ABSTRACT

Background: We examine the effect of heat waves on mortality, over and above what would be predicted on the basis of temperature alone. **Methods:** Present modeling approaches~~,~~ may not fully capture extra effects relating to heat wave duration, possibly because the mechanisms of action and the population at risk are different under more extreme conditions. Modeling such extra effects can be achieved using the commonly left-out effect-modification between the lags of temperature in distributed lag models. The ~~estimation and~~ size of the additional heat effects ~~has been shown~~appears to be sensitive to the complexity (e.g. the degrees of freedom) allowed for in the overall temperature-mortality relationship. **Results:** ~~We find, u~~Using data from Stockholm, Sweden, and a variety of modeling approaches, that heat wave effects ~~persist over a high degree of model complexities with the additional effects being~~amount to a stable and statistically significant 8.1~~3~~-11.6% increase in excess deaths per heat wave day. The effects explicitly relating to heat wave duration (2.0~~1.9~~ –3.9% excess deaths per day) were more sensitive to model choice, and appeared to be smaller in more complex temperature-mortality relationships. ~~. We find that P~~Problems aro~~i~~se with over-fitting the overall temperature-mortality relationship, for example, when allowing for a very ~~many~~ large number of degrees of freedom. **Conclusions:** Modeling additional heat wave effects, e.g. between lag effect-modification, can give a better description of the effects from ~~high~~ extreme temperatures, particularly in the non-~~very~~ elderly population. We speculate that it ~~may be~~is biologically plausible to differentiate ~~and heat waves, and differentiation of~~ effects from heat and heat wave duration ~~may be biologically plausible~~.

Comment [AGB1]: Should this be in the methods section? It sounds like a result.

Comment [AGB2]: Should be in the methods section?

On the estimation of heat-intensity and heat-duration effects in time series models of temperature-related mortality in Stockholm, Sweden

Background

Heat stress can lead to fatal consequences due to: dehydration; increased cardiovascular stress; kidney dysfunction; and electrolyte disorders [1, 2]. At a population level, many studies show mortality tends to rise with higher temperatures [3]. Two approaches are generally used to quantify excess mortality: studies that focus exclusively on heat waves (so called episode studies); and studies that use time series ~~analyses~~ to estimate the effects of temperature on mortality by averaging over hot days and heat waves. Heat waves are commonly referred to as a period of extreme heat stress relative to the normal climate, although the exact definition varies according to the number of consecutive days of heat, temperature variable(s) and heat threshold. Many time series studies, assuming the association between temperature and mortality is non-linear, report associations between heat and mortality that are immediate or delayed by up to a week [4, 5]. However, the validity of this approach is challenged by research that reports an additional effect for heat waves [6]. Other studies have reported that ~~increasing~~ heat-related mortality is sensitive to the duration of heat waves regardless of the intensity of the ambient heat (e.g. in France during the 2003 heat wave [7]). A number of studies have since explored additional heat waves effects with respect to their timing, intensity and location [6, 8-13]. All studies found statistically significant additional risks that may relate to the duration of heat waves and the cumulative extreme heat exposure. The main differences between the studies were the models used to estimate ~~of~~ the heat-mortality relationship and the ~~study~~ location.

Comment [AGB3]: Duration too?

The ~~underlying~~ reason why the overall temperature-mortality relationship may not fully explain effects during heat waves is because the physiological effects of high temperatures and heat waves are different. For example, cumulative heat stress ~~over many days~~during a prolonged heat wave is more likely to cause dehydration. Cumulative heat stress is also more strongly related to cardiovascular deaths [8, 13]. Differences in age stratified relative risks to heat and to heat waves have shown that the population at risk may differ, with the middle aged population potentially at the highest risk during heat waves [8, 13].

We ~~aim to~~ explain why ~~the~~ additional heat wave effects are not perfectly captured in models of temperature-related mortality, and illustrate the estimation of additional heat wave effects using empirical data. We also ~~aim to~~ explore how the additional heat wave effect is ~~affected~~ dependent on~~by~~ the complexity of temperature-mortality model. Using prior studies and our own results, we argue that future studies should evaluate potential additional effects from heat waves by decomposing heat exposure into a temperature term and an added heat wave ~~effect~~ term. Increasing model complexity will not suffice if there is no differentiation between heat wave days and non-heat wave days.

Modelling weather-related mortality

Time series methods based on daily data have been developed and applied in studies of the short-term health effects of environmental factors like air pollution and weather [14, 15]. Models often include lagged effects of exposure and adjustment for potential mortality displacement [14, 16, 17]. Studies have also explored: the use of non-linear functions to adjust for confounding (e.g., season), allowing non-linear exposure-response relationships, and the use of model fitting criteria [17, 18].

Why additional heat wave effects?

