Distributed Lag Non-Linear Models for the impact of heat waves on elderly people living in the regions of central-eastern Italy

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SUMMARY

Background: Prolonged periods of extreme heat, usually referred to as heat waves, have a significant impact on health, especially in the most vulnerable populations. In the present study, we investigated the effect of heat waves on mortality in the elderly population living in the regions of central-eastern Italy.
Methods: We considered 10 cities located between the Marche and Abruzzo regions during the period 2011–2021. The association between heat waves and mortality risk was analysed for each city using non-linear distributed lagged temperature and humidity functions, a method that accounts for non-linear lagged effects, including the harvest effect, a phenomenon where mortality decreases temporarily after an initial peak due to early deaths of vulnerable individuals. We then performed a multivariate meta-analysis on all cities to jointly synthesise multiple results on mortality risk during heat waves, taking into account their correlation.
Results: In the first days after the heat wave, the relative risk (RR) tends to increase, then decreases with a lag of about 4 days and then stabilises around the reference value (RR = 1), with a slight increase around day 21–22.
Conclusion: The study shows a significant increase in risk in the presence or after the occurrence of a heat wave. The heterogeneous behaviour of some cities could be due to other factors (e.g. pollution) that need to be investigated. The aggregate analysis allows a more robust estimate of the overall effect, reducing the uncertainty arising from individual local analyses.

Keywords: Distributed Lag Nonlinear Models, Multivariate Meta-Analysis, Heat Waves, Multivariate Time Series

INTRODUCTION

It is important to analyse the health impact of extreme heat and heat waves, especially on the elderly population, as their frequency and intensity are expected to increase under projected climate change scenarios.

Many epidemiological studies have documented that prolonged periods of extreme heat, i.e. the heat waves, are associated with a significant increase in mortality.

Sometimes the effects of prolonged exposure to extreme temperatures are not limited to the period in which they are observed but are delayed in time.

The short-term effects of exposure to high levels of extreme temperatures affect health within a few days of the event. This is known as the “harvesting effect”: heat waves hit the most vulnerable people after a short period of time. After the initial effect, the number of cases decreases a few days later.

In [1] the authors analyzed the mortality risk during heat waves in several USA cities through generalized linear models, combining individual estimates of the effect of heat waves with hierarchical Bayesian models.

Gasparrini et at. introduced the Distributed Lag Non-Linear Models (DLNM) to describe the complex relationship between extreme heat and heat waves and mortality [2–5].

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DLNM models describe the exposure-response relationship to extreme heat or an intense pollution event through a sequence of possible future scenarios. The associated risk was estimated using a non-linear distributed lag temperature function, which accounts for non-linear lag effects and term harvesting.

In [6], the authors used time-series regression analysis to estimate site-specific temperature-mortality associations and then performed a meta-analysis of multiple geographical locations.

Alicandro et al. in [7] analysed the excess of mortality due the Omicron variant in Italy during April-July 2022, in particular at working age, by using over-dispersed Poisson regression models.

In this study, we considered 10 cities located between Marche and Abruzzo in the period 2011–2021, using distributed nonlinear lag functions of temperature and humidity, which take into account nonlinear lag effects. We first analysed the impact of extreme temperatures on health, considering each day as independent. In particular, we took as reference temperatures the 95th and 99.9th percentiles of annual temperatures, which vary depending on the city considered, and studied the risk trend in the days immediately following the occurrence of the extreme temperature. We then estimated the effect of several consecutive days of extreme heat (heat wave) on mortality among the elderly, depending on its duration and time lag. In the presence of heat waves, the risk increases in intensity and duration compared to the previous case where the temperature was set regardless of whether extreme temperatures could continue in the following days. There are similarities and differences in how different cities respond to heat waves. After analysing each city using the DLNM technique, we performed a multivariate meta-analysis across all cities to summarise the multiple findings on mortality risk during heat waves, taking into account their correlation.

DATA AND METHODS

Data

As case studies, we considered 10 cities located between the Marche and Abruzzo regions: Alba Adriatica, Ancona, Pescara, San Benedetto del Tronto, Giulianova, Martinsicuro, Pineto, Roseto, Silvi, Tortoreto, in the period 2011–2021. The series of daily all-cause mortality data consist of the number of deaths among the inhabitants of each town and were extracted from ISTAT.

