COVER PAGE:

Title: Association of inter and intra-day temperature change with mortality.

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FOOTNOTES PAGE:

Running head: Association of temperature variation with mortality.

List of abbreviations:

CI: Confidence intervals

DTR: diurnal temperature range

DF: degrees of freedom

MMT: minimum mortality temperature

MMP: minimum mortality percentile

RR: relative risk

Keywords: ambient temperature, mortality, variation, diurnal temperature range

ABSTRACT (word count: 198)

This study evaluates the association between temperature variation and mortality, and compares it with the contribution due to mean daily temperature in six cities with different climates. Quasi-Poisson time series regression models were applied to estimate the associations in terms of relative risks (RR, 95% confidence intervals (CI)) of mean daily temperature (99^{th} / 1^{st} percentile, temperature of minimum mortality as reference), inter-day (difference between mean temperature of two neighboring days) and intra-day variation (diurnal temperature range, DTR) (referred to median variation) with mortality in London, Madrid, Stockholm, New York, Miami and Houston (date range 1985-2010). All cities showed a substantial increase in mortality risk associated with mean daily temperature, with RRs reaching 1.428 (95%CI: 1.329 to 1.533) for heat in Madrid and 1.467 (1.385 to 1.555) for cold in London. Inconsistent results for inter-/intra-day change were obtained, except for some evidence of protective associations in Madrid in hot and cold days (0.977 (0.955 to 0.999) and 0.981 (0.971 to 0.991)), and in cold days in Stockholm (0.989 (0.980 to 0.998)). Our results indicate that the association between mortality and temperature variation is generally minimal compared to mean daily temperatures, although further research is needed on intra-day changes.

MANUSCRIPT (word count: 3,028 words)

BACKGROUND

During the last decades, the association between daily mortality and temperature has been extensively investigated in wide variety of settings, both at community and/or country level (1–7), or even comparing country-wide estimates (8,9). These studies have examined the associations with heat and/or cold using the level of mean or maximum daily temperature reached on a specific day as exposure variable, although accounting for lagged contributions. Most results indicate a U-, J- or V-shaped exposure-response, with associations with heat lasting 3-5 days, and more delayed risk of cold which extends up to two or three weeks (9,10).

However, the extent to which the dependency with heat or cold is due to the high or low temperature value registered in a specific day, or in fact related to the variation in temperature between or within days, is an unresolved issue. This problem has aroused some interest lately, considering that unstable weather patterns, including sharp drops or increases in temperature, are predicted to occur more frequently in the future (11). A number of studies have evaluated the health risk due to temperature variation using various indices, such as diurnal temperature range (DTR) as intra-day indicator (difference between daily maximum and minimum temperature), and the change in mean temperature between two neighboring days as inter-day indicator (12–17). DTR has been associated with an increased risk for several health outcomes, both in terms of mortality or morbidity for different cardiovascular and respiratory causes, in recent investigations in Asia and Australia (15,17–20). In contrast, limited investigations have been carried out about the impact of inter-day variation in temperature. The current evidences show a non-linear association with higher risk in the extremes for both mortality and respiratory outcomes in children (12,16,21).

Evidence suggest that sudden changes in ambient temperature might affect population health since the thermoregulatory system of the human body responds inefficiently to drops or increases in temperature occurred a very narrow interval of time, with potentially different mechanisms suggested for each case (22). Individuals might feel unprepared to these sharp variations in temperature between and within days, not only physiologically but also regarding behavioural patterns (23). Increase in cardiovascular workload, increased blood pressure, severe inflammatory reactions and infections have been suggested as potential underlying mechanisms which worsen health status, mainly in susceptible individuals, and finally increase the probability of death (24–27).

Despite identifying associations, clear conclusions have not been reached regarding the role of temperature variation to the overall contribution of heat and/or cold on health. This may be due in part to the lack of a conceptual model for estimating and interpreting the relative contribution of different temperature indices. In particular, the composite association with multiple temperature measures cannot be easily disentangled without some assumptions. The objective of this paper is first to offer a more comprehensive illustration of the association of temperature with mortality, using data from 6 large cities in 4 countries worldwide with different climates and with the definition of temperature indices based on a consistent set of assumptions. Second, we aim to compare the association between mean daily temperature and temperature change with mortality.