Additional heat wave effects may appear as an artefact if models employ an overly simple exposure-response relationship that does not ~~satisfactorily~~ adequately capture ~~describe~~ the non-linear~~ity of~~ effect with higher temperatures. In this case the additional effect is related directly to the potential misspecification of the ~~non-linearity of the~~ effect. This is illustrated in Figure 1 where a linear relationship and a non-linear relationship are fitted to explain the relative risk (RR). Assuming that the ~~f~~actual relationship is non-linear, an additional heat wave effect~~s~~ would try to compensate the difference between these two curves. This type of misspecifications can be addressed by allowing a more flexible non-linear exposure response relationship.

Comment [AGB4]: But is wrongly assumed to be linear?

~~However, a~~Additional heat wave effects can~~are likely to~~ also arise due to cumulative heat stress. ~~, and also from changes in the population at risk (susceptible groups).~~ It is tempting to believe that cumulative stress can be estimated just like ~~any~~ other delayed effects of heat exposure effects, e.g. by distributed lag models. This is not the case. Distributed lag models allow temperature a few days or weeks prior to day *t* to affect mortality on day *t*, and ~~are in that sense~~so are perfectly able to capture delayed effects of temperature. However, distributed lag models assume the delayed effects are related to the temperature on day *t* only. This means that delayed lag effects are independent of other lag days, for example, days *t-1* and *t-2*. They cannot model health effects caused by the temperature being above a heat threshold for a number of consecutive days. Thus, the distributed lag effect at a certain day of the heat wave does not estimate the effects relating to persistent heat stress. In order to estimate the effects relating to several days consecutive heat exposure above a certain threshold one would need to include non-linear interactions (effect-modifications) between the temperature lag effects. Here the non-linearity relates to the fact that the additional heat wave effects are thought to~~s~~ appear above some extreme temperature threshold. Thus, short-term cumulative stress of extreme heat can be described by lag effect-modification~~interactions~~.

For illustration we consider the simple case where the effects of temperature are assumed to be ~~linear~~dichotomous according to a threshold of the 98th percentile of the temperature distribution. ~~.~~

$$T_t = \begin{cases} 1 & if\ temperature\ at\ time\ t > 98th\ percentile \\ 0 & else \end{cases}$$

~~This type of variable assumes a non-linear exposure-response.~~ T~~he~~he effect of extreme temperature (T) on mortality up to lag 3 is then in a non-constrained distributed lag model be~~can be~~ estimated~~described~~ in a ~~by a~~ regression model:

$$mortality_t \sim Poisson(mean_t)$$

$$log(mean_t) = intercept + T\cancel{temperature}_t + T\cancel{temperature}_{t-1} + T\cancel{temperature}_{t-2} + confounders_t. \qquad (a)$$

T~~Now~~ his~~e~~ model ~~above~~ assumes that the effect of extreme temperature on day t is independent of whether the temperatures on day $t-1$ and $t-2$ are also extreme. This ~~may, however,~~would not ~~always~~ be the case if there are additional effects from persistent periods of extreme heat ~~that are related to the length of the extreme heat period~~. Then, ~~if we believe that~~ mortality on day t is also conditional on the temperatures on day $t-1$ and $t-2$. To capture ~~then~~ this in a regression model we can add ~~can be described through~~ two- and three-way interactions of the lag terms~~as~~. In the model below we assume there are additional conditional relationships only between lags that are consecutive in time (e.g. an extended period without relief from the extreme temperatures),~~:~~

$$log(mean_t) = intercept + T\cancel{temperature}_t + T\cancel{temperature}_{t-1} + T\cancel{temperature}_{t-2} + T\cancel{temperature}_t \times T\cancel{temperature}_{t-1} \cancel{+ temperature_t \times temperature_{t-2}} + \cancel{+ temperature_{t-1} \times temperature_{t-2} +} T\cancel{temperature}_t \times T\cancel{temperature}_{t-1} \times T\cancel{temperature}_{t-2} + confounders_t \qquad (b)$$

When the number of lags studied is large (or if heat waves are long) this type of model ~~can~~will require a large number of interaction terms to be estimated, ~~and~~ resulting in

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collinearity (similarly to~~as~~ the ~~non-~~unconstrained distributed lag model). To avoid this we can add all the interaction terms together to create one variable denoting extended heat wave periods. ~~Such a~~This binary indicator variable is set to 1 if at least two or more proceeding days ~~are~~ exceed~~ing~~ the extreme temperature threshold, and 0 ~~else~~otherwise. We refer to this variable as a heat wave indicator variable (HWI). Note that our HWI is equal to $T_t \times T_{t-1}$, but ~~that~~ it also includes days where $T_t \times T_{t-1} \times T_{t-2}$ =1. Thus, the HWI variable describes the two-way interaction that was previously described in model (b). A new model including this variable can be expressed as,

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$$\log(mean_t) = intercept + T_t + T_{t-1} + T_{t-2} + HWI_t + confounders_t \qquad (c)$$

