Trends in temperature-related age-specific and sex-specific mortality from cardiovascular diseases in Spain: a national time-series analysis

Hicham Achebak, Daniel Devolder, Joan Ballester

Summary

Background Climate change driven by human activities has increased annual temperatures in Spain by around 1°C since 1980. However, little is known regarding the extent to which the association between temperature and mortality has changed among the most susceptible population groups as a result of the rapidly warming climate. We aimed to assess trends in temperature-related cardiovascular disease mortality in Spain by sex and age, and we investigated the association between climate warming and changes in the risk of mortality.

Methods We did a country-wide time-series analysis of 48 provinces in mainland Spain and the Balearic Islands between Jan 1, 1980, and Dec 31, 2016. We extracted daily cardiovascular disease mortality data disaggregated by sex, age, and province from the Spanish National Institute of Statistics database. We also extracted daily mean temperatures from the European Climate Assessment and Dataset project. We applied a quasi-Poisson regression model for each province, controlling for seasonal and long-term trends, to estimate the temporal changes in the province-specific temperature-mortality associations with distributed lag non-linear models. We did a multivariate random-effects meta-analysis to derive the best linear unbiased prediction of the temperature–mortality association and the minimum mortality temperature in each province. Heat-attributable and cold-attributable fractions of death were computed by separating the contributions from days with temperatures warmer and colder than the minimum mortality temperature, respectively.

Findings Between 1980 and 2016, 4 576 600 cardiovascular deaths were recorded. For warm temperatures, the increase in relative risk (RR) of death from cardiovascular diseases was higher for women than men and higher for older individuals (aged ≥90 years) than younger individuals (aged 60–74 years), whereas for cold temperatures, RRs were higher for men than women, with no clear pattern by age group. The heat-attributable fraction of cardiovascular deaths was higher for women in all age groups, and the cold-attributable fraction was larger in men. The heat-attributable fraction increased with age for both sexes, whereas the cold-attributable fraction increased with age for men and decreased for women. Overall minimum mortality temperature increased from 19·5°C between 1980 and 1994 to 20·2°C between 2002 and 2016, which is similar in magnitude to, and occurred in parallel with, the observed mean increase of 0·77°C that occurred in Spain between these two time periods. In general, between 1980 and 2016, the risk and attributable fraction of cardiovascular deaths due to warm and cold temperatures decreased for men and women across all age groups. For all the age groups combined, between 1980–94 and 2002–16, the heat-attributable fraction decreased by –42·06% (95% empirical CI –44·39 to –41·06) for men and –36·64% (–36·70 to –36·04) for women, whereas the cold-attributable fraction was reduced by –30·23% (–30·34 to –30·05) for men and –44·87% (–46·77 to –42·94) for women.

Interpretation In Spain, the observed warming of the climate has occurred in parallel with substantial adaptation to both high and low temperatures. The reduction in the RR and the attributable fraction associated with heat would be compatible with an adaptive response specifically addressing the negative consequences of climate change. Nevertheless, the simultaneous reduction in the RR and attributable fraction of cold temperatures also highlights the importance of more general factors such as socioeconomic development, increased life expectancy and quality, and improved health-care services in the country.

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See **Comment** page e281

Centre for Demographic Studies, Autonomous University of Barcelona, Barcelona, Spain (H Achebak MSc, D Devolder PhD); **and Climate and Health Program, Barcelona Institute for Global Health, Barcelona, Spain** (H Achebak, J Ballester PhD)

Correspondence to: Dr Joan Ballester, Climate and Health Program, Barcelona Institute for Global Health, 08003 Barcelona, Spain **joan.ballester@isglobal.org**

Introduction

Increasing concentrations of greenhouse gases due to human activities are inducing an unequivocal rise in global temperatures.[1] As a consequence of this anthropogenic warming, the world population is progressively more exposed to moderate and extreme warm temperatures and less exposed to moderate and extreme cold temperatures, which has serious implications for various health outcomes.[2,3]

Several studies addressing the potential future impacts of climate warming on temperature-related mortality have suggested an increase in heat-related deaths and a

Research in context

Evidence before this study

We searched PubMed from database inception until Dec 1, 2018, for articles published in English using the search terms "temperature", "heat", "cold", AND "mortality", "deaths", "cardiovascular mortality". Studies that assessed temporal variations in the association between heat and mortality showed a reduction in the relative risk (RR) of mortality due to heat across many settings, mostly in developed countries, despite the observed rise in temperatures. By contrast, some evidence has indicated a decline in cold-attributable mortality risk in the past 30 years, but few studies have investigated the impact of cold temperatures and available evidence is inconclusive. Little is known about the effect of heat and cold exposure on mortality risk and attributable mortality among population subgroups, and particularly the most susceptible populations, by sex, age, and cause of death.

Added value of this study

This is the first study to comprehensively assess the impact of the 1°C increase in ambient temperature that has been observed in Spain since 1980, and the effect of this increase on the Spanish population by sex, age, and specific cause of death. The effect of warm and cold temperatures on cardiovascular disease mortality in Spain, either expressed as RR (ie, level of vulnerability) or attributable fraction (ie, mortality burden attributable to non-optimum temperatures), differed by sex and age group and decreased over the study period for both sexes and across all age groups. The concurrent timing and magnitude of the increases in minimum mortality temperature and annual mean temperatures support the hypothesis that the global warming observed in recent decades has been accompanied by substantial adaptation to both warm and cold temperatures in Spain.

