days of duration. These results are comparable in magnitude to our estimates for similar models reported in

the last 3 rows of Table 2, and can be probably explained by the limited flexibility of the functions used to account for the main effect, a pattern also reported by Hajat and colleagues.²² The results on the effect of wave duration are consistent with some findings already reported in the literature.³⁴⁻³⁵

We estimated the proposed association between heat, heat waves and mortality by averaging the effects across different cities and different wave periods, and this average relationship might not accurately represent every specific heat-wave event. The approach we propose showed quite good performance when applied to predict mortality during the extreme heat wave in Chicago in 1995 (eAppendix [<http://links.lww.com>], Section S3), but might be biased in describing some waves in some cities if these heat waves are unusual with respect to variables not included in the analytic model and acting as modifiers of the temperature-health association. For instance, a potential synergistic effect between air pollution and heat has been suggested, although specific analyses have reported conflicting results.^{2,36-37} The evidence is unclear also for an effect modification by socio-economic characteristics,^{16,38-40} while more robust for the prevalence of air conditioning.^{2,41-42} These issues may be addressed in further research.

In this paper we provide a novel analysis of the impact of heat waves on mortality. Our results suggest that the excess risk during heat-wave periods is largely explained by the immediate and lagged effect of daily temperatures, with just a small added impact due to sustained heat limited to waves lasting more than 4 days.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Kovats RS, Hajat S. Heat stress and public health: a critical review. *Annual Review of Public Health*. 2008; 29:41–55.
2. Anderson BG, Bell ML. Weather-Related mortality: how heat, cold, and heat waves affect mortality in the United States. *Epidemiology*. 2009; 20(2):205–213. [PubMed: 19194300]
3. Baccini M, Biggeri A, Accetta G, Kosatsky T, Katsouyanni K, Analitis A, Anderson HR, Bisanti L, D'Ippoliti D, Danova J, Forsberg B, Medina S, Paldy A, Rabczenko D, Schindler C, Michelozzi P. Heat effects on mortality in 15 European cities. *Epidemiology*. 2008; 19(5):711–9. [PubMed: 18520615]
4. Basu R. High ambient temperature and mortality: a review of epidemiological studies from 2001 to 2008. *Environmental Health*. 2009; 8(1):40. [PubMed: 19758453]
5. Basu R, Samet JM. Relation between elevated ambient temperature and mortality: a review of the epidemiologic evidence. *Epidemiologic Reviews*. 2002; 24(2):190–202. [PubMed: 12762092]
6. Kovats RS, Kristie LE. Heatwaves and public health in Europe. *European Journal of Public Health*. 2006; 16:592–9. [PubMed: 16644927]
7. Semenza JC, Rubin CH, Falter KH, Selanikio JD, Flanders WD, Howe HL, Wilhelm JL. Heat-related deaths during the July 1995 heat wave in Chicago. *New England Journal of Medicine*. 1996; 335(2):84–90. [PubMed: 8649494]

