Universitat Autònoma de Barcelona

TRENDS IN TEMPERATURE-RELATED MORTALITY IN SPAIN: ASSESSING EARLY ADAPTATION TO WARMING CLIMATE

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PHD THESIS

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PREFACE

The present PhD thesis consists of a compilation of academic publications in peer-reviewed journals focusing on the same research topic. The PhD candidate is the first author in all of them and, as such, he independently designed the studies, did the statistical analyses, interpreted the results and wrote the articles. These contributions are preceded by an introduction to the research topic and followed by a final discussion of the outcomes of the investigation. The introduction in Part I puts the *research in context*, formulates the *research questions, hypotheses and objectives* of the investigation, and presents an *overview of the publications* in Part II of the thesis. Finally, Part III provides the *conclusions* arising from the results obtained in the empirical studies, and describe the main *limitations* of the investigation along with the potential lines for *future research*.

AGRAÏMENTS

En primer lloc desitjo expressar el meu enorme agraïment als directors d'aquesta tesi doctoral, els Drs. Daniel Devolder i Joan Ballester, per la seva sàvia guia i plena dedicació durant els últims quatre anys. També vull expressar la meva gratitud al Dr. Albert Esteve per brindar-me la gran oportunitat de desenvolupar la meva investigació en el si del Centre D'estudis Demogràfics amb el suport financer de la Secretaria d'Universitats i Recerca de la Generalitat de Catalunya i del Fons Social Europeu; als Drs. Iñaki Permanyer i Juan Antonio Módenes per formar part de les comissions de seguiment de doctorat; als Drs. Xavier Rodó i Joan Ballester per acollir-me al Programa en Clima i Salut de l'Institut de Salut Global de Barcelona; a Pau Rubio, Marta Solano, Carol Pozo i la resta de l'equip de premsa de l'ISGlobal per la difusió dels resultats de la meva recerca; a Soco Sancho i Esther Brinquis pel seu suport en tot tipus de tràmits acadèmics i administratius; i a totes aquelles persones amb les que he estat interactuant al llarg d'aquest anys. Per últim, vull donar les gràcies als meus pares i germans per ajudar-me a arribar fins aquí.

ABSTRACT

Anthropogenic greenhouse gas emissions have increased annual temperatures in Spain by around one degree Celsius since 1980. However, little is known about the extent to which the association between temperature and human mortality has been modified as a result of the rapidly warming climate. The overarching aim of this PhD thesis is to assess the recent trends in the mortality risk and burden associated with heat and cold, and in this way, have a better understanding of an eventual early adaptation response of the Spanish society to the negative consequences of rising temperatures. For this purpose, the research is structured around three empirical studies published in academic journals, which constitute the core of the present PhD dissertation. Overall, results from these studies point to a reduction in the mortality risk and burden associated with warm and cold temperatures during the period 1980-2016. The reduction in the impact of heat on mortality could be compatible with an adaptive response specifically addressing the negative consequences of climate change. Nevertheless, the simultaneous reduction in the impact of cold temperatures also highlights the importance of the mechanisms of adaptation that are not necessarily related to climate change, such as socioeconomic development, improvements in health care and social services, or an increase in the awareness of the risks of the environmental factors, among many other factors.

RESUMEN

Las emisiones antropogénicas de gases de efecto invernadero han aumentado las temperaturas anuales en España alrededor de un grado centígrado desde 1980. Sin embargo, se sabe poco sobre el grado en qué la relación entre temperatura y mortalidad humana se ha visto modificada como consecuencia del rápido calentamiento del clima. El objetivo general de esta tesis doctoral es evaluar las tendencias recientes en el riesgo y carga de mortalidad asociada al calor y al frío, y de esta manera, determinar si existe una adaptación por parte de la sociedad española a las consecuencias negativas del aumento de las temperaturas. Para ello, la investigación se estructura en torno a tres estudios empíricos publicados en revistas académicas, que constituyen el núcleo de la presente tesis doctoral. En general, los resultados de estos estudios apuntan a una reducción en el riesgo y carga de mortalidad asociada a las temperaturas cálidas y frías durante el período de estudio 1980-2016. La reducción en el impacto del calor sobre la mortalidad podría ser compatible con una respuesta adaptativa que aborde específicamente las consecuencias negativas del cambio climático. Sin embargo, la reducción simultánea del impacto de las temperaturas frías también pone de relieve la importancia de los mecanismos de adaptación que no están directamente ligados al cambio climático, como el desarrollo socioeconómico, las mejoras en los servicios sanitarios y sociales, o una mayor concienciación sobre los efectos en la salud de los factores ambientales, entre muchos otros factores.