Implications of all the available evidence

In Spain, the observed climate warming has occurred in parallel with substantial adaptation to both warm and cold temperatures. The reduction in the risk and attributable fraction of cardiovascular deaths associated with heat would be compatible with an adaptive response specifically addressing the negative consequences of climate change. Nevertheless, the simultaneous reduction in the risk of mortality and impact of cold temperatures also highlights the importance of more general factors such as socioeconomic development, increased life expectancy and quality, and improved health-care services in the country. These adaptions to cold temperatures are not necessarily associated with an adaptive response specifically addressing the negative consequences of climate change (ie, they would have also occurred in a non-warming scenario), and therefore, our results show that this adaptive response to climate change might be more limited than the contribution of more general factors. Thus, the substantial adaption observed within the Spanish population during this period of rapid climate warming might not be sustained at higher ambient temperatures when warming begins to occur at a faster rate.

reduction in cold-related deaths,[4,5] resulting in a positive or negative long-term net effect in mortality depending on the location and magnitude of the warming.[6] However, most of these analyses assumed no changes in vulnerability (expressed as relative risk [RR]) over time. The eventual incidence of climate warming on temperature-related mortality will not only depend on the change in the levels of exposure to warm and cold temperatures, but also on any underlying change in the vulnerability of the exposed populations.[7]

A decrease in risk is often considered a sign of adaptation, occurring as a result of a physiological acclimatisation response within the population to changes in temperature (intrinsic adaptation), or through non-climate driven factors contributing to the reduction of the risks (extrinsic adaptation), such as socioeconomic development or improved health-care services.[8] In a warming climate, the reduction in heat-related mortality risks is likely to be the result of a combination of both adaptation processes, but an eventual decrease in vulnerability to cold temperatures in the context of rising temperatures would only be explained by non-climate driven mechanisms.

To date, many studies[9–12] have reported a reduction in the RR of mortality due to heat across a number of settings, mostly in developed countries, despite the observed rise in temperatures, and the associated increase in the frequency, intensity, and duration of extreme heat events. By contrast, some evidence[13,14] suggests that the risk of cold-related mortality has declined in recent years, but few studies have assessed the impact of cold temperatures and evidence remains inconclusive.[15] Moreover, little is known about the effect of cold and heat exposure on the risk and impact (ie, heat-attributable mortality and cold-attributable mortality) among population subgroups, and particularly the most susceptible populations by sex, age, and cause of death. From a public health perspective, analysis of cause-specific mortality is more important than analysis of all-cause mortality since total mortality includes many causes of death that have a weak association with temperature, which might hide diverging patterns between different types of cause-specific mortality, and because the mechanisms by which ambient temperatures trigger mortality might vary for different causes of death.

In this study, we assessed sex-specific and age-specific trends in heat-related and cold-related cardiovascular disease mortality between 1980 and 2016 in Spain, where a rapid increase in annual temperatures (0·33°C per decade) has been observed since 1980. Findings from this study have important implications for health policies designed to adapt to warming temperatures in a country that has been characterised as a major climatic hotspot within the Mediterranean region.[16]

Methods

Data sources

For this country-wide time-series analysis, we extracted daily cardiovascular disease mortality data (as the primary cause of death) disaggregated by sex, 15-year age groups (0–14, 15–29,..., 75–89, ≥90 years), and province for the study period of Jan 1, 1980, to Dec 31, 2016. Data were extracted from the Spanish National Institute of Statistics. Causes of death were coded by the International Classification of Diseases, ninth revision (ICD-9) codes 390–459 for the years 1980–98 and ICD tenth revision (ICD-10) codes I00–I99 for the years 1999–2016, but both classifications contained the same disaggregation of causes of death. No obvious differences in cardiovascular mortality from specific diseases were identified between years 1998 (using ICD-9) and 1999 (using ICD-10; appendix p 6).

We obtained daily mean temperatures from the E-OBS gridded dataset (version 16; resolution of 0·25°×0·25°) from the European Climate Assessment and Dataset, and transformed these temperatures into regional estimates.[17] Both mortality and temperature datasets had no missing values.

Statistical analysis

Ambient temperatures are mainly correlated with cardiovascular and respiratory diseases, but the two disease types have evolved differently during the study period (1980–2016) in Spain,[12] and therefore, we separated the analyses for a more detailed description of their evolution, their relationship with temperatures, and the recent evolution with warming conditions. Statistical analysis was done in two stages. We first applied standard time-series quasi-Poisson regression models allowing for overdispersion for the whole study period (1980–2016) and data subsets of 15-year moving periods (1980–94, 1981–95,..., 2002–16) in each of the 48 Spanish provinces to derive estimates of province-specific temperature–mortality associations, reported as RR by sex and age group. The models included a natural cubic B-spline of time with 8 degrees of freedom (df) per year to adjust for seasonal and long-term trends, and a categorical variable to control for the day of the week. We used a distributed lag non-linear model to model the associations between temperature and mortality. This model is based on the definition of a cross-basis function combining exposure–response and lag-response associations.[18] We modelled the exposure–response curve with a quadratic B-spline, with one internal knot placed at the 75th percentile of the daily temperature distribution, and the lag-response curve was modelled with a natural cubic B-spline with an intercept and three internal knots placed at equally spaced values in the log scale. We extended the lag period to 21 days to account for the long-delayed effects of cold temperatures and short-term harvesting (ie, deaths brought forward by only a few days due to temperature).[19] The overall effect of temperature on a specific day on the RR of death was defined as the sum of the effects on that day and the 21 subsequent days. We did not use additional knots for the exposure–response function (ie, tenth and 90th percentiles[19]) because the estimates of RR at extreme warm and cold temperatures were not sensitive to the choice of only one internal knot. The Poisson regression model for the whole study period was as follows:

$$\text{Log}\,E\,(Y)\text{=intercept} + cb + dow + \text{S (time, 8 df} \times \text{year)}$$

where Y denotes the series of daily mortality counts; cb the cross-basis matrix produced by distributed lag non-linear model; dow the day of the week; and S the natural cubic B-spline of time. The modelling choices were tested in sensitivity analyses by varying the number of knots in the exposure–response function, the number of lag days, and the number of degrees of freedom used to control for the seasonal and long-term trends (appendix pp 204, 205).