8. Le Tertre A, Lefranc A, Eilstein D, Declercq C, Medina S, Blanchard M, Chardon B, Fabre P, Filleul L, Jusot JF, Pascal L, Prouvost H, Cassadou S, Ledrans M. Impact of the 2003 heatwave on all-cause mortality in 9 French cities. *Epidemiology*. 2006; 17(1):75–9. [PubMed: 16357598]
9. Poumadere M, Mays C, Le Mer S, Blong R. The 2003 heat wave in France: dangerous climate change here and now. *Risk Analysis*. 2005; 25(6):1483–94. [PubMed: 16506977]
10. Luber G, McGeehin M. Climate change and extreme heat events. *American Journal of Preventive Medicine*. 2008; 35(5):429–435. [PubMed: 18929969]
11. O'Neill MS, Ebi KL. Temperature extremes and health: impacts of climate variability and change in the United States. *Journal of Occupational and Environmental Medicine*. 2009; 51(1):13–25. [PubMed: 19136869]
12. Gosling SN, McGregor GR, Lowe JA. Climate change and heat-related mortality in six cities Part 2: climate model evaluation and projected impacts from changes in the mean and variability of temperature with climate change. *International Journal of Biometeorology*. 2009; 53(1):31–51. [PubMed: 19052780]
13. Conti S, Meli P, Minelli G, Solimini R, Toccaceli V, Vichi M, Beltrano C, Perini L. Epidemiologic study of mortality during the Summer 2003 heat wave in Italy. *Environmental Research*. 2005; 98(3):390–9. [PubMed: 15910795]
14. Huynen MM, Martens P, Schram D, Weijnenberg MP, Kunst AE. The impact of heat waves and cold spells on mortality rates in the Dutch population. *Environmental Health Perspectives*. 2001; 109(5):463–70. [PubMed: 11401757]
15. Rey G, Jougl E, Fouillet A, Pavillon G, Bessemoulin P, Frayssinet P, Clavel J, Hemon D. The impact of major heat waves on all-cause and cause-specific mortality in France from 1971 to 2003. *International Archives of Occupational and Environmental Health*. 2007; 80(7):615–26. [PubMed: 17468879]
16. Hajat S, Kovats RS, Lachowycz K. Heat-related and cold-related deaths in England and Wales: who is at risk? *Occupational and Environmental Medicine*. 2007; 64(2):93–100. [PubMed: 16990293]
17. Pattenden S, Nikiforov B, Armstrong BG. Mortality and temperature in Sofia and London. *Journal of Epidemiology and Community Health*. 2003; 57(8):628–33. [PubMed: 12883072]
18. Armstrong B. Models for the relationship between ambient temperature and daily mortality. *Epidemiology*. 2006; 17(6):624–31. [PubMed: 17028505]
19. Curriero FC, Heiner KS, Samet JM, Zeger SL, Strug L, Patz JA. Temperature and mortality in 11 cities of the eastern United States. *American Journal of Epidemiology*. 2002; 155(1):80–7. [PubMed: 11772788]
20. Hertel S, Le Tertre A, Jockel KH, Hoffmann B. Quantification of the heat wave effect on cause-specific mortality in Essen, Germany. *European Journal of Epidemiology*. 2009; 24(8):407–14. [PubMed: 19517255]
21. Kaiser R, Le Tertre A, Schwartz J, Gotway CA, Daley WR, Rubin CH. The effect of the 1995 heat wave in Chicago on all-cause and cause-specific mortality. *American Journal of Public Health*. 2007; 97(Suppl 1):S158–62. [PubMed: 17413056]
22. Hajat S, Armstrong B, Baccini M, Biggeri A, Bisanti L, Russo A, Paldy A, Menne B, Kosatsky T. Impact of high temperatures on mortality: is there an added heat wave effect? *Epidemiology*. 2006; 17(6):632–8. [PubMed: 17003686]
23. Samet JM, Zeger SL, Dominici F, Curriero F, Coursac I, Dockery DW. The National Morbidity, Mortality, and Air Pollution Study (NMMAPS). Part 2. Morbidity and mortality from air pollution in the United States. 2000 Health Effects Institute. [PubMed: 11354823]
24. Samet JM, Zeger SL, Dominici F, Dockery D, Schwartz J. The National Morbidity, Mortality, and Air Pollution Study (NMMAPS). Part 1. Methods and methodological issues. 2000 Health Effects Institute. [PubMed: 11098531]
25. Michelozzi P, Accetta G, De Sario M, D'Ippoliti D, Marino C, Baccini M, Biggeri A, Anderson HR, Katsouyanni K, Ballester F. High temperature and hospitalizations for cardiovascular and respiratory causes in 12 European cities. *American Journal of Respiratory and Critical Care Medicine*. 2009; 179(5):383–389. others. [PubMed: 19060232]