RESUM

Les emissions antropogèniques de gasos d'efecte hivernacle han augmentat les temperatures anuals a Espanya al voltant d'un grau centígrad des de 1980. No obstant això, se sap poc sobre el grau en què la relació entre temperatura i mortalitat humana s'ha vist modificada com a conseqüència del ràpid escalfament del clima. L'objectiu general d'aquesta tesi doctoral és avaluar les tendències recents en el risc i càrrega de mortalitat associada a la calor i al fred, i d'aquesta manera, determinar si hi ha una adaptació per part de la societat espanyola a les conseqüències negatives de l'augment de les temperatures. Per a això, la recerca s'estructura al voltant de tres estudis empírics publicats en revistes acadèmiques, que constitueixen el nucli de la present tesi doctoral. En general, els resultats d'aquests estudis apunten a una reducció en el risc i càrrega de mortalitat associada a les temperatures càlides i fredes durant el període d'estudi 1980-2016. La reducció en l'impacte de la calor sobre la mortalitat podria ser compatible amb una resposta adaptativa que abordi específicament les conseqüències negatives del canvi climàtic. No obstant això, la reducció simultània de l'impacte de les temperatures fredes també posa de relleu la importància dels mecanismes d'adaptació que no estan directament lligats al canvi climàtic, com el desenvolupament socioeconòmic, les millores en els serveis sanitaris i socials, o una major conscienciació sobre els efectes en la salut dels factors ambientals, entre molts altres factors.

CONTENTS

PART I INTRODUCTION

PART II ORIGINAL PUBLICATIONS

PART III FINAL COMMENTS

PART I

INTRODUCTION

1. RESEARCH IN CONTEXT

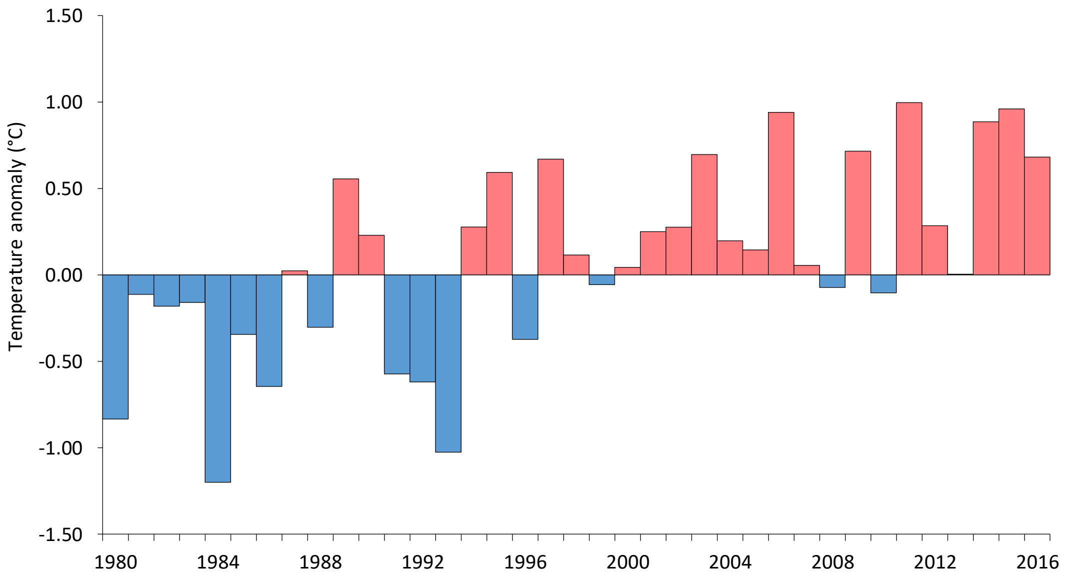
Climate warming and human health

The increase in atmospheric greenhouse gas concentrations due to human activities has induced a steep rise in global temperature since the mid-1970s[1], which, in turn, has been associated with more frequent, more intense and longer lasting extreme heat waves[2]. The decade 2006-2015 was the warmest on record before the begging of this thesis, with earth's mean surface (land and ocean) temperature 0.83-0.87 °C higher than the average over the 1850-1900 period[3]. The increase in Europe was larger than the global average, as average annual temperature increased by 1.45-1.59 °C for the same period[3]. Such a change in temperature has important considerations for population health, as both heat and cold exposure lead to increased risk of hospitalisation and death[4]. Warmer conditions are expected to contribute to an increase in heat-attributable morbidity and mortality, and to a concomitant decrease in cold-attributable hospitalisations and deaths around the world[5].

Panel 1: Evolution of the annual mean temperature in Spain

Spain arises as a major climatic hotspot within Europe because of local atmosphere-ocean-land feedbacks within the climate system[6]. Annual temperatures in mainland Spain and the Balearic Islands increased, on average, at a rate of 0.33 °C per decade since 1980 (figure 1). The warming was larger in summer (June-August: 0.39 °C/decade) than in winter (January-March: 0.23 °C/decade). The year 2011 was the warmest year in the series, with an average temperature of 15.6 °C, a value that is 1.0 °C higher than the annual average of the reference period 1981-2010.