In the second stage, we did a multivariate random-effects meta-analysis to estimate the mean RR values

See Online for appendix

For more on the **E-OBS gridded dataset** see http://ensembles-eu.metoffice.com

For the **European Climate Assessment and Dataset** see http://www.ecad.eu

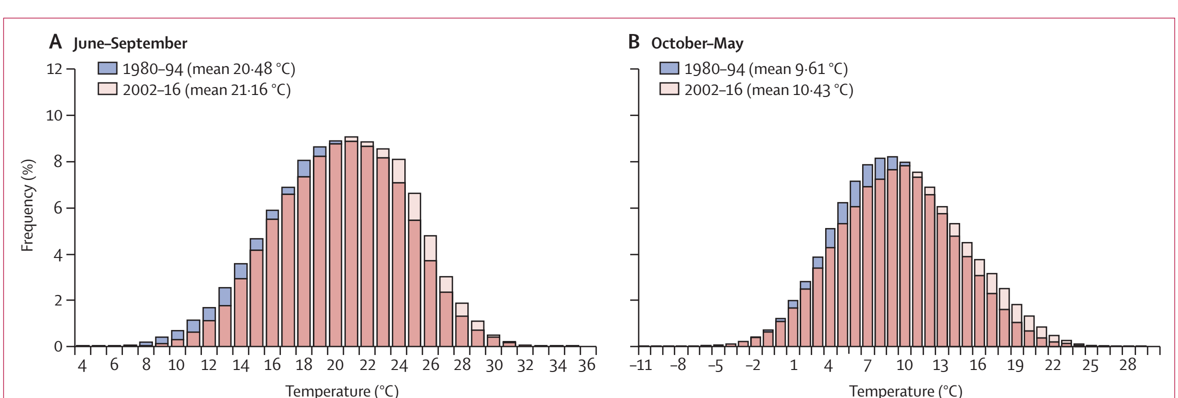

Figure 1: **Distribution of daily mean temperatures in Spain between 1980 and 1994 and 2002 and 2016**
Daily mean temperatures between June and September (A) and between October and May (B).

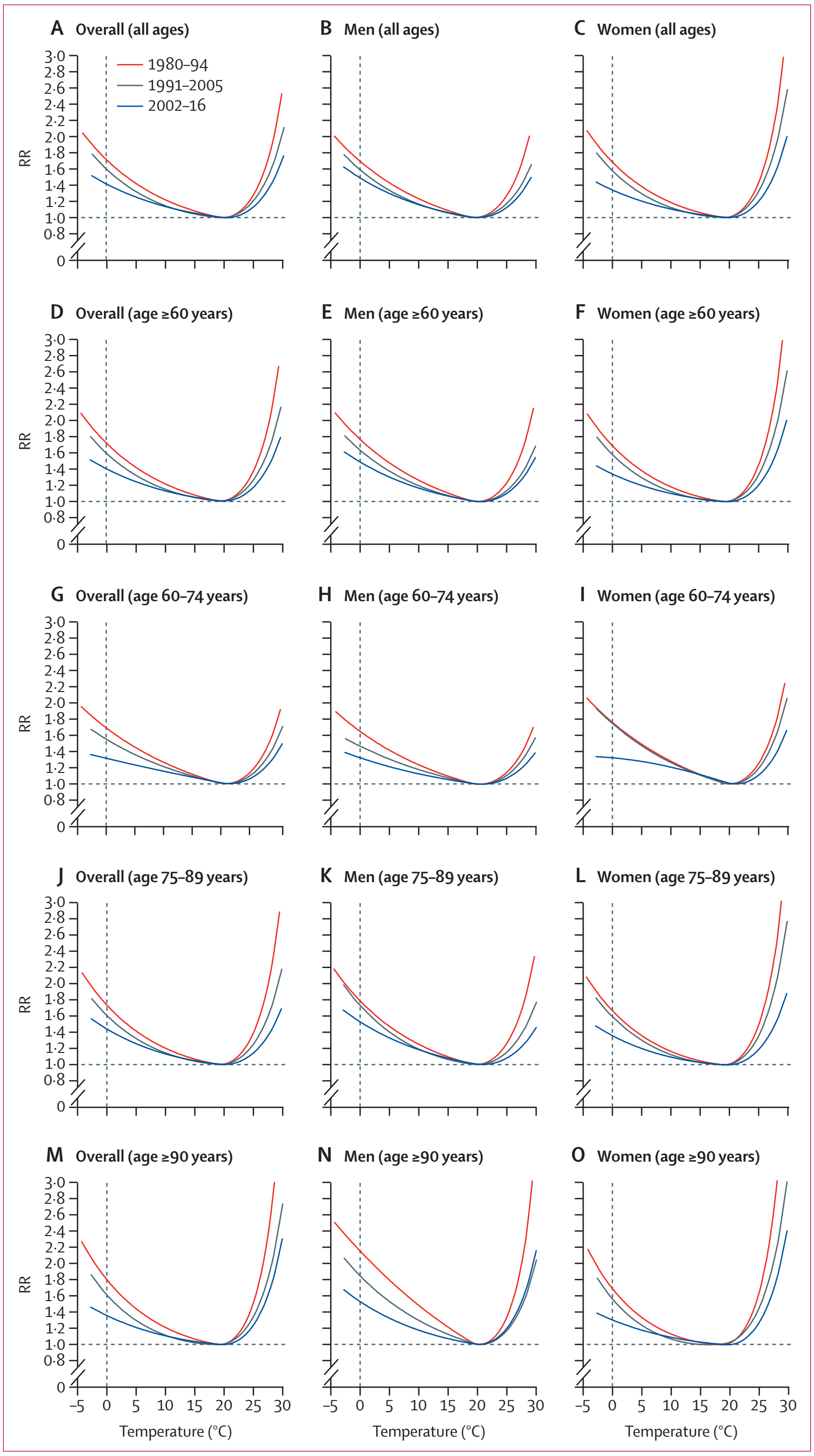

Figure 2: **RR of death from cardiovascular diseases in Spain for 15-year time periods between 1980 and 2016**
95% empirical CIs are shown in the appendix (pp 9, 10). RR=relative risk.

associated with the temperature–mortality curves across provinces,[20] and to derive the best linear unbiased prediction of the temperature–mortality associations in each location. We then extracted the minimum mortality temperature from the country-level and province-specific RR curves.