26. Dominici F. Time-series analysis of air pollution and mortality: a statistical review. Research report - Health Effects Institute. 2004; (123):3–27. discussion 29-33. [PubMed: 15757000]
27. Gasparrini A, Armstrong B, Kenward MG. Distributed lag non-linear models. *Statistics in Medicine*. 2010 Epub ahead of print May 7. DOI: 10.1002/sim.3940.
28. van Houwelingen HC, Arends LR, Stijnen T. Advanced methods in meta-analysis: multivariate approach and meta-regression. *Statistics in Medicine*. 2002; 21(4):589–624. [PubMed: 11836738]
29. Jackson D, White IR, Thompson SG. Extending DerSimonian and Laird’s methodology to perform multivariate random effects meta-analyses. *Statistics in Medicine*. 2010; 29(12):1282–1297. [PubMed: 19408255]
30. White IR. Multivariate random-effects meta-analysis. *Stata Journal*. 2009; 9(1):40–56.
31. R Development Core Team. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing; Vienna, Austria: 2010.
32. Stata. StataCor LP; College Station, Texas: 2009.
33. Peng RD, Dominici F, Zeger SL. Reproducible epidemiologic research. *American Journal of Epidemiology*. 2006; 163(9):783–789. [PubMed: 16510544]
34. Diaz J, Jordan A, Garcia R, Lopez C, Alberdi JC, Hernandez E, Otero A. Heat waves in Madrid 1986-1997: effects on the health of the elderly. *International Archives of Occupational and Environmental Health*. 2002; 75(3):163–70. [PubMed: 11954983]
35. Hajat S, Kovats RS, Atkinson RW, Haines A. Impact of hot temperatures on death in London: a time series approach. *Journal of Epidemiology and Community Health*. 2002; 56(5):367–72. [PubMed: 11964434]
36. Medina-Ramon M, Schwartz J. Temperature, temperature extremes, and mortality: a study of acclimatization and effect modification in 50 United States cities. *Occupational and Environmental Medicine*. 2007; 64:827–833. [PubMed: 17600037]
37. Ren C, Williams GM, Morawska L, Mengersen K, Tong S. Ozone modifies associations between temperature and cardiovascular mortality: analysis of the NMMAPS data. *Occupational and Environmental Medicine*. 2008; 65(4):255–60. [PubMed: 17890300]
38. Stafoggia M, Forastiere F, Agostini D, Biggeri A, Bisanti L, Cadum E, Caranci N, de’ Donato F, De Lisio S, De Maria M, Michelozzi P, Migliorini R, Pandolfi P, Picciotto S, Rognoni M, Russo A, Scarnato C, Perucci CA. Vulnerability to heat-related mortality: a multicity, population-based, case-crossover analysis. *Epidemiology*. 2006; 17(3):315–23. [PubMed: 16570026]
39. Basu R, Ostro BD. A multicounty analysis identifying the populations vulnerable to mortality associated with high ambient temperature in California. *American Journal of Epidemiology*. 2008; 168(6):632–7. [PubMed: 18663214]
40. O’Neill MS, Zanobetti A, Schwartz J. Modifiers of the temperature and mortality association in seven US cities. *American Journal of Epidemiology*. 2003; 157(12):1074–1082. [PubMed: 12796043]
41. Barnett AG. Temperature and cardiovascular deaths in the US elderly: changes over time. *Epidemiology*. 2007; 18(3):369. [PubMed: 17435447]
42. Davis RE, Knappenberger PC, Michaels PJ, Novicoff WM. Changing heat-related mortality in the United States. *Environmental Health Perspectives*. 2003; 111(14):1712–1719. [PubMed: 14594620]

