Ischaemic heart disease mortality and weather temperature in Barcelona, Spain

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Background: Association between ischaemic heart disease (IHD) mortality and extreme values of weather temperature has been the focus of many previous studies. To what extent moderate changes in temperature also influence IHD mortality in milder regions, where either low temperatures or heat waves are exceptional, has been less investigated. To further contribute to these issues we have investigated the association between weather temperature and IHD in Barcelona, Spain. Methods: A transfer function model was specified. The dependent variable was the daily time series of IHD while, weather temperature, relative humidity and air pollutants were the covariates. We also controlled for influenza epidemics and annual seasonality. In order to relax the restrictive assumptions (functional form and normality) imposed by the transfer function, this was modelled non-parametrically. The influence of unusual periods and outliers of weather temperature and humidity was also assessed. Results: A non-linear relationship between weather temperature and IHD existed. Our results suggested a temperature threshold (estimated in 21.06°C) in the relationship between IHD and weather temperature. The estimated value of the threshold was higher (23°C) for very humid days (relative humidity above 85%). The risk of an IHD death increased approximately 2.4% with every 1°C drop of temperature below 4.7°C and approximately 4% with every 1°C rise above 25°C. Conclusion: Our findings corroborated that not only the threshold but also the magnitude of the association presents a different range depending on the latitude, and is wider for southern locations. We suggest that the effect of temperature could account for the regional variations in IHD mortality.

Keywords: ischaemic heart disease mortality, weather temperature, semi-parametric transfer function, unusual periods and outliers, weather temperature

Association between ischaemic heart disease (IHD) mortality and weather temperature has been the focus of many previous studies.[1–16] Most of them, however, have been restricted to the effects of extreme temperatures, in particular cold.[2,3,6,7,9–13,15] A very well-defined conclusion from these studies is that there is an excess risk of death from IHD during winters attributable to low outdoor temperatures. Obviously most of these studies have been performed in regions with cold winters.[4,5,9,10,15] Heat waves have also been extensively investigated, showing a clear-cut association between increased temperature and IHD mortality.[16]

To what extent moderate changes in temperature also influences IHD mortality in milder regions where either low temperatures or heat waves are exceptional, has been less investigated. We are aware of a study in Taiwan[2] showing that, even at a temperature of 9°C (the lowest temperature in the study), there was an increased risk of death. The risk showed a decreasing trend together with increasing temperature up to 26°C. Some other studies have shown evidence of the relationship between temperature and IHD mortality in warm climates.[17–19]

The effect of moderate changes in temperature on IHD mortality is potentially important because large unexplained regional variations in IHD morbidity and mortality have been reported.[20] In addition to other non-identified factors, weather temperature may account for part of these regional variations. To contribute further to these issues we have investigated the association between weather temperature and IHD mortality in Barcelona, Spain.

METHODS

Data and sources

Daily deaths from IHD (ICD–9 410–414), for persons 45 years old and older, from 1 January 1986 to 31 December 1991, were supplied by the Municipal Health Institute, Barcelona City Council. Weather temperature data consisted of daily 24h averages. Other weather variables, such as humidity, could have an impact on mortality.[2,21] For this reason, separate records of the daily 24h average relative humidity were also considered. These data were obtained through the National Meteorological Institute from Barcelona airport, 8 km to the south-west of the city. Air pollutants have been shown to be associated with cardiovascular mortality.[22,23] In the present analysis, pollutants are considered the most important confounding factors. Daily levels of 24h averages of black smoke,

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sulphur dioxide, nitrogen dioxide and also of 1h maximum values for each day of ozone, were considered for the entire city. We also used information about the weeks in which influenza epidemics occurred in Barcelona (provided by the Municipal Health Institute).

Transfer function model

A transfer function model (a dynamic regression model relating two or more time series[24]) was specified. We considered the daily time series of IHD mortality as the dependent variable and weather temperature, relative humidity and air pollutants as the covariates. In this type of model, the possible relationship between the response and each one of the explanatory variables is dynamic in the sense that the effects of such explanatory variables could last more than one period and not necessarily be instantaneous, that is there is a dynamic structure (say a lag structure) of the explanatory variable involving the current value of the variable as well as several lags. The specificity of the transfer function models in relation to other dynamic models is the presence of a particular model building strategy. In this sense, the lag structure of each dynamic relation is not specified following a trial and error process but a formal established method.