For the weather data, we obtained hourly measurements of temperature, humidity and other variables from worldweather.wmo.int. This data is divided into 4 groups, each of which includes some nearby cities. The first group includes Ancona, the second San Benedetto del Tronto and Martinsicuro, the third Alba Adriatica, Tortoreto, Giulianova and Roseto, the fourth Pineto, Silvi and Pescara. The maximum temperature is calculated as the highest hourly value recorded for each day, while the average temperature and humidity are calculated as the average of the hourly values recorded for each day.

Statistical analysis

The same common DLNM model was applied to each community and the studies were then aggregated using meta-analysis.

DLNM models were implemented, which allow us to describe in detail both the non-linear nature of the association between temperature and mortality, and the lag with which the effects manifest themselves.

We consider the following formula:

$$log\left(E\left(Y_t\right)\right) = \alpha + \sum_{j=1}^{v_x} \sum_{k=1}^{v_l} r^T\left(t\right)_{j.}\, c_{.k} \beta_{jk} \qquad (1)$$

where the process Y_t measures the number of deaths, assumed to follow an overdispersed Poisson distribution for each day $t, 1 \le t \le n$. The symbol $E\left(Y_t\right)$ denotes the expected number of deaths on day t. The vector $\vec{x}$ is the $N-$dimensional exposure series, in particular, we first consider the maximum temperature on day t as x_t. The vector $\vec{l}$ is the lag: $\vec{l} = \left(0,1,\ldots,L\right)$. C is the $\left(L+1\right) \times v_l$ matrix of the basis variable derived by applying the specific basis function to the lag vector $\vec{l}$. The $n \times v_x \times \left(L+1\right)$ matrix element $r^T\left(t\right)_{j.}$ represents the basis variable for the lagged exposure at time t. The parameters β_{jk} are to be estimated.

Then we take the heat wave as the exposure variable $\vec{x}$. The heat wave variable is a binary indicator: it takes the value 1 if a heat wave occurs, otherwise it takes the value 0.

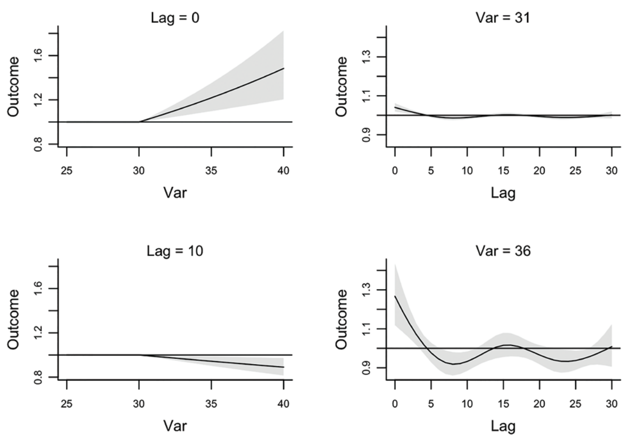
RESULTS

To assess the effect of temperature on mortality in the over-75s, R programs were developed, based on data from the different cities analysed, starting with the package dlnm [2] created by Gasparrini et al. The analysis considers both immediate and delayed effects, up to a maximum of 30 days.

We first analysed model (1) using a cross base with a natural cubic spline with 5 degrees of freedom, which captures the non-linear lagged effects over 30 days and the effects of temperature (maximum daily temperature) above a threshold of 30°. We also include as confounders the day of the week as a categorical variable to account for weekly seasonality, the day of year, in order to describe the seasonal effect within each year, and mean daily humidity as an instantaneous, not lagged variable.

The relative risk (RR) depends on both the temperature and the delay. Fig. 1 illustrates how the temperature-related risk evolves over time in Ancona. In the top left graph, where the lag is zero, the immediate effect of temperature on mortality is observed: the risk increases with temperature, following an exponential trend. For temperatures above 30°C, the increase in risk is almost linear, while the statistical uncertainty (grey area) increases significantly above 35°C. In the lower left graph, the risk flattens out with a lag of 10 days, indicating that temperature no longer has a significant effect on mortality after this interval. The graphs on the right show the evolution of the risk by fixing certain temperatures. At a temperature of 31°C (95th percentile, top right graph), the initial risk is slightly above 1 (~1.040, $CI = (1.019; 1.062)$), and remains above 1 for about four days before stabilising around 1 with longer lags. The narrow confidence interval indicates a reliable estimate. At 36°C (99.9th percentile, bottom right graph) the initial risk is significantly higher, around 1.267 ($CI = (1.118; 1.435)$), and remains above 1 for about four days. It then decreases, but after about 15–16 days, a slight increase in risk is observed. For longer lags, uncertainty increases and moderate oscillations are observed. These results suggest that very high temperatures have an immediate effect on mortality.