The model (c) with the HWI will not differentiate between two and three way interactions (e.g. two and three days of heat wave), ~~but~~as it assumes the additional effect is the same independent of the length of the heat wave. We might, however, have reason to suspect that longer heat waves are associated with larger additional effects ~~than shorter heat waves are~~. In this case we can construct a new variable with distinct values for shorter and longer heat waves. ~~Such a variable could constitute the number of consecutive heat wave days over the lags studied.~~ We refer to ~~such a~~ this variable as a heat wave duration variable (HWD). In the case where we use only 3 lag days we ~~can~~ define HWD as to equal $T_t \times T_{t-1} + T_t \times T_{t-1} \times T_{t-2}$. In this example the HWD variable takes the values 0, 1, and 2 ~~as~~ depending on how many consecutive days of extreme temperatures there are in before day t. The effect ~~associated with different~~of heat wave durations can be ~~constrained and~~ estimated as a linear or non-linear function, or as a factor variable directly yielding the interactions. A non-linear function would be sensible if, for example the effect of duration, increased quickly and then remained high. Assuming linearity ~~of the duration effect~~ we get the regression model:

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Comment [AGB5]: A crappy sentence, but I thought it might be worth explaining.

$$\log(mean_t) = intercept + T_t + T_{t-1} + T_{t-2} + HWD_t + confounders_t \qquad (d)$$

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The model (d) ~~does~~ estimates the effects of the duration of heat waves as a linear function avoiding potential collinearity induced by explicitly including many lag interaction variables. The models above~~ve~~ assume a dichotomous exposure-response relationship~~linearity~~ for ~~temperature which~~temperature, and that effects of temperature and heat waves are not extended over more than 3 lag days. However, the same principle can be used when fitting a distributed lag model ~~as well as non-linear exposure-response relationship is often not the case, and the inclusions of several lags that are highly correlated suggest the use of a distributed lag model is preferred. However, the lag interactions shown above are not incorporated in distributed lag models, and need to be additionally modeled if there are combined effects. The parameterization above would need a large number of parameters to be estimated (particularly of more lags days are incorporated). Complexity might be reduced by using dummy variables corresponding to all these interactions above a certain temperature threshold, but this assumes the effect-modification over different lags is the same and does not depend on the length of the heat wave. Alternatively, creating a variable denoting the consecutive days with extreme temperatures (a duration variable), would allow longer heat waves to have larger effects compared to shorter heat waves. Modeling the duration variable as a linear term or using a non-linear spline can be viewed as a similar approach to using the interactions, or as using effect-modifications by lag day, with the advantage that this approach reduces the complexity and potentially collinearity of the model compared with using multiple interaction terms.~~

~~We note that recent studies on this topic have all concluded that there were additional heat wave effects and these were not described by the distributed lags of temperature [6, 8, 9, 11-13]. using continuous variables~~ and a larger number of lag days.

Model choice and additional heat wave effects

While~~ the~~ recent studies found significant additional effects from heat waves, particularly in ~~less~~ cold~~er~~ climates ~~regimes~~~~areas less adapted to heat~~ (such as the northern parts of the US and Sweden [9, 19]), the size of this effect has been estimated using~~ widely~~ different approaches~~methods~~ [9, 10, 12, 13]. The main differences were: i) the complexity of the model used for the exposure-response relationship between temperature and mortality; ii) allowing for spatial heterogeneity in the additional heat wave effect; iii) allowing for heterogeneity in the additional heat wave effects between population sub-groups.

The study presenting~~with~~ the smallest additional effect from heat waves found the size of the effects to be almost negligible when the exposure-response relationship was allowed a very flexible parameterization using two dimensional cubic spline functions for temperature and lag day and modeling the main effect in a first stage model and the effect-modification in a second stage [12]. However, the estimates were for all-cause mortality independent of geographical differences in U.S. cities, while there is evidence that heat wave effects may be very sensitive to age, cause of death and location [8, 9, 13, 19]. In particular, additional heat wave effects were negligible in the southern US, and large in the north east of the US [1, 9, 19].

Two studies~~Gasparrini et al.~~ estimated the overall temperature-mortality relationship using non-linear distributed lags and two-dimensional spline functions, and then tested the sensitivity of this parameterization [10, 20]. Other studies used less complex linear and/or non-linear exposure response relationships, with a small number of lag days of between 1 and 3 [6, 8, 9, 13, 21]. The lag days in these studies w~~h~~ere chosen according to prior literature and ~~through using~~ model fit criteria.

Bobb et al. argued against fitting one model across a range of climates (using the same degrees of freedom, splines and temperature measures), as they found that in most cities there were two or more models with a similar fit to the data [19]. Interestingly, after averaging over many different models they found larger effects of temperatures on heat wave days compared to non-heat wave days [19].