In particular we followed a model building strategy called double prewithening.[25] In order to stabilize its variance, the IHD mortality time series was transformed by taking natural logarithms (plus 0.0001 in order to prevent the possibility of missing values). Secondly, univariate autoregressive integrated moving average (ARIMA) models for the IHD mortality and each one of the explanatory variable time series were first estimated, saving the residuals. Then, the sample cross-correlations between the residuals of the estimated ARIMA for the response and the residuals of each covariate were computed. These cross-correlations were compared with asymptotic standard errors ($1/\sqrt{n}$, where n was the number of observations) which are appropriate for the hypothesis of independence of each pair of series. This procedure allows identification of the systematic part of the model, that is the lag structure mentioned above.

In addition to the covariates, a dummy variable indicating the day of occurrence of an influenza epidemic was entered in the model. Annual seasonality (i.e. a cycle with a period of 1 year) was controlled for by means of seasonal dummy variables (December was considered the reference). Unusual periods and outliers of both weather temperature and humidity were detected following an iterative procedure based on likelihood ratio tests.[26,27] Dummy variables were entered in the model in order to control for outliers and unusual periods in temperature and humidity time series. In order to model possible synergistic effects of weather temperature and humidity a dummy interaction variable was introduced. The cut-off points for these dummies were determined through non-parametric smoothing plots of IHD mortality versus temperature and relative humidity.[28] Possible residual autocorrelation was controlled for by means of the appropriate ARMA structure for the noise component of the model, which was assessed by inspecting the residual autocorrelation and partial autocorrelation functions.

Semi-parametric modelling of the transfer functions

The transfer function model, however, imposes a particular functional form (depending on the transformations and the time lags finally chosen) in the relationship between the dependent and independent variables. Because this assumption could be very restrictive the previously determined transfer functions, between IHD mortality and each one of the explanatory variables were modelled non-parametrically.[29]

The aim is to allow the data to reveal the relationships directly. Specifically, a linear spline with equally spaced knots (a piecewise regression) was tried for each lag of each one of the response covariate relationships. Although the functional form is guaranteed to be continuous, the shape of the curve could not be monotonic (it would be monotonic if the partial sums of the different slopes were of the same sign). The range of each covariate was divided into 20 intervals (the break points were at 5th, 10th,..., 90th and 95th percentiles of the covariate). This number of intervals was chosen in order to reduce the bias while the variance is moderately increased.[29] Note that a piecewise linear regression is actually the general form of a linear regression. In fact, it was observed that, for all the explanatory variables except for temperature, the relationship was parametrical (although not necessarily linear). In this case the best fitting transformation of the covariate was chosen. In addition, the 20 initial intervals of the temperature were finally summarized in seven. The whole procedure is labelled semi-parametric, because parametric components were permitted in the final transfer function model.

All the semi-parametric transfer function models were estimated by non-linear unconditional least squares.[24] Wald's test[30] was used in order to test both linear or non-linear restrictions without regard for the assumption of normality. All the computations were carried out with RATS.[31]

RESULTS

As shown in *table 1* neither the maximum daily average weather temperature (35.45°C) nor the maximum daily average relative humidity (95.5%) correspond to summer. With the exception of ozone, the winter levels of air pollutants were higher than the summer ones. Likewise, daily means IHD mortality were higher in winter (6.1) and lower in summer (4.1). These facts could suggest a possible non-linear relation between IHD mortality and its covariates.

The transfer function component allowed determining the dynamic relationships between mortality and its covariates (i.e. lag structure). Cross-correlations permitted the identification of up to three lags statistically different from zero for weather temperature and air pollutants (five for ozone) and only the current value was statistically significant for humidity. That is, on a certain day IHD

mortality was affected by weather temperature, for instance, for up to 3 days (that day, the previous day and 1 and 2 days before the previous day).