Figure 1. Annual mean 2-meter temperature anomaly for years 1980-2016 relative to the average for the 1981-2010 reference period



Data source: E-OBS gridded dataset (https://www.ecad.eu)

Analytical approaches and methods in temperature-mortality studies

The available literature on the effects of ambient temperature on mortality has been rapidly growing in recent years, and particularly since the record-breaking summer 2003 heat wave in Europe, which was characterised by an unprecedented increase in mortality, with more than 70,000 premature deaths in western European countries alone[7]. These studies were characterised by the use of a range of analytical approaches and methods:

Effects of specific episodes

Some studies focused on the assessment of specific extreme weather episodes such as heat waves and cold spells. In the analysis of this kind of episodes, the mortality impact is generally quantified by comparing the observed number of deaths during the extreme event with a baseline usually derived from the same days in previous years (i.e., expected mortality)[7–9] or the other non-extreme days in the same month[10]. Alternatively, the excess in mortality is computed including an indicator variable for heat/cold wave days in a regression model[11] (see next paragraph). The comparison between studies was not straightforward given that they use different heat/cold wave definitions with regard to the temperature threshold, temperature variable (see the section "Temperature variables"), and duration of the event.

Effects of temperature

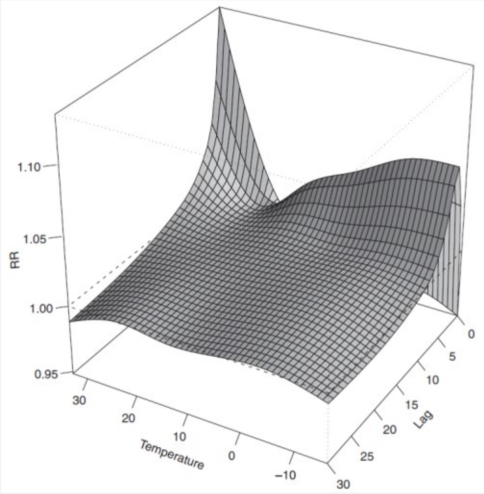
Other investigations offered, however, an assessment of the exposure-response association across the whole range of temperatures[11,12], thus providing quantitative estimates of both the cold and heat effects and the comfort temperature, also referred to as Minimum Mortality Temperature (MMT). In this kind of analysis, the daily variability of temperature and mortality are compared while controlling for seasonal and long-term trends in mortality, as well as other short-term time-varying confounders such as the day of the week, humidity or air pollution.

Effects of specific episodes and temperature

Only a few studies[11,13–15] have brought together both analytical approaches to decompose the effects of heat waves into: (a) the independent health risk of daily temperature levels, and (b) the added health risk due to the duration of extreme heat. This was done by including both a continuous term for temperature and a heat wave indicator variable in a regression model. Note that the evidence on the added heat waves effects on morality is mixed. Some studies reported that heat waves lead to an additional risk due to consecutive days of extreme temperatures[11,13], while others found that these effects are similar to what would be experienced if high temperatures days occurred independently[14,15].

Panel 2: Modelling temperature-mortality associations

The vast majority of studies assessing temperature-mortality relationships rely on time-series analysis using generalized linear models within the quasi-Poisson family. In this approach, the degree of association between daily counts of death and ambient temperature is computed while controlling for seasonal and long-term trends in mortality and other potential short-term time-varying confounder factors (humidity, air pollution, etc.). The non-linear and delayed associations between temperature and mortality are usually characterised with a distributed lag non-linear model (DLNM)[16]. This model is based on the definition of a so-called cross-basis function, which operates in a bi-dimensional space describing simultaneously the shape of the relationship along the exposure range (exposure-response function) and its distributed lag effects (lag-response function). The 3-D graph below shows estimates of relative risk (RR) of mortality along temperature range (exposure-response relationship) and lags (lag-response relationship) obtained from a DLNM.



Source: Gasparrini et al. (2010)

Temperature variables

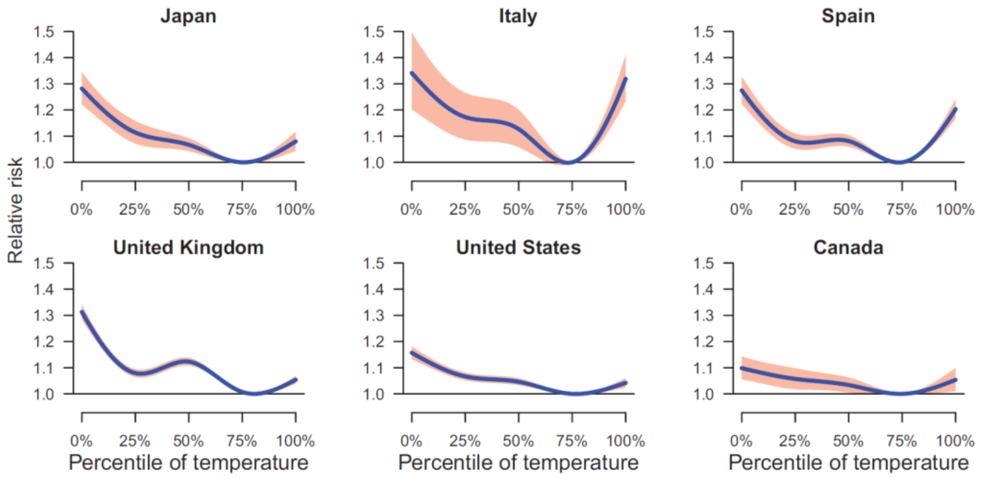
The characterisation of the exposure to ambient temperature in urban areas usually rely on observations from the nearest meteorological station, although gridded data from climate models and reanalyses at different spatiotemporal resolutions are increasingly used to achieve greater spatial coverage (i.e., rural areas)[17,18] and to inspect local or small-scale mortality effects in large cities or metropolitan areas[17]. Daily mean near-surface air temperature, either with or without control for confounding by relative humidity, is the most commonly used temperature variable to predict daily mortality, as it summarises the overall exposure throughout the entire day. Alternatively, combined indices of air temperature and humidity, such as apparent temperature[19,20] or humidex[9], are used as a measure of perceived temperature and heat stress, respectively[21]. However, no evidence exists for improved prediction by temperature indices in comparison to a single temperature variable[21,22]. On average, the different temperature variables had a similar predictive ability due to their strong correlation[21].