Estimation of additional heat wave effects in Stockholm, Sweden

Methods

We applied a non-linear distributed lag model to the effects of temperature in Stockholm County, Sweden, on total mortality during the years 1990–2002. Table 1 describes the basic characteristics of the data ~~used in the study~~. ~~A more detailed description of the data is given in Rocklöv et al {Rocklov, 2011 #2045}.~~ We used daily maximum temperature as the predictor of daily mortality, adjusting for long-term time trends, seasonality, days of the week and national holidays in a non-linear distributed lag framework. This is model (1).

To estimate ~~capture~~additional heat wave effects (e.g. ~~an~~ lag effect-modifications)~~added heat wave effect related to duration,~~ we incorporated the variables HWI and HWD~~a~~ as ~~were~~ described in a previous section~~variable that sequentially increased with heat wave duration~~. The frequencies of the HWD and HWI variables are ~~described~~ in Table 2. ~~For example, days with no heat wave are set to zero and days with heat waves are numbered according to the consecutive day of extreme heat.~~ Heat waves were defined as at least two days with maximum daily temperature above the 98th percentile. So, on the second day with a temperature over the threshold, the variable was 1, and on the 7th consecutive day the variable was 6. The first day of temperature above the threshold was set to 0 corresponding to no accumulated heat effects ~~of heat~~. We first fitted the effect of heat wave duration as a smooth function (penalized spline with 4 degrees of freedom) ~~firstly~~, but as it showed an approximately linear association we fitted ~~it~~ a linear term. The model with the ~~additional~~ parameter for duration of heat waves, HWD, is model (2). The duration term estimates the effect-modification of cumulative lag terms above the 98th percentile indirectly, with the prior assumption that the length of the heat wave period can influence the mortality response.

In model (3) we estimated the additional effects from heat waves (maximum temperature above 98th percentile for at least two days) using an indicator variable, HWI. This model does not estimate additional effects due to heat wave duration explicitly, but the average additional excess mortality during the heat wave periods. The heat wave indicator estimates the effect modification of lag terms above the 98th percentile assuming all days above this threshold are equally contributing to the mortality response.

As equations the three models are:

$$Mortality_t \sim Poisson(\mu_t)$$

$$log(\mu_t) = intercept + S(temperature_t, lag.df, var.df) + S(time_t, var.df{=}6\ per\ year) + DOW_t + HD_t \quad (1)$$

$$log(\mu_t) = intercept + S(temperature_t, lag.df, var.df) + S(time_t, var.df{=}6\ per\ year) + DOW_t + HD_t + HWD\cancel{\ duration}_t \quad (2)\ \cancel{(2)}$$

$$log(\mu_t) = intercept + S(temperature_t, lag.df, var.df) + S(time_t, var.df{=}6\ per\ year) + DOW_t + HD_t + HWI\cancel{\ indicator}_t \quad (3)$$

Here *t* is the time in days, *S* is a cubic spline function, the spline function of temperature is two dimensional with lag degree of freedom given by *lag.df* and variable degree of freedom given by *var.df*. HWD~~ duration~~ is a linear variable denoting the day of the heat waves, HWI~~ indicator~~ is an indicator variable for heat waves. $time_t$ estimates~~models~~ trends and seasonal changes using a spline with 6 degrees of freedom per year (78 degrees of freedom in total), *DOW* denotes the day of week, and *HD* denotes national holidays.

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We used the "dnlm" package in R [22]. We tested degrees of freedom for temperature from 3 to 8. The lagged effects of temperature were examined over 20 days and allowed 2, 4 or 6 degrees of freedom. The Akaike Information Criterion (AIC) was used to judge the optimal degrees of freedom.

We first calculated the AIC from models based on all ages and then repeated the same calculations in ages 80 years and above, and 45~~-~~–79 years of age.

Comment [AGB6]: This isn't really about the AIC, is it? I thought it was about testing for differences by age.

We calculated the variation inflation factor as VIF = 1/(1–R-squared) to assess if the variance estimation was inflated through multi-collinearity introduced by having both temperature and heat wave terms in the same model. The variation inflation factor (VIF) of the duration variable and temperature was estimated to 1.048, and for the heat wave indicator variable to 1.058. ~~This indicated~~So collinearity was not a concern for model~~s~~ 2 ~~and~~ or 3.