Figure 1. Plot of RR by temperature in Ancona at specific lags (left), RR by lag at 95th and 99.9th percentiles of temperature distribution (right)



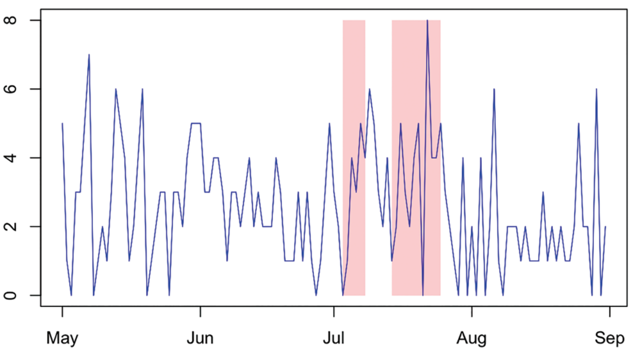
Heat waves

After analysing the impact of daily temperatures considered independently, other codes were developed in R to study the impact of heat waves. As the available data is limited to the last 10 years, during which there has been a significant increase in the mean temperature, we have adopted the following definition of a heatwave: a period of at least three consecutive days on which the maximum daily temperature exceeds the baseline. The baseline is defined as the sum of the historical daily mean temperature and historical daily standard deviation for each day between 2011 and 2021.

The aim is to estimate for how many days the effect of the heat wave on mortality persists in relation to its duration. Compared to the previous case, in which a temperature was fixed independently of the consecutive days in which it lasted, the risk increases in intensity and duration. The inclusion of the lag term allows us to examine how the effect of a heat wave evolves over time, identifying both an immediate increase in risk and possible delayed effects, such as the harvesting effect.

The graph in Figure 2 shows the evolution of deaths among people over 75 in Ancona in the period May-September 2015, highlighting the days characterised by heat waves with red rectangles. It can be observed that heat waves are mainly concentrated in the central summer months, between June and August, with variable duration. However, not all waves are associated with a clear increase in mortality, suggesting that factors such as the intensity of the event and the population's ability to adapt may play a decisive role. We chose to focus on Ancona in 2015 because it experienced the longest heat wave of the 2011–2021 period, lasting 12 days. In particular, one of the highest mortality peaks of the entire period was recorded immediately after the first wave in July. Furthermore, the absolute maximum of eight deaths occurred within the second, longer wave, suggesting a possible cumulative effect between the previous and the current wave. Finally, a comparison of the pre- and post-wave periods shows greater stability before the event, while mortality peaks become more irregular afterwards, confirming the impact of heat waves on the elderly population.

Figure 2. Deaths of over-75s during the hot months of 2015 in Ancona, red zones indicate heat waves



The graph in Figure 3 provides a rough idea of how the duration of the heat wave affects the risk of death, as shown in the graph. To construct it, the baseline mortality on days without heat waves was estimated by calculating the average daily number of deaths among people aged 75 and over during these periods. This average is used as a reference to assess the increase in risk on days with heat waves. For each heat wave, the average mortality within the corresponding time window was then calculated. The relative risk (RR) was obtained as the ratio of the average mortality during the heatwave to the baseline mortality:

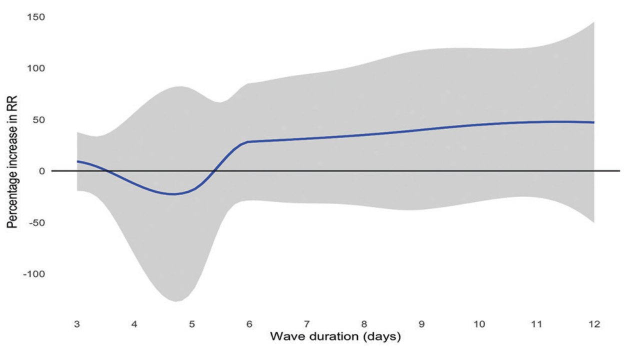
$$RR = \frac{\text{Average mortality during the heatwave}}{\text{Baseline mortality}}$$