METHODS

Weather and mortality data collection

Daily mortality data registered in London, Madrid, Stockholm, New York, Miami and Houston were collected for different study periods between 1986 and 2010. We included total mortality in all cities, excepting for the last three locations where deaths for non-external causes were available. Meteorological data on daily mean, maximum and minimum temperature were also obtained during the same study periods. Additional details about the characteristics of the study series are provided in Web Table 1.

Definition of temperature exposure indices

Including absolute value and changes in temperature together in a regression model may produce identifiability issues, if no constraints are enforced. For instance, the same health impact in a given day can be modelled as the linear dependency of mean daily temperature in the same day and the day before (as two variables in a distributed lag model), or equivalently as the linear associations of mean daily temperature in one of the two days and temperature change between them. The two models give identical fitted values, so which model is better is not identifiable from the data. Although such complete non-identifiability does not necessarily occur when non-linear curves are modelled, near equivalence of competing models can easily create problems in estimating and interpreting regression models which include multiple temperature indices. Below we propose definitions of temperature indicators based on more reasonable, realistic and biologically plausible assumptions which ensure identifiability and facilitate interpretation.

The index of mean daily temperature x_t^{mean} is computed as the average between the daily maximum and minimum (New York, Houston, Miami) or the 24-

hour average of hourly measurement in day t (London, Madrid, Stockholm). Similarly to previous studies, the association is allowed to vary non-linearly and with a distributed lag (8,9).

The index of inter-day change is defined as the relative change in temperature between two neighboring days. It is assumed that the associated risk may depend on the season or the current mean temperature: for instance, a 5°C increase in temperature may be detrimental if mean daily temperature is already high, while the same increase may produce no increased risk in cold months. To implement this assumption, we built two independent inter-day temperature variation ("b" super index indicating between-day variation in temperature) indicators: Δx_t^{binc}, for increase in temperature and Δx_t^{bdec} decrease in temperature, computed as the difference in mean temperature between the same and previous day, only if above and below of the minimum mortality temperature (MMT), respectively. The city-specific MMT value was estimated from simple temperature-mortality models, as explained below in the statistical methods section. The applied formulae for the estimation of inter-day change indicators are the following:

$$\Delta x_t^{binc} = \ max[x_t^{mean} - \max(x_{t-1}^{mean}, MMT)\,, 0] \quad (1)$$

$$\Delta x_t^{bdec} = \max[\min(x_{t-1}^{mean}, MMT) - \ x_t^{mean}, 0] \quad (2)$$

where index b indicates between day and Δ the variation in temperature. For example, temperatures of 25ºC today and 18 ºC yesterday, with a MMT of 20ºC, correspond to $\Delta x_t^{binc} = 5°C$ and $\Delta x_t^{bdec} = 0°C$. Similarly, temperatures of 10ºC and 16ºC with the same MMT produces an index of $\Delta x_t^{binc} = 0°C$ and $\Delta x_t^{bdec} = 6°C$.

Similarly, the change in temperature within a day, or DTR, computed as the difference between the daily maximal and minimal temperature, might also be perceived differently depending on the current mean temperature. So, two different intra-day variation indices were estimated to better identify the association relative to the mean daily temperature: that is, DTR in hot days (Δx_t^{whot}) considered as those days with a mean daily temperature above the MMT, DTR in cold days when x_t^{mean} below MMT (Δx_t^{wcold}), according to the formulae below:

$$\Delta x_t^{whot} = x_t^{max} - x_t^{min}, if\ x_t^{mean} > MMT, else\ 0 \quad (3)$$

$$\Delta x_t^{wcold} = x_t^{max} - x_t^{min}, if\ x_t^{mean} < MMT, else\ 0 \quad (4)$$

where the index w indicates intra-day (within day) variation ($whot$ for hot days, $wcold$ for cold days), and max, min the maximum and minimum temperature values in each t day.