Results

The AIC values associated with each model for mortality in all ages are ~~shown~~ in Table 4~~1~~. Overall the models including additional heat wave variables (model 2 and 3) gave a better fit to the data compared with model 1 for the same degrees of freedom. The two best fits are a simple parameterization using an indicator variable or a heat wave duration variable with *3 df* for temperature and *2 df* for the lagged effects as main effect. These models resulted in a small marginal heat effect on non-heat wave days (Figure 2), while more flexible parameterizations for the main temperature effect estimated a larger effect (Figures 2 and 3). However, with increasing complexity of the main temperature-mortality relationship the model fit decreased and the bendiness of the estimated two dimensional spline functions increased considerably as can be seen in Table 53~~1~~ and Figures 2–4. Figures 2–4 also show that models including ~~an~~ additional heat wave effects predict a lower mortality increase for high temperatures at short lags compared with the model with no heat wave variable. The effect of heat on lag 0 is then higher in the model without an additional heat wave effect. This shows that the model without an additional heat wave effect would estimate higher marginal excess mortality on days with high temperatures that were not part of the heat wave compared to the model with the additional heat wave effect. It appears that models with an explicit allowance for additional heat wave effects do a better job of describing the temporal distribution of heat-related deaths.

~~When studying~~In the age group 80 years and above the inclusion of additional heat wave variables did~~o~~ not substantially improve the model fit ~~when comparing over the different degrees of freedoms as is described in~~ (Table 4). In the age group 45~~–~~–79 years~~ of age~~, however, the inclusion of an additional heat wave variable ~~in the model~~ substantially improve~~s~~d the model fit according to the AIC (Table 5), while it is not possible to distinguish between the model including the HWD (model 2) and HWI (model 3) in terms of model fit.

~~Thus, the models are shifting part of the marginal heat wave effect to non-heat wave days, as illustrated in~~ F~~f~~igures 5 and 6 ~~for~~ show the effects of a 5 unit increase in maximum daily temperature from 26 °C to 31°C (the heat wave threshold is 27.5 °C). Figure 5 shows the excess mortality predictions for day 4 of a heat wave (including the 0–3 day lagged effects) ~~for a range of different~~while varying the degrees of freedom of the main temperature-mortality relationship, and ~~for~~ showing the results for ~~the~~ three different models. ~~The~~ In broad terms, the heat wave predictions ~~from the different models~~ are similar with more complex model fits, ~~while~~ but models 2 and 3 (which include terms for heat wave effects) predict higher excess mortality for the less complex temperature-mortality parameterizations. ~~Even~~ However, even for complex parameterizations, the model without an additional heat wave ~~variables~~effect ~~no added heat wave~~ predicts a few percent lower excess mortality compared to the two heat wave models.

Comment [AGB7]: What are you using a substantial improvement? 10 or more? There don't seem to be that many that are 10 or more.

Figure 6 shows the corresponding marginal excess mortality predictions for a single hot day (non-heat wave day; lag 0 only). The model without the added heat wave effect (model 1) predicts higher mortality on non-heat wave days compared to the models that differentiate between heat wave and non-heat wave days (model 2 and 3). Thus, model 1 (without the additional heat wave effect) may over-estimate the effect of heat on non-heat wave days, while it appears to under-estimate the effect from heat on heat wave days. Models 2 or 3 do better in this sense, differentiating the effects between heat wave days and non-heat wave days through the variables capturing the effect modification between the lags of temperature. The more complex parameterizations of model 2 and 3 strongly indicate over-fitting in graphical examinations, whilst having better AIC values. ~~However, in order to be physiologically plausible, a simpler model fit is to be preferred for this data.~~

~~The estimates and confidence intervals of the added effects relating to heat wave duration and the heat wave indicator variables are in Table 2. Using the best model identified by the AIC (Table 1), there was an additional heat wave effect with a relative risk of 1.037 (95% confidence interval of 1.014, 1.060). Thus on the fifth day of a heat wave the relative risk from the overall temperature-mortality association would be multiplied by 1.156 (1.037^4). The heat wave duration effects estimates ranged between 1.039 and 1.019, and became smaller and non-statistically significant with more complex model fits.~~

The optimal fit of model 3 estimated a relative risk of 1.112 (95% confidence interval of 1.050, 1.176) associated with heat wave days (95% confidence interval of 1.050, 1.176). The effects ranged between 1.116 and 1.083, and all estimates were statistically significant at the 5% level.

We did not assess the estimates' sensitivity to the parameterization (*df*) of long-term time trends, as this appears to have~~has~~ less influence on the heat wave effect [12, 19].

Comment [AW8]: This comment on over-fitting seems to be awkwardly placed. Should it be included in the following paragraph?