From here, the percentage increase in risk was calculated as:

$$Percentage\,increase = (RR - 1) \cdot 100$$

The resulting graph uses a smooth curve to highlight the general trend. Initially, the risk is positive but moderate, then it decreases until it is around 4–5 days. However, during this period there is a widening of the confidence interval, indicating greater uncertainty in the estimates due to the lack of data for waves of this duration. After this point, the risk shows a clear exponential increase as the duration of the wave increases, confirming that the longest waves are particularly dangerous for the mortality of the elderly.

Figure 3. Percentage increase in risk as a function of wave duration in Ancona



To investigate the effect of heat waves on the mortality of people over 75 years of age, we considered model (1), which incorporates a quasi-Poisson family with non-linear effects of the lag function. We chose a natural cubic spline with five degrees of freedom and a linear exposure-response relationship. We also included the day of the week, the day of the year and mean daily humidity as confounders. The heatwave variable was included as a binary indicator (1 if a heatwave occurred, 0 if it did not).

In Ancona (Figure 4), the effect of heat waves on mortality lasts about 6 days. The initial risk is high (about 1.071, CI(0.991;1.157)) but gradually decreases over time. The reliability of the estimates is confirmed by the relatively narrow confidence intervals, indicating a robust model. After the seventh day, the risk is no longer statistically significant, suggesting that the impact of heat waves in this city is intense but short-lived.

In Pescara (Figure 5), the effect of heat waves on mortality also lasts for about 4 days. The initial relative risk is slightly lower than in Ancona (~ 1.019, CI(0.990;1.050)) and gradually decreases over time. The confidence intervals are similar to those observed in Ancona and still provide a reasonable level of confidence in the estimates. After the fourth day, the risk is no longer statistically significant, suggesting that the impact of heat waves in this city is milder but follows

Figure 4. Lag-response for heat wave days in Ancona

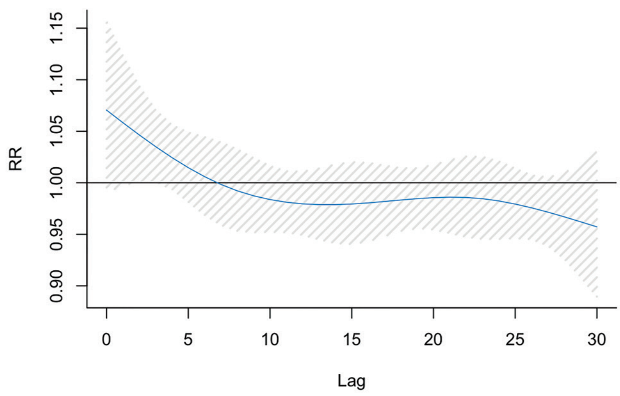
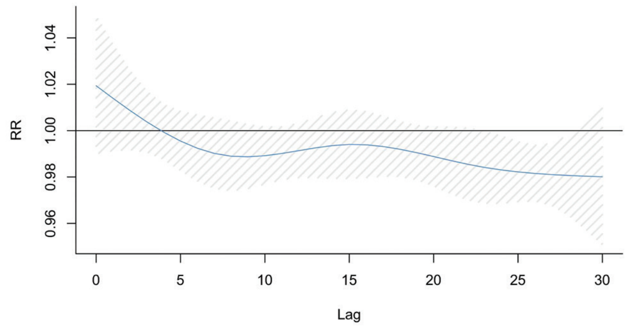


Figure 5. Lag-response for heat wave days in Pescara



a similar temporal pattern. These results underline that the characteristics of heat waves, their intensity - duration and local environmental conditions - play a crucial role in determining their impact on mortality. In addition, different populations react differently to them.

Sensitivity Analysis

To assess the robustness of the results to model specification, a sensitivity analysis was conducted by varying the degrees of freedom (df) used in the lag-response function of the distributed lag non-linear model (DLNM). The original model employed 5 degrees of freedom to capture the temporal structure of the lagged association. For the sensitivity analysis, alternative models were estimated using 3 and 6 degrees of freedom, representing lower and higher levels of spline flexibility, respectively. The goal was to evaluate whether the estimated exposure-lag-response relationship and effect estimates were influenced by the choice of df. The overall association patterns remained consistent across all three specifications. While minor variations were observed, particularly at longer lag periods, the magnitude and direction of effects did not materially change. These results suggest that the findings are robust to the specification of the lag spline, reinforcing the reliability of the main conclusions.