Residual autocorrelation was controlled for the ARMA structure of the noise component. In this sense, it presented several moving average processes, mixing regular and irregular patterns. There was evidence of weekly (lag 7 significant in the autocorrelation or the partial autocorrelation functions) and monthly (lags 29, 30 and 31) seasonality but not of longer periods (i.e. quarterly, annual or biannual). In addition, there were several moving average terms which corresponded to outliers or unusual periods of mortality (other lags different from above). There was also evidence of annual seasonality (captured by seasonal dummies). In this sense, compared to December, summer months were those of lowest IHD.

The association between weather temperature and IHD mortality showed a downward gradient between 1.7°C (the minimum of temperature) and 4.70°C and an upward gradient for weather temperature higher than 21.06°C (*table 2* and *figure 1*). The right wing of the curve is larger than the left one (*figure 1*). There were significant relative risks (RR) for weather temperature in the ranges 1.70°C – 4.70°C, 21.06°C – 23.95°C and 24.96°C – 35.45°C ($p<0.05$) and a nearly significant RR in the range 23.96°C – 24.95°C ($p<0.1$). The risk increased approximately 2.4% with every 1°C drop in temperature below 4.7°C. The risk of IHD death for temperatures above 25°C was increased approximately 4%. IHD mortality decreased 0.06% each 1% of humidity increase ($p<0.05$). The risk of IHD death increased 4.4% for every simultaneous unit drop in both temperature below 6.5°C and relative

Table 1 Descriptives of variables for the entire period and for summers and winters, Barcelona, 1986–1991

	All days (n=2153)			Summer days (n=706)			Winter days (n=721)		
	Mean	SE	Range	Mean	SE	Range	Mean	SE	Range
IHD[a]	5.070	2.515	0.000–21.000	4.115	2.095	0.000–13.000	6.076	2.741	0.000–21.000
TEMP[b]	15.691	5.920	1.700–35.450	22.607	2.456	13.250–27.950	9.958	2.825	1.700–19.000
HUMI[c]	75.449	9.481	26.250–95.500	75.264	7.144	46.250–90.750	74.614	11.187	26.250–94.000
BLSMK[d]	43.991	22.472	11.286–206.500	35.165	14.064	11.571–125.571	51.634	26.808	11.571–206.500
SO_2 [e]	35.439	19.844	2.230–124.000	29.651	17.319	3.990–14.000	43.224	21.650	2.230–124.000
NO_2 [f]	53.472	19.383	5.150–141.000	46.520	19.144	5.150–23.730	57.831	18.522	5.870–141.800
O_3 [g]	72.629	34.917	7.020–283.350	91.636	32.939	14.080–83.350	51.797	24.355	7.020–138.190
INFL[h]	0.158	0.365	0.000–1.000	0.000	0.000	0.000–0.000	0.467	0.500	0.000–1.000

a: Daily ischaemic heart disease mortality ICD–9 410–414, 45 years old and older
b: Average 24h weather temperature (°C)
c: Average 24h relative humidity (%)
d: Average 24h black smoke ($\mu g/m^3$)
e: Average 24h sulphur dioxide ($\mu g/m^3$)
f: Average 24h nitrogen dioxide ($\mu g/m^3$)
g: One hour maximum ozone ($\mu g/m^3$)
h: Influenza epidemic ocurring on a particular day=1 and 0 otherwise

Table 2 Relative risk (RR) of ischaemic heart disease death for each 1°C of increase in weather temperature and relative risk for each 1% of increase in relative humidity (95% confidence intervals)

	RR	95% CI
Daily average weather temperature (°C)		
1.70–4.70°C	1.024 **	(1.001–1.048)
4.71–6.89°C	0.995	(0.948–1.045)
6.90–8.25°C	0.985	(0.956–1.015)
8.26–21.05°C	0.995	(0.983–1.007)
21.06–23.95°C	1.013 **	(1.001–1.025)
23.96–24.95°C	1.036 *	(0.991–1.083)
≥24.96°C	1.041 **	(1.037–1.045)
Daily average relative humidity	0.999 **	(0.999–1.000)
Weather temperature and relative humidity interaction		
Daily average temperature ≤6.5°C and daily average humidity ≤70%	1.044 **	(1.001–1.089)
Daily average temperature ≥23°C and daily average humidity ≥85%	1.096 **	(1.005–1.194)

* $p<0.10$, ** $p<0.05$ (Wald's test)
The model also includes seasonal dummies, air pollutants (black smoke, sulphur and nitrogen dioxide and ozone) and indicator variable for influenza epidemics and ARIMA error structure.