Discussion

Estimates of additional heat wave effects in models of temperature-related mortality can be interpreted as a constrained form of non-linear effect-modifications between lags of high temperature (~~,~~ or, similarly lag interactions). This can explain why such effects have been found to significantly contribute to additional deaths during heat waves in previous studies of temperature related mortality, over and above the effects of temperature overall. ~~Our results may dispel~~This dispels the widespread belief that such effects are incorporated through distributed lag models. From a mechanistic perspective including additional effects from heat waves are supported through the physiological stress incurred by cumulative exposure being potentially different from the stress from shorter periods of extreme heat, and can also result in differences in the population at risk such as contrasting susceptibility with age [8-10, 13, 19]

We found the additional heat wave effects ~~a~~were more important in middle age populations and the elderly compared to the very elderly~~ in the study location~~. We found the size of the heat wave effect depended on the complexity of the main temperature-mortality parameterization, more specifically on the *df* used for modeling non-linearity of temperature and lagged effects. This indicates that there is, not surprisingly, some overlap between the effects of hot days and the effects of heat waves. Our results show, however, that there is also likely to be an independent extra effect of heat waves that is not captured by hot days, e.g. an effect modification. Differences in the temperature-mortality parameterization probably explain many of the differences between the conclusions of recent studies on the effects of heat waves [6, 8, 9, 11-13, 19, 21] In our example we found that a simple model for the temperature-mortality association was better than a complex model. The additional heat wave effects are substantial and important to account for in order not to underestimate mortality risks during heat wave days. We conclude that it is important not to over fit the data by using too complex non-linear lag parameterizations, and that simple parameters for the additional effects of heat waves are useful. However, the more complex parameterizations appear to better capture effects and the high end. However, it appear it is not reasonable to distribute the degrees of freedom uniformly over the temperature and lag scales as such assumption gave rise to over-fitting in regions of the temperature and lag scale where the relationship is not very complex. Overall, m~~M~~odel fit improved as the complexity of the model and flexibility of the splines were reduced. These simpler models also had larger additional heat wave effects, as reported elsewhere [6, 8, 9, 11-13, 19, 21].

Some studies have used two-stage model to describe the effects from temperature using distributed lag non-linear models in the first stage and the additional effect associated with heat waves in a second step [10, 12]. We note, however, this deviates from the conventional framework for modeling of effect-modifications, and that it can potentially affect the estimates of additional heat wave effects downward.

We achieved a better model fit using an indicator variable for heat waves rather than the duration variable when studying all ages; nevertheless, models with the duration variable performed better than the models without additional heat wave components, and similarly well in the age group 45-79 years of age.

Conclusions

We conclude that it is important to continue to explore the magnitude of additional heat wave effects in future studies of temperature-related mortality, e.g. temperature lag effect-modifications. ~~and t~~It appear also important to~~o~~ fit models that are location sensitive in the parameterization (choice of *df*), as well as in the evaluation of potential additional heat wave effects. Fitting a complex distributed lag non-linear model may reduce the heat wave signal and over-estimate mortality on non-heat wave days, compared to a model including a heat wave term. It is important to be able to differentiate between extended periods of heat and single days of extremely high temperatures, since several rec~~s~~ent studies have shown that duration of heat exposure is related to mortality risk. Increasing the accuracy of heat-wave mortality models will assist public health authorities to direct preventive actions when and where they are most needed. Future studies should continue to study and identify potential differences in the population at risk to heat and heat waves, as well as describe the mechanistic differences.

Authors' contributions

JR designed the study, analysed the data, interpreted the results and drafted the manuscript. AB helped design the study, advised in the analysis of data, interpreted the results and helped draft the paper. AW interpreted the results, advised in the analysis and helped draft the paper.

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References

1. Kilbourne EM: **The spectrum of illness during heat waves**. *Am J Prev Med* 1999, **16**(4):359-360.
2. Parsons K: **Human Thermal Environments. The effects of hot, moderate and cold temperatures on human health, comfort and performance, 2nd ed**. *New York: CRC Press; 2003* 2003.
3. Kovats RS, Hajat S: **Heat stress and public health: a critical review**. *Annu Rev Public Health* 2008, **29**:41-55.
4. Baccini M, Biggeri A, Accetta G, Kosatsky T, Katsouyanni K, Analitis A, Anderson HR, Bisanti L, D'Ippoliti D, Danova J *et al*: **Heat effects on mortality in 15 European cities**. *Epidemiology* 2008, **19**(5):711-719.
5. Braga AL, Zanobetti A, Schwartz J: **The time course of weather-related deaths**. *Epidemiology* 2001, **12**(6):662-667.
6. 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):632-638.