The mortality burden attributable to non-optimum temperatures by period and province, reported as the attributable fraction of deaths, was estimated using the methodology of Gasparrini and Leone.[21] The overall RR corresponding to each day of the series was used to calculate the attributable fraction of deaths on that day and the next 21 days. We then computed the daily attributable number of deaths by multiplying the daily attributable fraction by the daily number of deaths. The overall number of attributable deaths caused by non-optimum temperatures was given by the sum of the contributions from all days of the series with temperatures higher or lower than the value of minimum mortality temperature derived from the best linear unbiased prediction, and its ratio with the total number of deaths provided the temperature-attributable fraction. The components attributable to cold and warm temperatures were in turn computed by separating the associations corresponding to days with temperatures lower or higher than the minimum mortality temperature, respectively. We calculated 95% empirical CIs (eCIs) of attributable risk using Monte Carlo simulations.

To ensure that the variation in minimum mortality temperature was not an important factor explaining the temporal changes in heat-attributable and cold-attributable deaths and the differences between sexes and age groups, we alternatively computed the attributable fractions for reference ranges of temperatures (ie, temperatures warmer than the 85th percentile for the definition of heat-related mortality, and colder than the median for cold-related mortality). We also considered the same reference point for computing the heat-attributable and cold-attributable fractions for both men and women (ie, the highest minimum mortality temperature for men and women in each province by age group).

We did not assess the associations between temperature and cardiovascular mortality specifically for individuals younger than 60 years because of the small number of daily death counts reported for those age ranges in most provinces, which led the model fitting to fail. Instead, we analysed data for individuals aged 60–74, 75–89, and 90 years and older because the number of deaths among these age groups was large enough to achieve model convergence, and because they represent the majority of cardiovascular deaths in Spain (93%).

All statistical analyses were done with R software (version 3.4.3) using the packages *splines* (*"bs"* for quadratic splines and *"ns"* for natural cubic splines), *dlnm* (for the first-stage regression), and *mvmeta* (for the second-stage meta-analysis).

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data and

had final responsibility for the decision to submit for publication.

Results

We collected data from 48 provinces in mainland Spain and the Balearic Islands between Jan 1, 1980, and Dec 31, 2016 (appendix p 4). The dataset included 4 576 600 cardiovascular disease deaths (38·2% of deaths due to natural causes). Cardiovascular mortality rates largely decreased over the study period for both men and women, and for all the age groups, particularly among people aged 90 years or older (appendix p 5). The decline in cardiovascular mortality was due to the reduction in deaths from cerebrovascular diseases, atherosclerosis, and acute myocardial infarction observed over the study period (appendix p 6). In parallel, the distribution of hot and cold temperatures has shifted towards higher values, generally with more moderate and extreme warm days and fewer moderate and extreme cold days between 2002 and 2016 than between 1980 and 1994 (figure 1).

Temperature-related cardiovascular disease mortality curves by sex and age group for the whole study period had an asymmetric U or V shaped curve (appendix pp 7, 8), indicating a monotonically increasing mortality risk for temperatures higher and lower than the case-specific minimum mortality temperature. The slope for warm temperatures was in all cases steeper than the slope for cold temperatures, and varied by sex and age group. The slopes for women were steeper than those for men and the slopes for older age groups (75–89 years and ≥90 years) were steeper than those for the younger age groups. By contrast, the slopes for cold temperatures were slightly steeper for men than for women, with the exception of the 60–74 year age group, and showed no clear pattern by age group.

All temperature–mortality risk functions showed a substantial reduction in risk of cardiovascular death at both hot and cold temperatures during the study period (figure 2; appendix pp 9–99). For example, the overall RR of death from cardiovascular disease at the first temperature percentile decreased from 1·618 (95% eCI 1·558–1·681) during the 1980–94 time period (first percentile 1·20°C) to 1·348 (1·289–1·409) during the 2002–16 time period (first percentile 1·65°C), and from 1·515 (1·416–1·621) during the 1980–94 time period to 1·277 (1·226–1·330) during the 2002–16 time period at the 99th percentile (99th percentiles 26·27°C [1980–94] and 26·57°C [2002–16]; figure 2A). The RR corresponding to the first temperature percentile (first percentile 1·41°C) for the whole study period decreased from 1·702 (1·633–1·775) between 1980 and 1994 to 1·408 (1·337–1·484) between 2002 and 2016, and the RR corresponding to the 99th temperature percentile (99th percentile 26·36°C) decreased from 1·962 (1·770–2·174) between 1980 and 1994 to 1·457 (1·369–1·551) between 2002 and 2016.

Between 1980 and 2016, the minimum mortality temperature progressively increased for both sexes, and across all age groups (figure 3). The pooled overall minimum mortality temperature increased from 19·5°C in 1980–94 to 20·2°C in 2002–16, which is similar in magnitude to the observed mean temperature increase of 0·77°C that occurred between these two time periods. The minimum mortality temperature decreased with age, and, with the exception of the 60–74 year age group, was higher for men than for women.