Temperature-mortality relationship

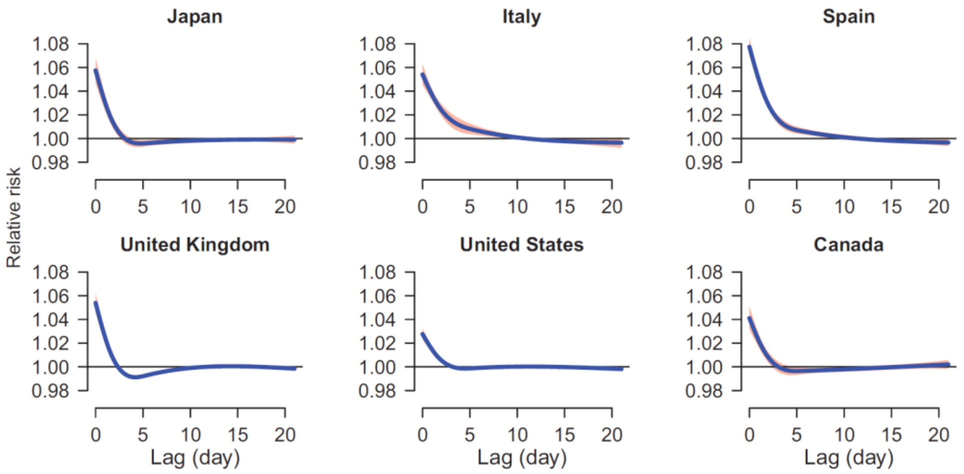
Previous epidemiological studies, focusing mainly on urban areas from extratropical countries, have reported an asymmetric U-, V- or J-shaped relationship between daily temperature and mortality, with increased relative risk (RR) for temperatures above and below the MMT[12,23] (e.g., figure 2a). This relationship results in a marked seasonality of temperature-related mortality, with higher mortality in winter than during other parts of the year and slight upturn in the summer due to heat. In general, the increase in heat-related risk is immediate and occurs in the few next days (e.g., figure 2b), while the increase in cold-related risk lasts up to three or four weeks with a protective effect at lags of 0-1 days[12] (e.g., figure 2c). The degree to which the association between temperature and mortality is related to the temperature recorded on a specific day, or due to the variation in temperature between and within days, was also investigated[24]. Results from this analysis showed the almost entire contribution of daily temperature to the mortality risk, while temperature variation (inter-/intraday) played a minor and inconsistent role[24].

Figure 2. Temperature-mortality relationship in different countries. The shaded areas represent 95% CIs.

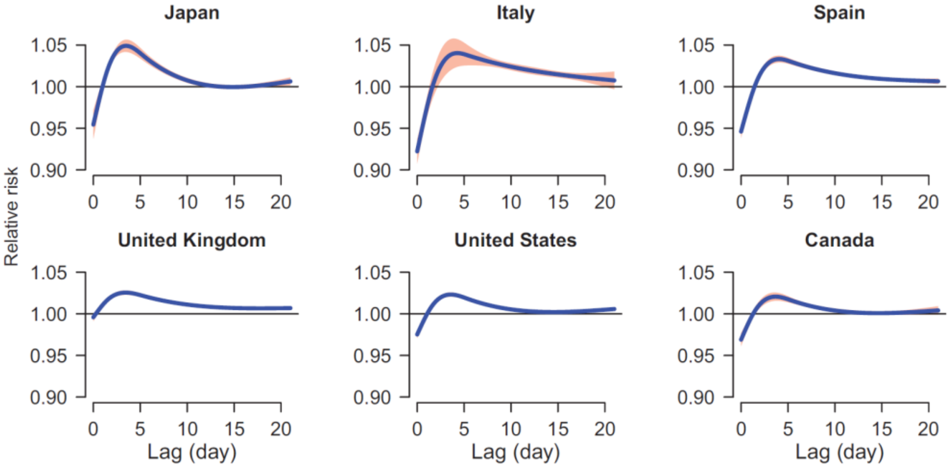
a) RR of non-accidental mortality over lags of 0-21 days



b) RR of non-accidental mortality by lag at the 99th percentile of the daily temperature distribution