7. Fouillet A, Rey G, Laurent F, Pavillon G, Bellec S, Guihenneuc-Jouyaux C, Clavel J, Jougla E, Hemon D: **Excess mortality related to the August 2003 heat wave in France**. *Int Arch Occup Environ Health* 2006, **80**(1):16-24.
8. 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.
9. Anderson GB, Bell ML: **Heat waves in the United States: mortality risk during heat waves and effect modification by heat wave characteristics in 43 U.S. communities**. *Environ Health Perspect* 2011, **119**(2):210-218.
10. Barnett AG, Hajat S, Gasparrini A, Rocklov J: **Cold and heat waves in the United States**. *Environ Res* 2012, **112**:218-224.
11. D'Ippoliti D, Michelozzi P, Marino C, de'Donato F, Menne B, Katsouyanni K, Kirchmayer U, Analitis A, Medina-Ramon M, Paldy A *et al*: **The impact of heat waves on mortality in 9 European cities: results from the EuroHEAT project**. *Environ Health* 2010, **9**:37.
12. Gasparrini A, Armstrong B: **The impact of heat waves on mortality**. *Epidemiology* 2011, **22**(1):68-73.
13. Rocklov J, Ebi K, Forsberg B: **Mortality related to temperature and persistent extreme temperatures: a study of cause-specific and age-stratified mortality**. *Occup Environ Med* 2011, **68**(7):531-536.
14. Dominici F: **Time-series analysis of air pollution and mortality: a statistical review**. *Res Rep Health Eff Inst* 2004(123):3-27; discussion 29-33.
15. Zeger SL: **A Regression-Model for Time-Series of Counts**. *Biometrika* 1988, **75**(4):621-629.
16. Schwartz J: **The distributed lag between air pollution and daily deaths**. *Epidemiology* 2000, **11**(3):320-326.
17. Zanobetti A, Wand MP, Schwartz J, Ryan LM: **Generalized additive distributed lag models: quantifying mortality displacement**. *Biostatistics* 2000, **1**(3):279-292.
18. Peng RD, Dominici F. , Louis T. A.: **Model choice in time series studies of air pollution and mortality**. *J R Statist Soc A* 2006, **169**:25.
19. Bobb JF, Dominici F, Peng RD: **A Bayesian model averaging approach for estimating the relative risk of mortality associated with heat waves in 105 U.S. cities**. *Biometrics* 2011, **67**(4):1605-1616.
20. Sattar A, Rubessa M, Di Francesco S, Longobardi V, Di Palo R, Zicarelli L, Campanile G, Gasparrini B: **The influence of gamete co-incubation length on the in vitro fertility and sex ratio of bovine bulls with different penetration speed**. *Reprod Domest Anim* 2011, **46**(6):1090-1097.
21. Rocklov J, Forsberg B: **The effect of temperature on mortality in Stockholm 1998--2003: a study of lag structures and heatwave effects**. *Scand J Public Health* 2008, **36**(5):516-523.
22. Gasparrini A: **Distributed Lag Linear and Non-Linear Models in R: The Package dlnm**. *Journal of statistical software* 2011, **43**(8):1-20.

Tables

Table 1. Descriptive statistics for daily deaths and environmental variables in Stockholm County, 1990–~~-~~2002, per season. Mean ± standard deviation (~~proportion~~ percent missing)

Daily deaths, all non-injury causes, all ages	40 ± 7.2
Ages 45~~-~~–79	18 ± 4.6

Ages 80+	20 ± 5.3
Mean temperature (˚C)	7.5 ± 7.6 (7 %)
range	–15.7, 26.4
Maximum temperature (˚C)	10.5 ± 8.6 (7 %)
range	–13.4, 33.5
Maximum temperature 98th percentile (˚C)	27.5 °C

Table 2. Values and frequencies taken by the heat wave duration and the heat wave indicator variable

Variable	Heat wave duration (HWD)								Heat wave indicator (HWI)	
Value	0	1	2	3	4	5	6	7	0	1
Frequency	4697	23	11	7	4	3	2	1	4697	51

Table 3. AIC values for the three models using 3 to 8 degrees of freedom for temperature and 2 to 6 degrees of freedom for lag, Stockholm, 1990–2002 in all ages

df Temperature Spline	No heat wave variable (model 1)	With heat wave duration variable (model 2)	With heat wave indicator variable (model 3)
	df Lag Spline= 2		

3	20052	20044	20040
4	20056	20047	20044
5	20059	20051	20048
6	20058	20051	20047
7	20062	20055	20052
8	20063	20057	20054
	df Lag Spline= 4		
3	20054	20049	20047
4	20055	20052	20051
5	20060	20059	20057
6	20061	20061	20059
7	20061	20061	20059
8	20067	20068	20065
	df Lag Spline = 6		
3	20061	20056	20053
4	20065	20063	20061
5	20075	20073	20071
6	20077	20077	20075
7	20082	20081	20079
8	20089	20089	20086

Table 4. AIC values for the three models using 3 to 8 degrees of freedom for temperature and 2 to 6 degrees of freedom for lag, Stockholm, 1990–2002 in ages 80 years of age and above			
df Temperature Spline	No heat wave variable (model 1)	With heat wave duration variable (model 2)	With heat wave indicator variable (model 3)

	df Lag Spline= 2		
3	17962	17961	17957
4	17966	17965	17961
5	17970	17969	17965
6	17971	17970	17966
7	17974	17972	17968
8	17977	17975	17971
	df Lag Spline= 4		
3	17958	17960	17958
4	17959	17961	17961
5	17967	17969	17968
6	17971	17973	17972
7	17977	17979	17977
8	17982	17984	17983
	df Lag Spline = 6		
3	17958	17959	17957
4	17961	17963	17963
5	17972	17974	17974
6	17980	17981	17981
7	17989	17991	17990
8	17997	17999	17998