The increase in minimum mortality temperature between 1980 and 2016 strongly correlated with the increase in mean temperatures observed for the same period (subperiod relationship slope range 0·90–1·35; figure 4). For the whole study period, the association between mean temperatures and minimum mortality temperatures for the 48 provinces was also strong and linear (slope range 0·88–1·01, p<0·001; appendix p 100). The magnitude of the association between mean

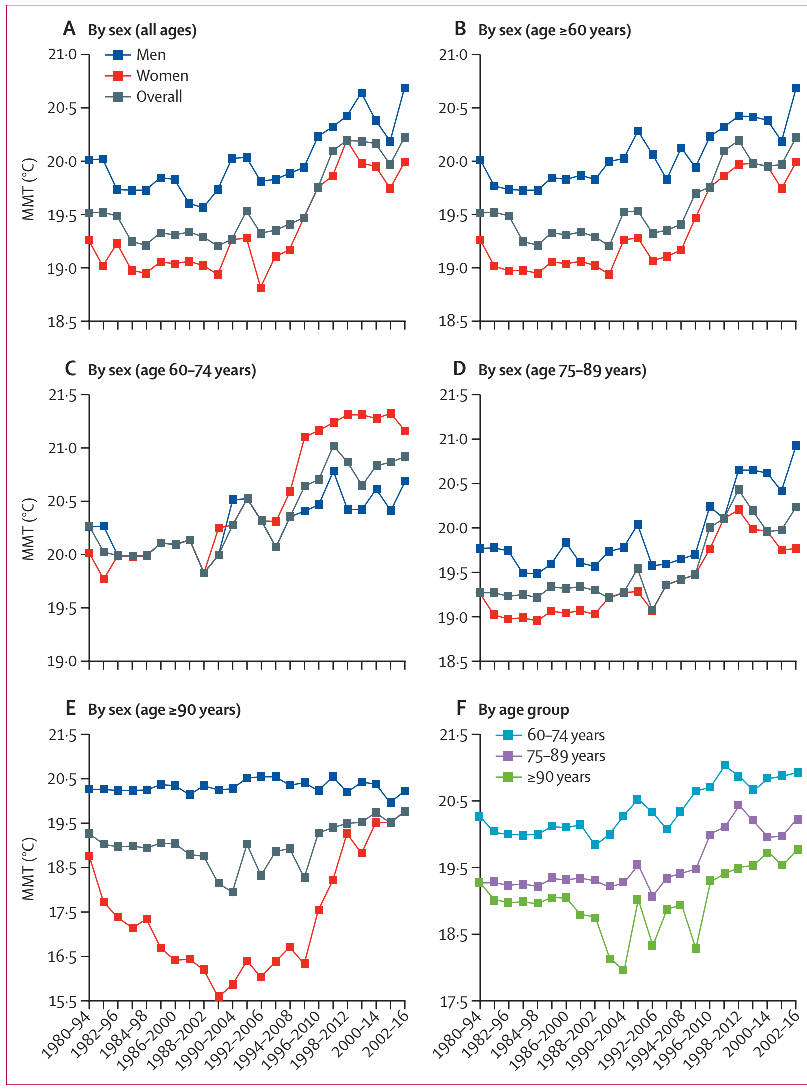

Figure 3: **Minimum mortality temperature for cardiovascular diseases by sex and age, 1980–2016**
MMT=minimum mortality temperature.

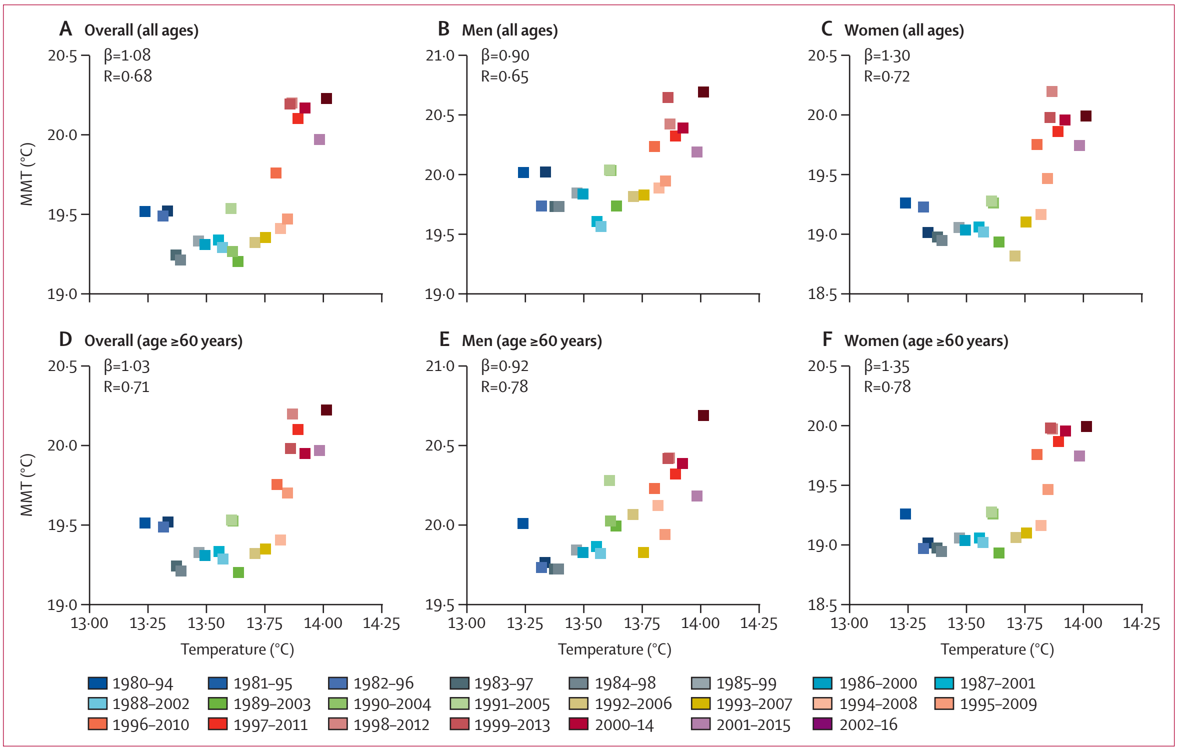

Figure 4: **Association between the mean temperature and minimum mortality temperature by time period**
MMT=minimum mortality temperature. β=slope. R=Pearson correlation.

temperature and minimum mortality temperature remained stable across the 48 provinces between the 23 subperiods of 15 consecutive years (appendix pp 101, 102).