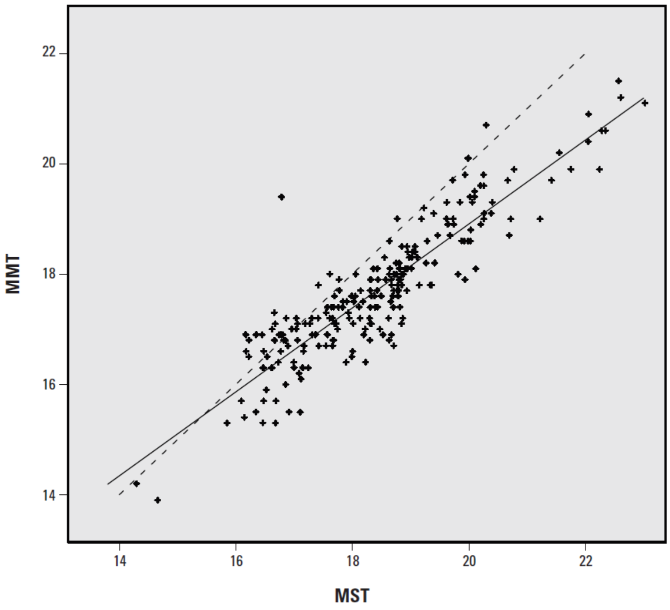
c) RR of non-accidental mortality by lag at the 1st percentile of the daily temperature distribution



Source: Guo et al. (2014)

The MMT typically ranges between the 60th and the 90th percentile of the daily distribution of temperatures in all the analysed countries or regions[12,23], and it is strongly correlated with the local climatological temperature[18,23] (e.g., figure 3). This geographical variation of MMT with temperature is interpreted in terms of physiological and behavioural adaptation of populations to the local climate[18]. In addition, changes over time in the MMT have also been documented[18,25], which is seen as an indicator of adaptation to climate warming. From a practical perspective, the MMT is commonly used as a reference point for the calculation of the mortality burden due to ambient temperatures, and to separate between heat (temperatures higher than MMT) and cold (temperatures lower than MMT) contributions[26].

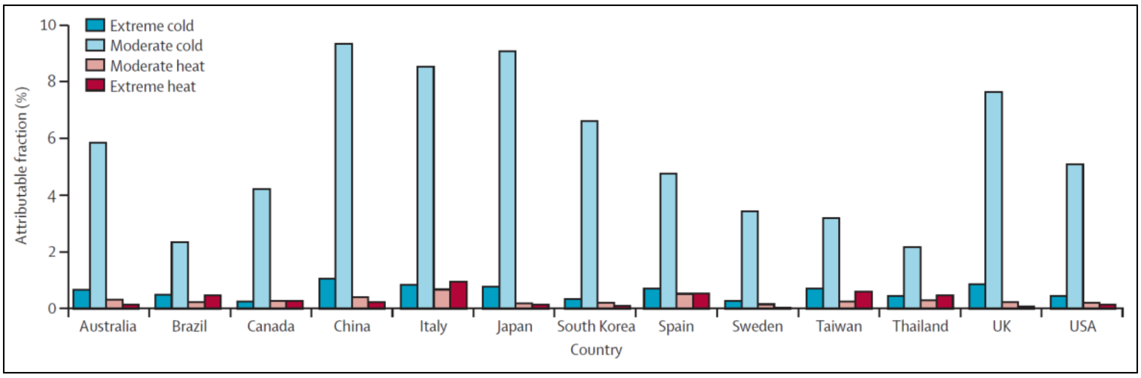
Figure 3. Geographic variations of MMT versus mean summer temperature (MST) in France. Each point represents the MMT and MST values in one of the 228 locations, during period 1968–2009. Solid line: regression line. Dotted line: MMT = MST



Source: Todd and Valleron (2015)

According to the best available global estimates[26], 7.71% (95% empirical CI 7.43-7.91) of all-cause mortality is directly attributable to ambient temperatures, with substantial differences between the relative contributions from heat and cold and from moderate and extreme temperatures. Cold is responsible for most of the temperature-attributable deaths (7.29%, 7.02-7.49), while heat only explained a small fraction (0.42%, 0.39-0.44). Extreme cold and hot temperatures contributed just 0.86% (0.84-0.87) of total mortality, while the prolonged exposure to moderate cold temperatures caused the vast majority of deaths (6.66%, 6.41-6.86). However, the total mortality burden largely varied across countries, reflecting differences in climate conditions and population vulnerability to ambient temperatures. The highest attributable mortality was found in Italy, China, and Japan, and the lowest estimates in Thailand, Brazil, and Sweden. In Spain, ambient temperatures were responsible for 6.52% (5.82-7.16) of mortality, 5.46% due to cold (4.79-6.07) and 1.06% (0.96-1.16) due to heat.

Figure 4. Fraction of all-cause mortality attributable to moderate and extreme hot and cold temperature by country. Extreme and moderate high and low temperatures were defined with the MMT and the 2.5th and 97.5th percentiles of temperature distribution as cut-offs.