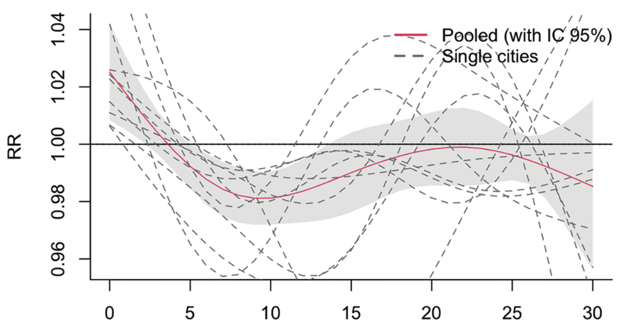
Regarding the heat wave model, we attempted to incorporate maximum temperature as a confounding factor. However, no significant changes were noted, only a very slight increase in risk (with a percentage variation < 3%).

To clarify the fact that neighbouring cities have the same temperatures, a meta-analysis was conducted, considering only the main cities that had a weather station. The results obtained were not very different to those of the model including all cities.

Multivariate meta-analysis

Having analysed the impact of heatwaves in each city using DLNM models, we applied a meta-analytic approach to synthesise the results at an aggregate level. This method allows us to combine estimates from different locations while accounting for variability and potential correlations, thereby improving the precision and generalisability of the results. We used a multivariate approach to model several parameters simultaneously, taking into account the dependency structure between the cities analysed. A random effects model was used to deal with heterogeneity between cities and to produce more robust estimates. Specifically, we estimated the relative risk (RR) of mortality associated with heat waves with a lag of up to 30 days. For this analysis, we examined the same 10 cities that were analysed individually at the beginning. The graph in Figure 6 shows the trend in the RR for the population aged 75 and over as a function of lag. The dashed lines represent estimates for individual cities, while the red solid line shows the pooled RR, with the grey area showing the 95% confidence interval. At the begin the RR is about 1.025 $(CI = (1.008;1.042))$. In the first days after a heat wave, the RR tends to decrease, remaining above 1 for about 4 days. It then stabilises under the reference value (RR = 1), with a slight increase around day 22: the most vulnerable population is affected first, followed by a temporary decline in mortality. This pattern suggests a possible delayed effect of heat waves, with an initial increase in risk followed by a period of compensation. The high variability between cities, highlighted by the dashed lines, reflects local differences in climate, demographics and health systems. However, the pooled analysis provides a more robust overall estimate, reducing the uncertainty from individual local analyses.

Figure 6. Effect of heat waves on mortality for over-75s



DISCUSSION

In the present study, we investigated the non-linear exposure-response relationship between temperature and mortality using multivariate time series data from ten cities in central-eastern Italy. The analysis was performed in three steps: in the first step, we examined the effect of extreme temperatures on mortality in people aged over 75 years, considering each day as independent. In particular, we used the 95th and 99.9th percentiles of annual temperatures as reference temperatures and observed the lagged effects of risk immediately after the day of extreme heat. In a second step, we considered heat waves, i.e. subsequent days in which an extreme temperature persists. In this case, risk is affected by the prolongation of hot days, and so is the lag. Although in some cases the weather data measurements are the same for neighbouring cities, the effect of the heat wave on the health of the elderly population could vary significantly because the time series counting the number of deaths could have a different distribution. Finally, we carried out a multivariate analysis to extrapolate from the characteristics of each city to the aggregate behaviour of the area in which the cities are located. Multivariate meta-analysis is a useful analytical tool [8] for studying complex associations between different cities and allowed us to obtain a behaviour that goes beyond the specificities of each city, providing an estimate of a lag of about 4–5 days for the area between Marche and Abruzzo. In this type of analysis, it is not necessary to interpret the parameters individually, since they are studied through their joint distribution. It could be interesting to include in the model variables of interest, such as the historical series of pollution rates, which would allow us to better understand, in addition to the weather data, the distribution of the delay after the heat wave.

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