Statistical methods

Generalized linear models with Poisson regression accounting for overdispersion were applied to estimate the association with mean daily temperature and with the terms of inter- and intra-day temperature variation on mortality in each city. The algebraic representation of the model is the following:

$$\log(\mu_t) = \alpha + s(x_t^{mean}, l; \boldsymbol{\beta}) + \gamma\Delta x_t^{binc} + \delta\Delta x_t^{bdec} + \varphi\Delta x_t^{whot} + \vartheta\Delta x_t^{wcold} + \sum_{i=1}^{p} f(z_t^i; \boldsymbol{\theta}) \quad (5)$$

where μ_t is the expected number of deaths in day t. The coefficients γ, δ, φ and ϑ represent the linear dependencies of the temperature variation terms considered for lag0. Non-linear and delayed associations with mean temperature were estimated through a distributed lag non-linear models, where the temperature indicator x_t^a was modelled through a cross-basis function (s) with a vector of coefficients $\boldsymbol{\beta}$ (28). Specifically, we applied a common exposure-response function for all cities consisting on a quadratic B-spline with three internal knots placed at the 10th, 75th and 90th percentiles of the variable, and a natural cubic spline with three equally-spaced knots in the log-scale and intercept as the lag-response function along lag l, with 21 days of lag. The other terms $f(z_t^i; \boldsymbol{\theta})$ in the model are a natural spline function of time (8 df per study year) and day of the week (as indicator variables). These modelling choices are based on previous work (8).

We first obtained the city-specific MMT using a simple model including only the cross-basis term of mean daily temperature, adopting an approach previously described (8). In the next step, all the other indicators of temperature variation were computed and added to the model. The association with mean daily temperature was summarized as overall cumulative contributions for heat and cold at the 99th and 1st temperature percentiles, respectively, using the MMT as reference. These were computed as the relative risks (RR) from the overall cumulative exposure-response relationships representing the net associations over the whole lag period (28). The associations with inter and intra-day temperature variation was expressed as the RR per change in a median value.

Sensitivity analysis

Several sensitivity analyses were performed in order to check the consistency of the results obtained in the main analysis. We restricted this assessment to the London data, to obtain simpler and easily interpretable results. The association estimates of mean daily temperature and the inter- and intra-day variation in temperature were again estimated changing the number of df (6, 10 df) used to control for the time trend and the knots placement (3 internal equally-spaced knots in the range of the variable) in the exposure-response function of the cross-basis term of mean temperature. In an additional sensitivity analysis, we obtained the temperature-mortality association estimates without including the terms of temperature variation in the model. We also estimated the risk estimates for non-external instead of total mortality, since three of the six cities included deaths for these causes only. We explored the association with extreme inter-day and intra-day changes by restricting the indices definitions to days with temperature variation above their 95th percentile, respectively. Finally, we obtained the estimates of the temperature indicators including the mean daily relative humidity in the model as a natural spline function with 3df.

The R code and data to reproduce the analysis for London is available at the personal web page of the last author (www.ag-myresearch.com).

RESULTS

Table 1 describes the six city-specific series of daily mortality and mean temperature data. The number of years included in each study period ranges from 22 (New York, Miami, Houston) to 14 (London). As expected, the median number of deaths per day is higher in the larger cities of London (161 deaths/day) and New York (169 deaths/day). A large variability in the mean temperature distribution is observed among cities, with median values ranging from 6.8°C (Stockholm) to 25.8°C (Miami). New York shows higher within-city variability, with mean daily temperatures ranging from -16.4°C to 34.4°C.

Table 1. Description of the study series.

Study Site	Study Date Range (years)	Daily Deaths[a]			Mean Daily Temperature (°C)				
		No.	Median	Range	Minimum	25th Percentile	Median	75th Percentile	Maximum
London	1993—2006	845,215	161	99—353	-3.1	7.5	11.5	16	29.2
Madrid	1990—2010	577,016	74	39—256	-1.8	8.9	14.2	21.6	32.4
Stockholm	1990—2010	201,197	26	9—51	-21.5	1.2	6.8	13.9	26.8
New York	1985—2006	1,367,085	169	101—290	-16.4	5.8	13.3	21.7	34.4
Miami	1985—2006	372,130	46	23—85	3.3	23.1	25.8	28.1	31.4
Houston	1985—2006	366,340	46	18—82	-8.1	12.3	22.2	27.5	33.3

[a]London, Madrid, Stockholm: total (all causes) deaths; New York, Miami, Houston: non-external deaths only.