Source: Gasparrini et al. *The Lancet* (2015)

Individual and community-level risk factors

The mortality impact of temperatures vary widely among populations groups and locations due to differences in vulnerability associated with individual-level (i.e., age, sex, pre-existing health status, race, education, occupation) and community-level factors (population structure and density, air pollution levels, socioeconomic inequalities, housing conditions such as prevalence and usage of air conditioning and heating, green and blue spaces, availability of public health and social services)[27,28]. At the individual level, the elderly with pre-existing or chronic cardiovascular and respiratory diseases are most at the risk of death under heat and cold stress conditions for a range of physiological reasons (impaired thermoregulation)[19,20]. Differences by sex, race and educational attainment have also been reported for heat, with susceptibility to heat higher in women[27,29,30], black people[31,32], and less educated[33]. At the community level, several city characteristics were found to modify the effect of heat, with a higher mortality impact associated with increases in population density[34] and socioeconomic inequalities[35], whereas higher prevalence of air conditioning[34] and share of green and blue spaces (i.e., urban vegetation and water bodies)[36] were linked with a decreased mortality risk from heat.

Adaptation to warmer temperatures

Many studies project a progressive increase in heat-related deaths and a concomitant decrease in cold-related mortality over the next decades, resulting in a substantial positive or negative net effect in temperature related mortality depending on the location and magnitude of the warming[37]. This future scenario is, however, subject to large sources of uncertainty, especially regarding the capacity of the societies to adapt to warmer conditions[38,39]. Changes in the health impact, either expressed as absolute (attributable number) or relative (attributable fraction) excess of deaths, essentially arise from the combination of variations in both exposure and vulnerability (panel 3). A decrease in vulnerability, often expressed as RR, is linked to adaptation processes, either occurring by means of a physiological acclimatization response of the population to changing temperature or planned interventions (*causal adaptation*), or independently from the warming through a range of non-climate driven factors contributing to the reduction of the risks (*spontaneous or non-causal adaptation*), such as socioeconomic development or improved healthcare services. Although in practice it is difficult to distinguish between both adaptation processes, the reduction in heat-related mortality risks in a warming climate 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.

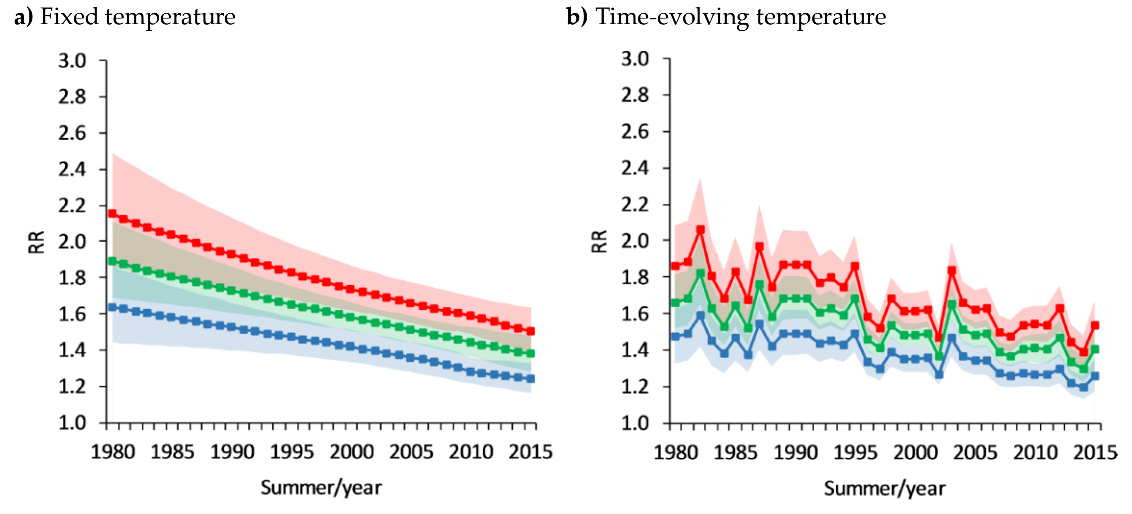
Panel 3: Changes in exposure, vulnerability and impact

The temporal change in the impact of temperature on mortality (attributable deaths) arises from the combination of the variation in two components: exposure (temperature) and vulnerability (RR of death).

$$\Delta \text{ Impact [attributable deaths]} = f(\ \Delta \text{ Exposure [Temperature]},\ \Delta \text{ vulnerability [RR]}\ )$$

Different definitions of adaptation are considered in the literature. In this thesis, the concept of adaptation is defined as the reduction of the risk of death. The change in vulnerability can be calculated in two different ways in a context of temperature change: calculating the evolution of the risks at a fixed value of temperature (figure 5a), or fixing a percentile and calculating the evolution of the risks at the time-evolving temperature that corresponds to the percentile in each subperiod (figure 5b). Importantly, the latter definition calculates the risks with regard to the time-evolving climatological values of the given location. Although both approaches are theoretically different, and they generate different quantitative results, they are qualitatively similar.