Heat-attributable and cold-attributable fractions of cardiovascular mortality reduced over the study period for both sexes and across all age groups (figure 5, figure 6; appendix pp 103–99), which are largely explained by the large reductions in RR (figure 2). For example, for all age groups combined, between 1980–94 and 2002–16, the heat-attributable fraction decreased by –42·06% (95% eCI –44·39 to –41·06) for men and –36·64% (–36·70 to –36·04) for women, and the cold-attributable fraction was reduced by –30·23% (–30·34 to –30·05) for men and –44·87% (–46·77 to –42·94) for women (figure 5, figure 6). The attributable fraction due to heat was generally larger for women than men in all the age groups, and the attributable fraction due to cold temperatures was larger in men than women with the exception of the 60–74 year age group. The heat-attributable fraction increased with age for both sexes (figure 5G, H), whereas the cold-attributable fraction increased with age for men (figure 6G) and decreased for women (figure 6H). For all age groups combined, during the study period the between-sex differences due to heat decreased (figure 5A), whereas between-sex differences due to cold temperatures remained stable (figure 6A).

The temporal changes in heat-attributable and cold-attributable deaths and between-sex and between-age differences were not affected by the variation in the minimum mortality temperature (appendix pp 200–03).

All sensitivity analyses suggested that the results reported were not dependent on modelling assumptions.

Discussion

To the best of our knowledge, this is the first study to assess the temporal changes in the effect of ambient temperature on sex-specific and age-specific cardiovascular mortality risk and attributable fraction, and to determine whether adaptation to heat and cold occurred in the context of rapid climate warming. The attributable fraction of cardiovascular deaths due to warm temperatures was higher for women than men in all age groups, and the attributable fraction due to cold temperatures was higher in men than women, with the exception of the 60–74 year age group. Moreover, heat-related cardiovascular disease mortality increased with age for both sexes, and cold-related cardiovascular disease mortality increased with age for men and decreased for women. Our results also showed a progressive increase in the minimum mortality temperature for both sexes and across all age groups during the study period, and a strong reduction in risk of cardiovascular mortality and attributable fraction due to heat and cold temperatures. These results strongly support the hypothesis that the climate warming observed in recent decades in Spain has been accompanied by substantial adaptation to both hot and cold temperatures.

In our study, the minimum mortality temperature increased simultaneously with the mean increase in ambient temperature observed during the study period, for both sexes and across all age groups. This change in minimum mortality temperature is consistent with earlier studies of non-external causes of mortality and all-cause mortality done in France[22] and Sweden,[23] respectively. In France, the minimum mortality temperature increased by 0·4°C per 0·4°C increase in mean winter temperature, and per 0·6°C increase in summer temperature between 1982–95 and 1996–2009.[22] These findings support the hypothesis of human adaptation to increasing temperatures.[22] However, in our study, the concurrent timing of the increase in minimum mortality temperature and annual mean temperatures implies that the temporal evolution of heat-attributable and cold-attributable mortality essentially depends on the changes in the shape and slopes of the exposure–response curves above and below the minimum mortality temperature, rather than on the warming itself. The increase in minimum mortality temperature implies a time-varying definition of warm and cold temperatures, which parallels the shift in the temperature distribution towards warmer temperatures. We also found a strong positive spatial correlation between mean temperature and minimum mortality temperature, which has been widely reported elsewhere,[22,24] but additionally, we showed that this association has remained stable with time. Physiological and behavioural adaptation of populations to local climate conditions is the main potential explanation for the strong association between minimum mortality temperature and annual mean temperatures, both in time and in space.

The effects of warm and cold temperatures on mortality from cardiovascular diseases in Spain, either expressed as RR (ie, level of vulnerability) or attributable fractions, decreased over the study period for both sexes and generally for all age groups. Our results for warm temperatures are consistent with those reported in previous studies.[9,11,12,25] Results for cold temperatures are more difficult to discuss in the context of existing literature since less evidence is available[13,14] and that which exists remains inconclusive.[15] In many studies, the general reduction in risk and attributable mortality due to heat has been associated with socioeconomic development and structural transformations, such as improvements in housing conditions and health-care systems (eg, improved treatment of heat-related morbidity),[11,14] reduction in risk factors (eg, smoking, healthier diet),[9] and planned adaptation policies led by governments and public health agencies.[26,27] From a theoretical perspective, the increases in annual mean temperature and minimum mortality temperature have been similar in magnitude and thus would favour the