Summary statistics of variables specifying temperature changes are reported in Table 2. Miami and Houston have experienced a higher percentage of days with an increase in temperature above the MMT between two neighboring days (between 25-40%), whereas in Stockholm almost half of the days included in the study period have registered a decrease in temperature below the MMT. New York and Houston show the sharpest inter-day increase (maximum: 7.2°C) and decrease (15.3°C) in temperature, respectively. More elevated DTR median values have been registered in hot days than in cold days between each location, except for Houston, with the highest median in DTR for cold days of 12.2°C among all cities. While Madrid shows the corresponding largest median value in hot days (12.7°C). The definitions of temperature changes are based on the estimated MMT, which show a limited variation between cities, in the range 18.5 to 23°C. However, the corresponding values in a relative scale of minimum mortality percentiles (MMPs) are more dependent on the climate, and vary from the 25th percentile in Miami to the 94rd in London. Moderate to low correlations between the different temperature indices are observed (Table 3).

Table 2. Summary statistics of estimated inter-day (increase and decrease) and intra-day (diurnal temperature range in hot and cold days) change in temperature.

Temperature Measure and Study Site	No. of Days	%	Minimum	25th Percentile	Median	75th Percentile	Maximum
			Inter-day change in temperature				
Increase in temperature, °C							
London	230	4.5	0	0.4	0.9	1.7	3.6
Madrid	1,479	19.3	0.1	0.6	1.1	1.9	5.8
Stockholm	329	4.3	0	0.4	0.8	1.4	3.7
New York	1,011	12.6	0.1	0.6	1.2	2.2	7.2
Miami	3,059	38.1	0.1	0.3	0.8	1.1	5.6
Houston	1,994	24.8	0.1	0.6	0.8	1.4	5.6
Decrease in temperature, °C							
London	2,437	47.7	0	0.6	1.2	2.1	7
Madrid	2,490	32.5	0.1	0.5	1.2	2.1	8
Stockholm	3,600	46.9	0	0.6	1.4	2.5	11.1
New York	3,123	39	0.2	1.1	2.2	3.9	13.6
Miami	1,031	12.8	0.2	0.5	1.6	3.3	10.8
Houston	2,007	25	0.2	1.1	2.2	4.4	15.3
			Intra-day change in temperature				
DTR in hot days (ºC)[a]							
London	327	6.4	4.9	9.2	11.4	13.1	19.1
Madrid	2,627	34.3	3.3	11.3	12.7	13.9	19.1
Stockholm	495	6.5	0.5	8.6	10.9	13	17.6
New York	1,645	20.5	2.8	7.2	8.3	10	22.2
Miami	6,067	75.5	2.2	6.1	7.2	8.3	16.7
Houston	3,771	46.9	1.7	8.9	10.6	12.2	21.7
DTR in cold days (ºC)[a]							
London	4,786	93.6	1	4.8	6.6	8.6	17.1
Madrid	5,027	65.5	0.6	6	8.3	10.6	17.2
Stockholm	7,149	93.2	0.1	3.2	5.9	8.9	21.4
New York	6,383	79.4	1.1	5	7.2	9.4	23.9
Miami	1,967	24.5	2.2	7.8	9.5	11.1	18.3
Houston	4,258	53.0	1.1	8.3	12.2	15	26.7

Abbreviations: DTR, diurnal range of temperature.
Temperature of minimum mortality, ºC (temperature percentile of minimum mortality): London, 20.0 (94th); Madrid, 18.5 (66th); Stockholm, 19.0 (94th); New York, 23.0 (80th); Miami , 23.0 (25th); Houston, 23.0 (53rd). (Computed from the regression model in each city).

[a] Descriptives computed excluding days with zero value of DTR. Number of days corresponds to the days when DTR was different than zero.

Table 3. Correlation (Pearson coefficient) between the mean daily temperature and the inter- and intra-day variation (diurnal temperature range) in temperature variables in each city.