Figure 5. Temporal evolution of the relative risk of death during the summer season (June-September) in Spain for the years 1980-2015



Source: Achebak et al. (2018)

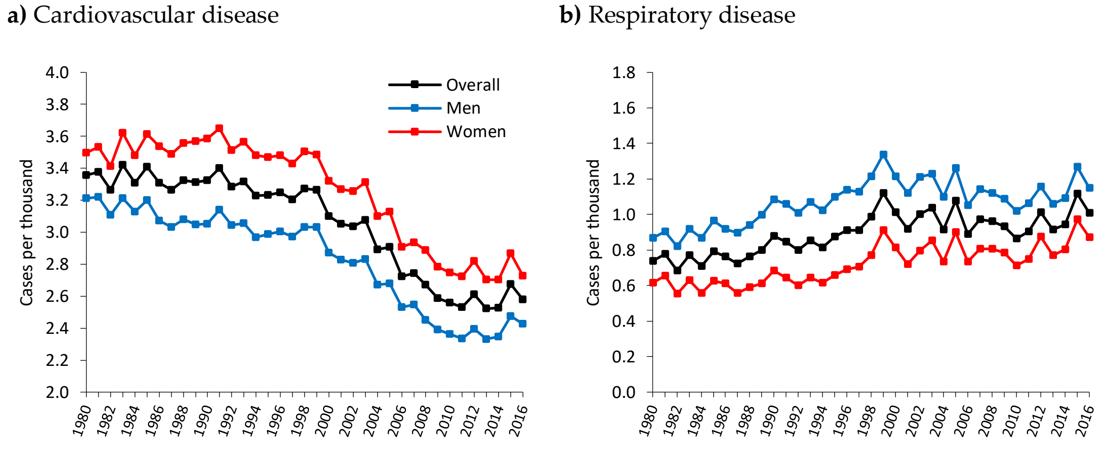
Temporal variation in the temperature-mortality associations

To date, a number of studies have reported reductions in mortality risk and burden associated with heat across a number of developed countries, despite the ageing of the population and the observed rise in temperatures[40–43]. By contrast, some evidence suggests that the risk of death associated with cold has declined in recent years, but few studies have assessed the impact of cold temperatures, and evidence remains inconclusive[43,44]. However, the analyses for both heat and cold were restricted to a limited number of representative cities in each country and, therefore, they did not provide information on rural populations. Moreover, little is known about the temporal changes in the effect of cold and heat exposure on the risk (i.e., RR) and impact (i.e., heat-attributable mortality and cold-attributable mortality) among population subgroups, and particularly the most susceptible populations by sex, age, and cause of death (e.g., from cardiovascular and respiratory disease). From a public health perspective, the analysis of cause-specific mortality is more important than the analysis of all-cause mortality since total mortality includes many causes of death that have no or 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.

Panel 4: Evolution of mortality from cardiovascular and respiratory diseases in Spain

Ambient temperatures are mainly correlated with several cardiovascular and respiratory diseases, but the two disease types have evolved differently during the last decades in Spain (figure 6), with a downward trend in cardiovascular deaths and an upward one in respiratory deaths. The underlying physiological mechanisms by which warm and cold temperatures trigger cardiovascular and respiratory morbidity/mortality are not well understood yet, but seem to be largely mediated by a thermoregulatory pathway.

Figure 6. Evolution of the mortality rate from cardiovascular and respiratory disease in Spain, 1980-2016



Data source: Spanish National Intitute of Statistics

Las but not least, even though it is well established that the impact of temperature on mortality varies by season in extratropical countries, being higher in winter than during other parts of the year[45], the possible change in the seasonal distribution of temperature-attributable mortality remains unexplored so far.

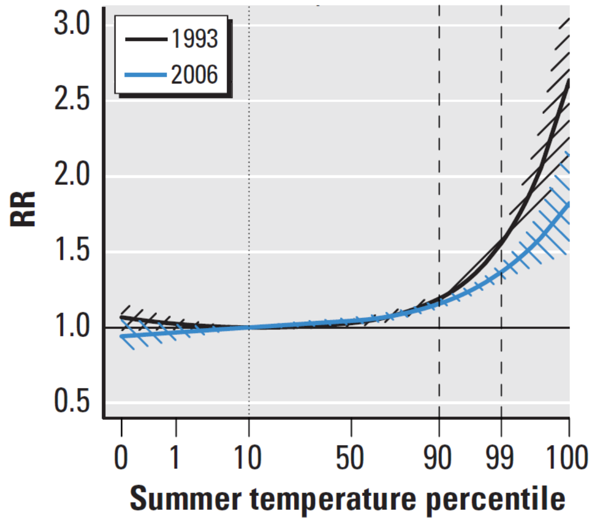
Panel 5: Temporal variation in the heat–mortality association in Spain

Results from a recent investigation showed a decline in heat-related mortality risk during the last decade in Spain[41], with RR associated to high temperatures significantly lower in 2006 compared with 1993 (figure 7). This suggests that the Spanish society is adapting to high temperatures despite the warming and the ageing of the population. Note that the proportion of people aged over 64 years increased from 11.6% to 15.0% in men and from 15.9% to 19.6% in women between 1991 and 2011 in the country[46].