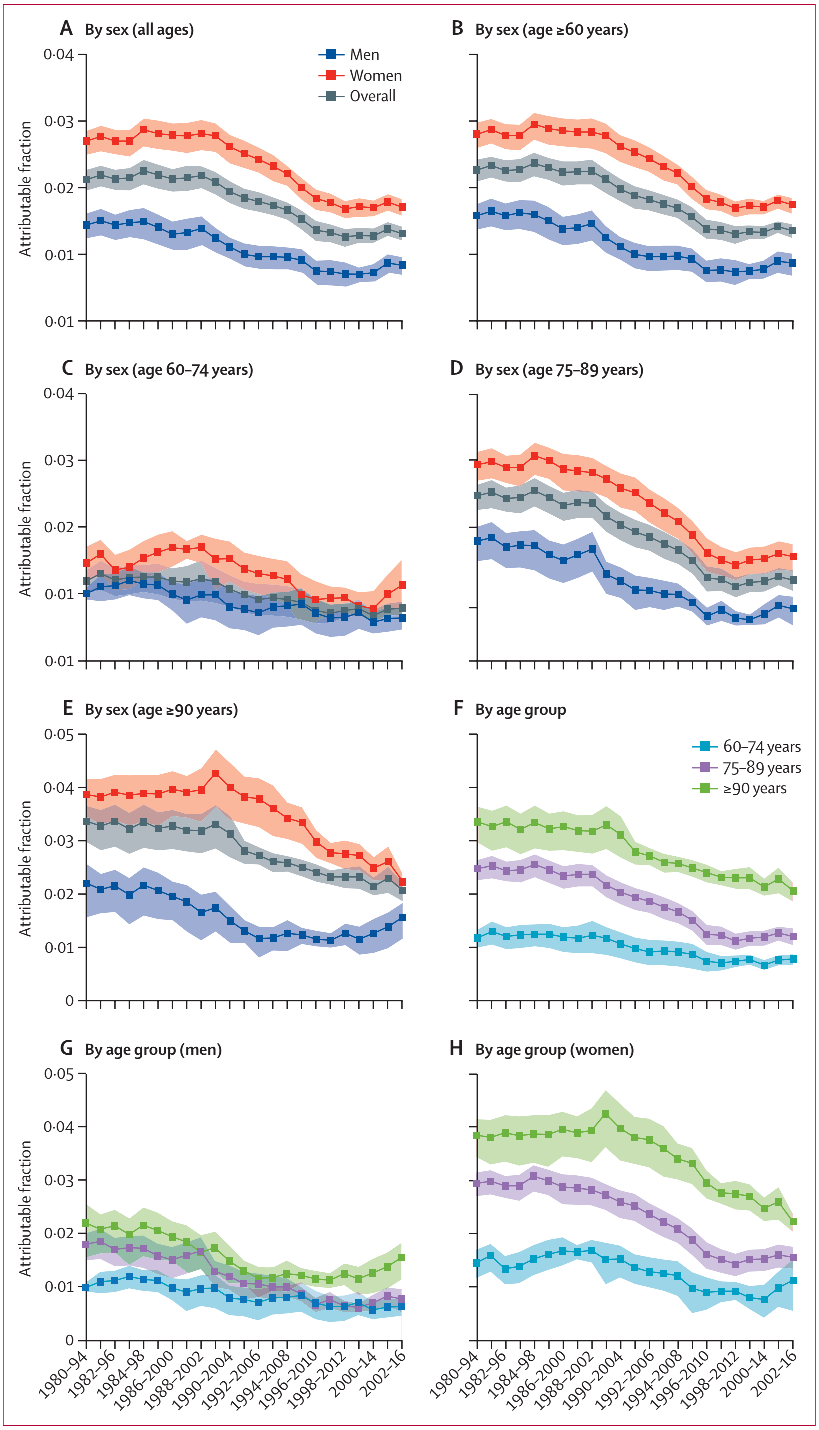

Figure 5: **Heat-attributable fraction of cardiovascular disease mortality in Spain by age and sex, 1980–2016**
Shaded areas represent the 95% empirical CIs.

view that the changes in vulnerability to heat among the Spanish population are the result of an acclimatisation response to the warming. Nevertheless, the reduction in risk of mortality due to cold temperatures also highlights the importance of socioeconomic development, improved