	Mean temperature	*Increase in temperature*	*Decrease in temperature*	*DTR hot days*	*DTR cold days*
London					
Mean temperature	1				
Increase in temperature	0.344	1			
Decrease in temperature	-0.227	-0.111	1		
DTR hot days	0.480	0.717	-0.165	1	
DTR cold days	0.036	-0.347	-0.036	-0.516	1
Madrid					
Mean temperature	1				
Increase in temperature	0.486	1			
Decrease in temperature	-0.378	-0.188	1		
DTR hot days	0.853	0.568	-0.348	1	
DTR cold days	-0.624	-0.445	0.203	-0.824	1
Stockholm					
Mean temperature	1				
Increase in temperature	0.299	1			
Decrease in temperature	-0.286	-0.100	1		
DTR hot days	0.436	0.674	-0.152	1	
DTR cold days	0.116	-0.243	-0.048	-0.370	1
New York					
Mean temperature	1				
Increase in temperature	0.423	1			
Decrease in temperature	-0.357	-0.164	1		
DTR hot days	0.648	0.626	-0.271	1	
DTR cold days	-0.377	-0.429	0.112	-0.710	1
Miami					
Mean temperature	1				
Increase in temperature	0.300	1			
Decrease in temperature	-0.558	-0.160	1		
DTR hot days	0.711	0.268	-0.432	1	
DTR cold days	-0.802	-0.312	0.438	-0.843	1
Houston					
Mean temperature	1				
Increase in temperature	0.389	1			
Decrease in temperature	-0.477	-0.176	1		
DTR hot days	0.791	0.418	-0.364	1	
DTR cold days	-0.702	-0.396	0.272	-0.819	1

Abbreviations: DTR, diurnal temperature range

Web Figure 1 illustrates the estimated associations between mean daily temperature and mortality, reported as bi-dimensional exposure-lag-responses and one-dimensional overall cumulative exposure-responses overall lag 0-21. In general, the six cities display U- or V- shaped relationships, with increasing risks for both high and low temperatures. We observe in Miami a wide interval of temperature with no-association ranging between 23°C (25^{th}) to 28°C (75^{th}).

Summary figures of the estimated associations with mean daily temperature and inter- and intra-day temperature variations are included in Table 4. Mean daily temperature was associated with a substantial increase in mortality risk with RRs reaching 1.428 (95%CI: 1.329 to 1.533) for heat in Madrid and 1.467 (95%CI: 1.385 to 1.555) for cold in London, reported at 99^{th} and 1^{st} percentiles versus MMT, respectively. In contrast, smaller and generally inconsistent associations are found for temperature variation indices. Results for intra-day variation are difficult to interpret, with detrimental risks in London, New York, Miami and Houston, and protective in Madrid and Stockholm. In detail, while a RR of 1.010 (95%CI: 1.000 to 1.020) is reported for DTR in hot days in New York, some evidence of protective associations of this index is observed in Madrid in hot and cold days (0.977 (95%CI: 0.955 to 0.999) and 0.981 (95%CI: 0.971 to 0.991)), and in cold days in Stockholm (0.989 (95%CI: 0.980 to 0.998)).

We did not observe any noticeable change in the RR estimates from London obtained in the different sensitivity analyses (Web Table 2).

Table 4. Estimated relative risks (with 95%, confidence interval) of mortality associated to mean daily temperature, inter-day and to intra-day variation in temperature.

	London		Madrid		Stockholm		New York		Miami		Houston	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Mean daily Temperature												
Heat	1.239	1.183, 1.297	1.428	1.329, 1.533	1.124	1.033, 1.223	1.267	1.212, 1.323	1.077	0.979, 1.185	1.026	0.955, 1.102
Cold	1.467	1.385, 1.555	1.280	1.202, 1.362	1.164	1.023, 1.323	1.189	1.127,1.255	1.171	1.097, 1.250	1.256	1.172, 1.346
Inter-day change in Temperature												
Increase in temperature	1.004	0.992, 1.017	1.003	0.995, 1.010	0.985	0.964, 1.008	0.997	0.992,1.002	1.004	0.998, 1.010	0.998	0.992, 1.004
Decrease in temperature	0.999	0.995, 1.002	1.002	0.997, 1.006	1.000	0.994, 1.006	0.999	0.996, 1.002	1.001	0.993, 1.009	0.997	0.991, 1.002
Intra-day change in Temperature												
DTR in hot days	1.010	0.985, 1.035	0.977	0.955, 0.999	0.984	0.943, 1.026	1.010	1.000,1.020	1.005	0.991, 1.019	1.005	0.990, 1.021
DTR in cold days	1.001	0.994, 1.008	0.981	0.971, 0.991	0.989	0.980, 0.998	1.003	0.998,1.009	1.004	0.985, 1.023	0.998	0.986, 1.010