Table 5. AIC values for the three models using 3 to 8 degrees of freedom for

temperature and 2 to 6 degrees of freedom for lag, Stockholm, 1990–2002 in ages 45 to 79 years of age			
df Temperature Spline	No heat wave variable (model 1)	With heat wave duration variable (model 2)	With heat wave indicator variable (model 3)
	df Lag Spline= 2		
3	17410	17405	17406
4	17415	17409	17410
5	17416	17412	17412
6	17416	17412	17413
7	17417	17415	17415
8	17419	17417	17417
	df Lag Spline= 4		
3	17418	17413	17413
4	17423	17418	17419
5	17428	17424	17425
6	17430	17428	17428
7	17426	17426	17426
8	17434	17434	17434
	df Lag Spline = 6		
3	17426	17421	17421
4	17435	17430	17430
5	17443	17440	17440
6	17448	17447	17446
7	17448	17448	17447
8	17456	17457	17456

Table 6. Relative risks (RRs) and confidence intervals (CI; 95%) associated with heat waves				
	Heat wave duration variable (model 2; unit: days of duration)		*Heat wave indicator variable (model 3; unit: heat wave= {yes, no})*	
df Tempera-ture Spline	*df* Lag Spline= 2			
	RR	CI	RR	CI
3	1.037	1.014, 1.060	1.112	1.050, 1.176
4	1.039	1.015, 1.063	1.116	1.053, 1.183
5	1.038	1.013, 1.062	1.114	1.050, 1.182
6	1.038	1.013, 1.063	1.114	1.049, 1.182
7	1.038	1.013, 1.063	1.114	1.048, 1.183
8	1.037	1.011, 1.062	1.111	1.045, 1.180
	df lag spline= 4			
3	1.032	1.008, 1.056	1.100	1.034, 1.169
4	1.028	1.002, 1.054	1.088	1.018, 1.162
5	1.026	0.998, 1.053	1.086	1.011, 1.165
6	1.023	0.994, 1.051	1.081	1.003, 1.165
7	1.022	0.992, 1.051	1.087	1.005, 1.174
8	1.020	0.990, 1.051	1.088	1.004, 1.179
	df lag spline= 6			
3	1.032	1.008, 1.056	1.102	1.037, 1.172
4	1.028	1.002, 1.054	1.090	1.020, 1.165
5	1.025	0.998, 1.053	1.088	1.013, 1.168
6	1.023	0.994, 1.052	1.083	1.005, 1.167
7	1.022	0.993, 1.052	1.088	1.006, 1.176
8	1.019	0.989, 1.050	1.088	1.003, 1.179

Figure legends

Figure 1. The fit of a linear (black) and a non-linear (grey) curve to data.

Figure 2. The distributed non-linear lag surface relating to a daily max temperature of 12 °C. The models to the left have no heat wave variables (1), the models in the middle include a heat wave duration variable (2), and the models to the right include a heat wave indicator variable (3). The figure shows parameterizations using 2 *df* for the lags and 3, 6, and 8 *df* for the variable in the rows starting from the top respectively.

Figure 3. The distributed non-linear lag surface relating to a daily max temperature of 12 °C. The models to the left are without additional heat wave variables (1), the models in the middle are include a heat wave duration variable (2), and the models to the right include a heat wave indicator variable (3). The figure shows parameterizations using 4 *df* for the lags and 3, 6, and 8 *df* for the variable in the rows starting from the top respectively.

Figure 4. The distributed non-linear lag surface relating to a daily max temperature of 12 °C. The models to the left are without additional heat wave variables (1), the models in the middle are include a heat wave duration variable (2), and the models to the right include a heat wave indicator variable (3). The figure shows parameterizations using 6 *df* for the lags and 3, 6, and 8 *df* for the variable in the rows starting from the top respectively.

Figure 5. The excess mortality predictions for day 4 of a heat wave with maximum daily temperatures at 31 °C as compared to 26 °C. The predictions include the 0–3 lagged effects over a range of different degrees of freedom of the main temperature-mortality relationship and: i) from a model with no added heat wave effect (model 1); ii) from a model with a heat wave duration parameter (model 2); iii) and from a model with the added heat wave effect as a dummy variable (model 3).

Figure 6. The excess mortality predictions for a single hot day (non-heat wave day) for maximum daily temperatures at 31°C as compared to 26°C. The predictions include only the lag 0 effect over a range of different degrees of freedom of the main temperature-mortality relationship and: i) from a model with no added heat wave effect (model 1); ii) from a model with a heat wave duration parameter (model 2); iii) and from a model with the added heat wave effect as a dummy variable (model 3).