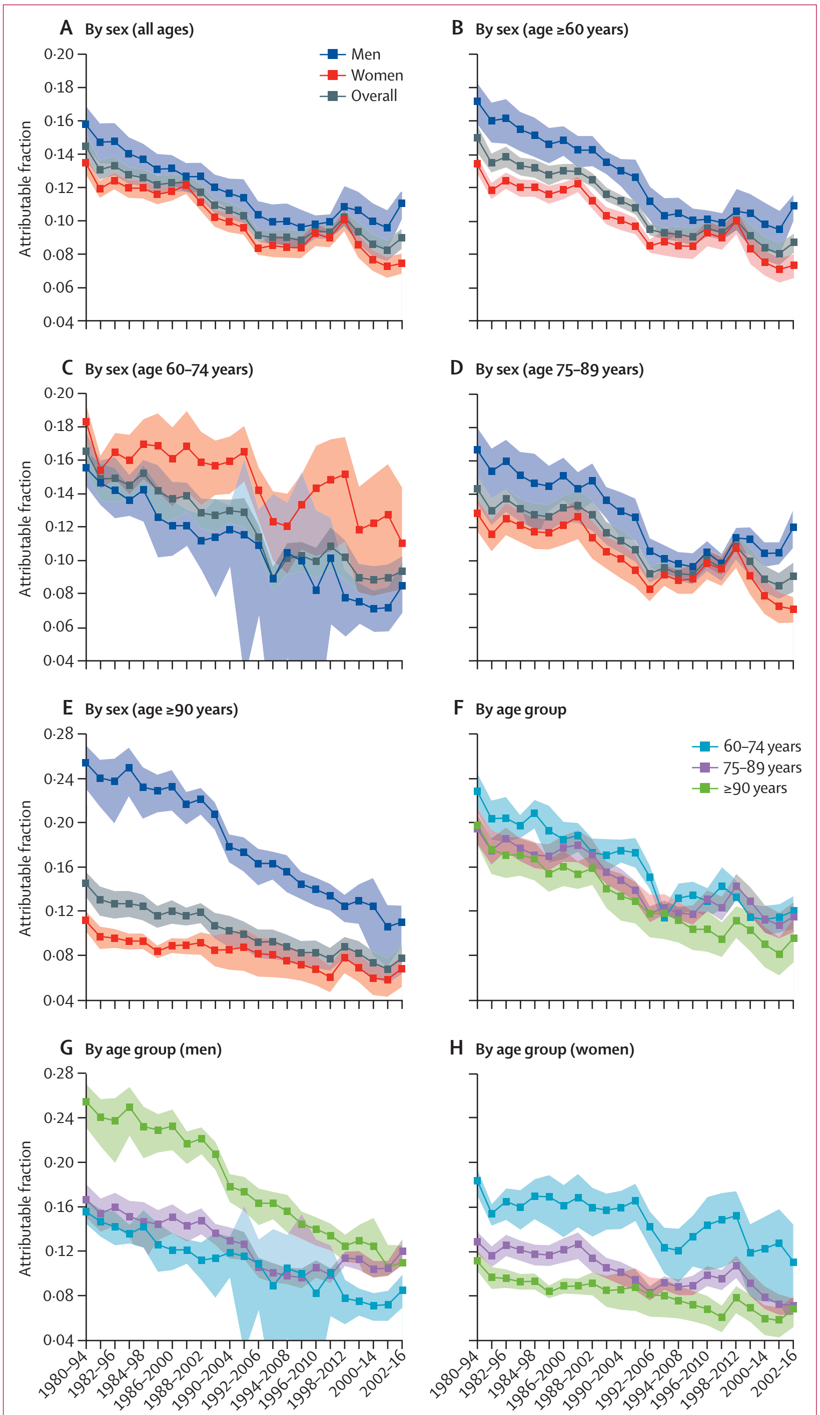

Figure 6: **Cold-attributable fraction of cardiovascular disease mortality in Spain by age and sex, 1980–2016**
Shaded areas represent the 95% empirical CIs.

health care, increased life expectancy and quality, and planned interventions.[13,15] In Spain, the gross domestic product (from €8789 per capita in 1991 to €22 813 in 2009), the life expectancy at birth (from 77·08 years to 81·58 years), health-care expenditure (from €605 per capita to €2182), social protection expenditure (from €1845 per capita to €5746), and the number of doctors (from 3930 per 1 million inhabitants to 4760 per 1 million inhabitants) have all increased during the study period.[28] Additionally, the proportion of households with central heating increased from 25·83% in 1991 to 56·86% in 2011,[29] and the proportion of households with air conditioning increased from 4·16% in 1991[29] to 35·5% in 2008.[30]

Since the implementation of the National Plan for Preventive Actions against the Health Effects of Excess Temperatures[31] by the Spanish Ministry of Health in 2004, in response to a heatwave in the summer of 2003, a rapid decrease in heat-related mortality was observed, specifically between 1989–2003 and 1998–2012. However, it is difficult to infer whether this accelerated decline in heat-related mortality is directly associated with the introduction of the National Plan[31] because this measure is only activated in the case of extreme heat events, whereas most of the heat-attributable burden is caused by moderate warm temperatures.[12]

In this study, the attributable fraction of deaths by sex and age group differed for warm and cold temperatures. The attributable fraction due to warm temperatures was higher for women than men across all the age groups, whereas the attributable fraction due to cold temperatures was higher among men than women across all ages, with the exception of the 60–74 year age group. Moreover, heat-related mortality increased with age for both sexes and the cold-related mortality increased with age for men and decreased for women. The findings of previous studies with regard to differences in temperature-related mortality between sex and age groups have been contradictory. Some studies have shown that men are more susceptible to cold and heat than women, whereas other studies have reported the opposite.[32,33] This spatial heterogeneity might be a result of differences in socioeconomic, cultural, and health-related factors. With respect to the effect modification by age, older people (aged ≥60 years) are considered the most at-risk population for heat,[11,34,35] whereas differences between age groups with regard to cold temperatures are found to be less conclusive.[32] For example, RRs for cold-related cardiovascular mortality were higher among younger age groups (aged <65 years) than older age groups (aged ≥65 years) in the USA,[34] Japan,[36] or South Korea.[35]

The underlying physiological mechanisms by which warm and cold temperatures trigger cardiovascular mortality are not well understood, but seem to be largely mediated by a thermoregulatory pathway. Several studies[37] have identified age-related changes in thermoregulation in response to heat and cold stress. During heat exposure, older individuals (aged ≥60 years) generally respond with attenuated sweat gland outputs, reduced blood flow to the skin, smaller increases in cardiac outputs, and less redistribution of blood flow from the splanchnic and renal circulations compared with younger individuals. These responses seem to be compatible with the increased risk of cardiovascular mortality with age for both men and women. Furthermore, during exposure to cold temperatures, older individuals generally respond with a reduced peripheral vasoconstriction (implies increased heat loss) and decreased metabolic heat production compared with younger individuals, although the ability to maintain body temperature does not differ with age among women.[38] These age-specific differences in thermoregulatory responses to cold exposure might explain some of the diverging patterns in the effects of cold temperatures observed between men and women in our study.

Sex has also been linked to physiological differences in thermoregulation, which might explain some of our results. Women have been reported to have a higher temperature threshold above which sweating mechanisms are activated, and a lower sweat output than men, which results in less evaporative heat loss and therefore a larger susceptibility to the effects of heat.[39,40] Conversely, men have larger decreases in core body temperature when exposed to cold,[41,42] which might explain the higher risk of cardiovascular mortality observed in response to cold temperatures.

Our study had two main limitations. We could not control for ambient air pollution or relative humidity in the models due to paucity of data, and therefore, we do not know the extent to which values, trends, and subgroup differences are affected by temporal changes in these factors. Although the available literature on the confounding effect of air pollution shows modest[34,43] or no modifying effect,[44] the effects of warm and cold temperatures on mortality remain unchanged when relative humidity is accounted for.[45] The use of combined indices of temperature and humidity, such as apparent temperature, did not predict mortality more accurately than the single measure of temperature,[46] and the assessment of the effect of temperature and humidity separately showed that humidity does not affect mortality.[47] In our study we did not describe the drivers of the observed reduction in heat-related and cold-related cardiovascular mortality in Spain, since this will be addressed in a future study.

Contributors

HA designed the study, did the statistical analysis, interpreted the results, and wrote the original draft. JB provided the data and contributed to the statistical analysis, the interpretation of the results, and drafting of the manuscript. DD contributed to the interpretation of the results and the drafting of the manuscript. All authors contributed to the submitted version of the manuscript and approved the final version.

Declaration of interests

We declare no competing interests.

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