Abbreviations: CI, confidence interval; DTR, diurnal temperature range; RR, relative risk.
Mean daily temperature (cumulated over lag 0-21; heat, 99th percentile; cold, 1st percentile; city-specific temperature of minimum mortality as reference), to inter-day and to intra-day variation in temperature (scaled to represent relative risks corresponding to median variation compared to none)

DISCUSSION

This study proposes a novel modelling strategy to characterize the relationship between temperature and mortality, assessing the contributions of different temperature indices. Our approach allows the relative association of absolute value and within and between-day changes in temperature with mortality to be disentangled and compared, thus providing a more detailed picture of the association. Our findings show that the overall mortality risk was in these cities almost entirely determined by mean daily temperature, while temperature change play a relatively minor role.

The different and conflicting conclusions of previous studies on inter or intra-day temperature variation may be explained by ad hoc modelling strategies, which in particular did not address identifiability issues arising when modelling effects of variation indices in the presence of mean daily temperature with distributed lag (29–31). Although some of these investigations controlled for mean daily temperature, this has been modelled with limited flexibility, in particular with regards to lag structure (12,31,32). In contrast, the modelling approach we propose entails definitions of temperature variation indices based on a set of simple but realistic assumptions. This method provides a straightforward framework for interpretation and better allows identifiability and comparison of contributions from multiple indices. In addition, associations with indices of temperature changes are estimated in models that finely control for the non-linear and delayed contributions of mean daily temperature through distributed lag non-linear models.

Our results consistently indicate very little evidence for associations between inter-day temperature variation and mortality in the six cities. This finding is in contrast with previous works suggesting temperature variation between neighbouring days as an independent risk factor, responsible for a significant contribution to the impact of temperature on mortality (21,30,33). However, this index was often defined as a simple difference between mean temperatures in two consecutive days, without accounting for the fact that the same change is likely to have different effects depending on the absolute temperatures (21,33). Also, our strategy flexible controls for the non-linear and delayed association with mean daily temperature, and involves more developed definitions, separating contributions due to changes above or below a referent mean daily temperature identified by the MMT. This approach extends previous attempts based on season-specific estimates (12,30).

Conclusions on the relative impact of intra-day temperature variation are less straightforward. In our analysis, the association was generally inconsistent and lower than previously reported in studies not accurately controlling for mean daily temperature (20,29,31). Our approach, based on the definition of intra-day variation in respect to the MMT, is comparable to but extends previous investigations reporting associations stratified by seasons (13,20,32), similarly to Kan and collaborators (29). The direction of the association is not consistent with previous studies, with protective associations for DTR in either hot or cold days in Stockholm and Madrid, although the estimated mortality risks are not as substantial as that estimated for mean daily temperature. The difference may be due to our more appropriate definition of this predictor and a more accurate control for the main effect of mean temperature. Future analysis will extend this approach to specific mortality causes, in particular those that results from more triggering hazards, such as acute myocardial infarction or sudden cardiac death, in order to obtain more clear evidence on the role of this temperature index.

Some limitations must be acknowledged. In particular, our approach limits the assessment of temperature variation to the same day of exposure, as a way to simplify the analytical strategy. We deem that identifiability problems might arise if delayed impacts were simultaneously accounted for both in absolute and change in temperature. However, we cannot disregard the possibility that temperature variation might have a long lasting and higher association during the following days after the exposure, as previous studies have attempted to model (31–33). However, it should be noted that most of these investigations have reported higher or similar estimates when delayed associations where not accounted for, thus suggesting that our strategy may be appropriate (13,31). Future studies should address this issue considering more flexible modelling strategies that properly disentangle the immediate and delayed contributions of two different and highly correlated temperature indicators. In addition, while we chose six cities to represent different baseline weather conditions, we have clearly not fully sampled the range of possibilities and studies of other locations are warranted, potentially giving limited external validity to our results. And finally, we do not disregard the possibility that potential temporal changes in effect might have occurred due to adaptation of the population to sudden changes in temperature, which should be further assessed in future studies.

In conclusion, this study found that the association between mortality and inter and intra-day variations in temperature was minimal in the cities studied, and that the association can largely be defined in terms of mean daily temperature only. This evidence can help improving the predicted impact of temperature and design preventive measures to limit the associated health burden.

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