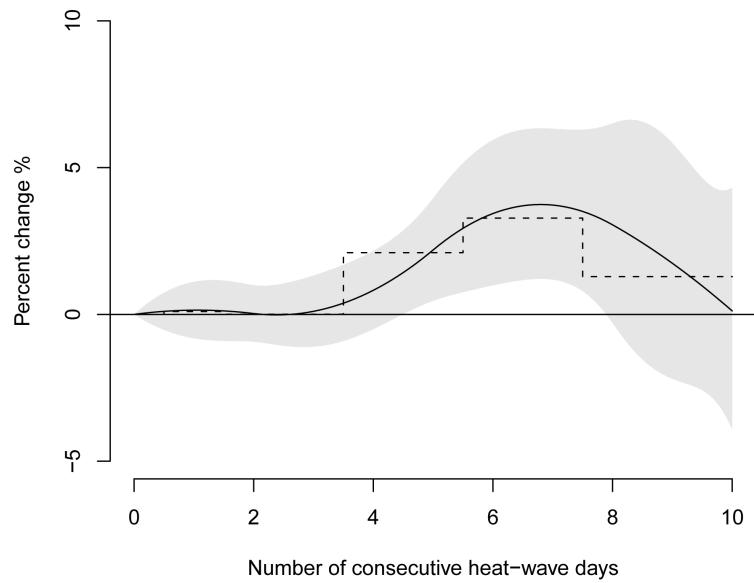


FIGURE. Average wave effect of consecutive heat wave days (above 97th percentile), as estimated by quadratic spline (continuous line) with 95% CI (grey area), and by a step function (dashed line)

TABLE 1
Pooled main and added effects with tests for heterogeneity (p-value) across cities under different heat wave definitions.

No. Days	Percentile	No. cities	Main effect			Added wave effect		
			% Increase (95% CI)	Test for heterogeneity	% Increase (95% CI)	Test for heterogeneity	Test for heterogeneity	
≥2	≥97th	108	4.9(3.3 to 6.5)	p≤0.001	0.3(-0.5 to 1.1)	p=0.536		
	≥98th	108	6.3(4.7 to 8.0)	p≤0.001	0.4(-0.5 to 1.4)	p=0.892		
	≥99th	108	8.0(5.7 to 10.4)	p≤0.001	0.2(-1.3 to 1.7)	p=0.005		
≥4	≥97th	108	5.4(3.9 to 6.9)	p≤0.001	0.7(-0.5 to 1.9)	p=0.186		
	≥98th	108	6.3(4.5 to 8.1)	p≤0.001	1.3(-0.3 to 2.9)	p=0.008		
	≥99th	105	7.7(5.4 to 10)	p≤0.001	2.8(0.4 to 5.3)	p=0.033		

^aThree communities do not show any days matching this heat wave definition and do not contribute to the estimates.

Table 2

Sensitivity analysis on the degrees of freedom (df) and spline type for seasonality and temperature-lag functions on the pooled added effect across cities, under 2 different heat wave definitions.

df for specific functions			≥ 2 days ≥ 97 th percentile	≥ 4 days ≥ 99 th percentile
Seasonality	Temperature	Lag	% Increase (95% CI)	% Increase (95% CI)
4	6	5	0.3(-0.5 to 1.1)	2.8(0.4 to 5.3)
2	6	5	0.3(-0.4 to 1.1)	2.8(0.4 to 5.2)
6	6	5	0.3(-0.4 to 1.1)	2.8(0.4 to 5.3)
4	4	5	-0.1(-0.9 to 0.7)	3.0(0.3 to 5.8)
4	7	5	0.1(-0.7 to 0.9)	2.5(0.1 to 5.0)
4	6	3	0.8(0.0 to 1.6)	3.0(0.2 to 5.8)
4	6	6	0.3(-0.5 to 1.1)	2.8(0.4 to 5.2)
4	2 ^a	5	1.0(0.3 to 1.8)	4.8(1.4 to 8.3)
4	6	1	3.6(2.8 to 4.4)	6.7(3.5 to 10.1)
4	2 ^a	1	3.7(2.8 to 4.5)	7.0(3.3 to 10.8)

^a A natural cubic spline is used here instead than a simple B-spline.