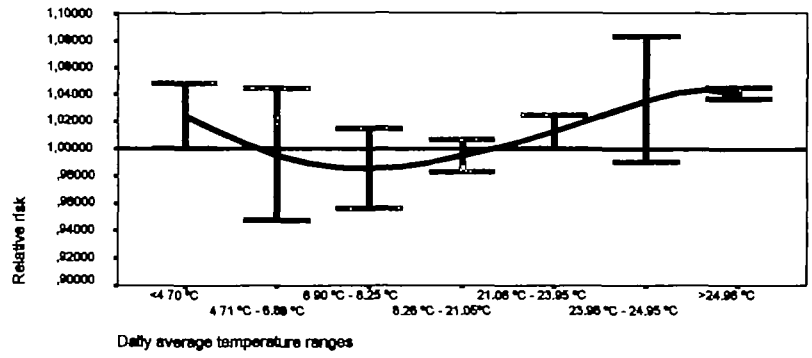

Figure 1 Relative risks of ischaemic heart disease death for each 1°C of increase in weather temperature.
The line is only a smooth connection of the point estimates

humidity below 70% ($p<0.05$). The risk augments 9.6% for every simultaneous rise in temperature above 23°C and humidity above 85%.

Both unusually high and low temperatures together with unusual humidity levels (regardless of whether these were lower or higher than usual) increased IHD mortality (*table 3*). Excess deaths were greater than expected. In this sense, for instance, while the expected risk of an IHD death was 2% on an unusual day (2 September 1986), the excess risk was equal to 20%, resulting in 16 deaths.

DISCUSSION

We found the existence of a non-linear relationship between weather temperature and IHD mortality. There was a downward gradient between 1.7°C (the minimum of temperature) and 4.70°C and an upward gradient for weather temperatures higher than 21.06°C. The right wing of the curve, however, is larger than the left one. On the same line, the relative risk of IHD death increased 4.4% for every simultaneous drop in temperature below 6.5°C and every drop of 1% in relative humidity below 70%. The risk increased 9.6% for every rise in both temperature and humidity above 23°C and 85% respectively. Results for unusual periods and outliers of weather temperature and relative humidity have corroborated these findings. Not only did 'hot' and 'humid' days increase mortality but also 'dry' days with temperature 'extremes'. These figures are in accordance with those reported previously for cardiovascular mortality for Barcelona[26] and for other temperate climates, such as other Mediterranean cities[32] and Queensland[17] and New South Wales[12] in Australia.

In addition a 'temperature threshold' or equivalently a V-shaped relationship between weather temperature and mortality, in the sense that mortality increases only during those days with temperatures above that threshold, has been reported for cardiovascular mortality.[21] The present results suggested a temperature threshold in the relationship between IHD mortality and weather temperature. The threshold was estimated at 21.06°C. The estimated value of the threshold was higher (23°C) for very humid days (relative humidity above 85%). Only 28 days (2% of all the days), however, were in these circumstances.

It has been pointed out that, because days with temperatures above the threshold do not necessarily occur during summer[26] the threshold tends to be higher for southern latitudes than for northern ones.[1,21] Furthermore, not only the threshold but also the magnitude of the association presents a different range depending on the latitude,[1] wider for southern locations.[2,17–19,26,32,33] The findings of this paper corroborated these hypotheses for IHD mortality. Because days with temperatures above that threshold not only occurred during summer the relation between temperature and IHD mortality did not

Table 3 Relative risk (RR) of ischaemic heart disease death (95% confidence intervals) for each day of occurence of an outlier or unusual period

	Temperature (°C)	Humidity (%)	RR	(95% CI)	ISCH
Temperature higher and humidity higher					
2 September 1986	23.050	84.000	1.205 **	(1.062–1.367)	16
20 November 1990	35.450	83.250	1.228 **	(1.082–1.394)	15
Temperature higher and humidity lower					
6 October 1987	20.150	57.250	1.245 **	(1.077–1.440)	6
Temperature lower and humidity lower					
25 August 1987	20.450	64.500	0.979 *	(0.959–1.000)	6
12 October 1987	16.800	59.750	0.819 **	(0.719–0.933)	5
Temperature lower and humidity higher					
29 May 1986	16.150	83.250	0.983 **	(0.971–0.996)	4

ISCH Daily ischaemic heart disease mortality ICD-9 410–414, 45 years old and older
** $p<0.05$ * $p<0.1$ (Wald's test)
The model also includes seasonal dummies, air pollutants (black smoke, sulphur and nitrogen dioxide and ozone) and indicator variable for influenza epidemics and ARIMA error structure

actually show a V-shape but a J-shape. Similar results were reported for cardiovascular mortality[21,26,32–37] and also for IHD mortality in other locations, such as Queensland[17] and New South Wales[12] in Australia and Taiwan.[2] The value of the threshold, as with other locations with temperate climates (Mediterranean cities,[26,32] Queensland[17] and New South Wales[12] in Australia), was estimated within a range that seems to comprise of lower values in northern latitudes[33] and higher figures in southern ones.[1,2,21] Lloyd[38] pointed out the lower risk of IHD in the Mediterranean region compared with Northern Europe (given a similar total fat intake) might be related to the degree of cold exposure.[9,39]

It seems that extreme temperature (hot temperatures in particular) has had the most important impact on IHD mortality, the effect of other meteorological variables being marginal. In fact, relative humidity had a relevant impact on mortality only when the temperatures exceed the threshold. This could be the point of the interactions between temperature and humidity in *table 2*. Likewise, Kalstein[21] pointed out that low afternoon humidity exacerbates heat-related mortality in some US cities.

From a statistical point of view, there are some points that deserve further discussion. The transfer function models assume a normal distribution for the dependent variable. In this sense we could have alternatively used a Poisson regression model. However, first of all, usual tests (χ^2) do not give more support to this latter distribution against the more simple alternative normality (of the log-transformed response). In fact, note that the variance in the daily numbers of IHD is always higher than the mean (*table 1*). Moreover, both estimation (non-linear unconditional least squares) and testing methods (Wald's test) are robust with respect to the actual data probability distribution. Because of the sparsity of the data, it was not possible to disaggregate IHD mortality counts into two or more age groups to account for the most important risk factor, namely age. However, it is possible that this risk factor might not vary very much given our definition of the response (45 years old and older).

Although our findings were in line with those reported by Pan et al.[2] for Taiwan, there were two important differences. In their case the relative risks of an IHD death for temperatures below the threshold (26°C) were higher than the unity and the left wing of the curve representing the association between IHD mortality and temperature was larger than the right one. One has to bear in mind, however, that Pan et al.[2] neither controlled for other covariates (other meteorological variables and air pollutants in particular) or took into account the time serial nature of the data. The lack of a proper statistical model questions their findings.

It has been reported that the three usual cardiovascular risk factors, regular cigarette smoking, blood pressure and total cholesterol, explained less than 25% of the variance in IHD mortality.[20] In this sense, the effect of temperature could account for the regional variations in IHD mortality. Several mechanisms could explain the findings of our paper. The failure to adapt physiologically to temperature changes or extremes causes stress on the heart.[10,12,40,41] It is known that cold increases blood pressure and angina symptoms.[7,42,43] However, Elwood et al.,[11] in the framework of the Caerphilly study showed that, although the effects on haemostasis, together with the effect on blood pressure, could explain a large part of the increase in IHD in winter, part of the variation in mortality remains unexplained. It is also possible that seasonal effects could be due to slower acting biological changes due mainly to behavioural differences in summer and winter. Finally, it could be possible that the effect of temperature is on respiratory disease and the apparent excess in IHD mortality in winter is simply due to miscoding of the cause of death.[3,11,33–35] However, studies which have tried to disentagle the associations between IHD mortality, respiratory disease and seasons have generally concluded that respiratory infection is not an important causative agent.[5,11,40,42–44]

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Received 9 September 1998, accepted 25 February 1999