The general downward trend in mortality risks in other countries has been attributed by some investigators to socioeconomic development and structural transformations, such as improvements in housing (higher prevalence and use of air conditioning) and healthcare services[40,41], or even to specific public health interventions (e.g., heat health warning systems)[47,48]. The large socioeconomic advances that occurred in Spain during the last decades might have largely contributed to the adaptive response to heat, thus reducing the effect of mortality risks over time. For example, the gross domestic product (from €8,798 per capita in 1991 to €22,813 in 2009), the life expectancy at birth (from 77.08 years to 81.58), the expenditure in healthcare (from €605 per capita to €2,182) and social protection (from €1,845 per capita to €5,746), and the number of doctors (from 3,930 per million inhabitants to 4,760 per million inhabitants) have all largely increased in Spain[49]. In addition, the prevalence of air conditioning, which has been postulated as a major contributor to the reduction in heat-related mortality in the United States[40], has also experienced a strong increase in Spanish households during the analysed period (from 5.3% in 1991[46] to 35.5% in 2008[50]).

Another potential contributing factor to the reduction of the mortality risks might have been the 'National plan for preventive actions against the effects of excess temperatures on health' from the Spanish Ministry of Health[51], which was implemented in 2004, just after the 2003 summer heat wave, in order to minimise the negative effects of summer extreme temperatures on the population's health, particularly among vulnerable groups such as the elderly, children, people with chronic disease, and disadvantaged persons.

Figure 7. **Temperature-mortality during summer months (June-September) for 1993 and 2006 in Spain, with 95% CIs.** Mortality is represented by daily counts of deaths for natural causes. The vertical lines represent the percentile of MMT (dotted) and the 90th and 99th percentiles of the summer temperature distribution (dashed).



Source: Gasparrini et al. *Environmental Health Perspectives* (2015)

2. RESEARCH QUESTIONS, HYPOTHESES AND OBJECTIVES

The overarching aim of this PhD thesis is to advance knowledge of the recent evolution in cardiorespiratory mortality risk and burden associated with ambient temperatures in Spain, and in this way, determine whether population adaptation to heat and/or cold has occurred in the current context of rapidly warming climate. Towards this aim, the present research was structured around a set of research questions (**Q**) and related hypotheses (**H**) and objectives (**O**).

Heat-mortality associations

Q1: Has the observed rise in temperatures contributed to an increase in heat-related mortality during the last decades in Spain, or instead, the changes in vulnerability to heat have completely offset the negative contribution of the warming? Are there differences by sex, age and cause of death?

H1: Heat-related mortality has decreased in Spain during the last decades despite the observed rise in temperatures.

O1: To assess the temporal variation of the impact of high ambient temperatures on mortality from circulatory and respiratory diseases by sex and age group, and to disentangle the contribution of rising temperatures and changes in vulnerability and adaptation.

Cold-mortality associations

Q2: Has cold-related mortality decreased during the last decades in Spain? And if so, was this decrease dominated by the contribution of the warming, or by the changes in vulnerability to cold? Are there differences by sex, age and cause of death?

H2: Cold-related mortality has decreased in Spain during the last decades as a result of population adaptation to cold.

O2: To study the temporal variation of the impact of cold temperatures on mortality from circulatory and respiratory diseases by sex and age group, and to disentangle the contributions of rising temperatures and changes in vulnerability or adaptation.

Seasonality of temperature-related mortality

Q3: Is climate warming affecting the seasonal distribution of temperature-related mortality? Is this different by sex, age or cause of death?

H3: There was no change in the seasonality of temperature-related mortality in Spain during the last decades.

O3: To analyse the potential changes in the seasonal cycle of temperature-related mortality from circulatory and respiratory diseases by sex and age group, and to disentangle the contributions of rising temperatures and changes in vulnerability or adaptation.

Minimum mortality temperature

Q4: Has the MMT shifted towards warmer values over time? Is this shift different by sex, age and cause of death?

H4: The MMT increased in parallel with the temperature rise observed in Spain over the last decades.

O4: To assess the temporal evolution of MMT in relation to annual temperature increase.

3. OVERVIEW OF THE PUBLICATIONS

The research activity carried out during the PhD programme is summarized in three independent peer-reviewed publications in academic journals, in which the candidate addresses the research questions formulated in the former section. The candidate is the first author in all of the published contributions and, as such, he independently designed the studies, did the statistical analyses, interpreted the results and wrote the research articles. These contributions are included in Part II of this thesis, but an overview of all of them is provided below.

Research paper I ***(Q1, H1, O1)***

In Achebak *et al.* (2018), the PhD candidate investigates whether the notable summer warming observed in Spain during the last decades has been associated with an upward trend in excess mortality attributable to heat or, on the contrary, a decrease in the population vulnerability to heat has contributed to a reduction of the mortality burden. Although the anthropogenic greenhouse gas emissions have increased summer (June-September) temperatures in the country by nearly one degree Celsius on average between 1980 and 2015, little was known yet about the extent to which the association between heat and human mortality has been modified by sex and specific diseases. The candidate analyses a dataset from 47 major Spanish cities for the summer months for the period 1980-2015, which includes daily temperatures and 554,491 deaths from circulatory and respiratory causes stratified by sex. He applies standard quasi-Poisson regression models, controlling for seasonality and long-term trends, and estimates the temporal variation in heat-related mortality with time-varying distributed lag nonlinear models. Results point to a reduction in the relative risks of mortality across the whole range of summer temperatures, which in turn contributes to a general downward trend in overall heat-attributable mortality despite the rise in summer temperatures. This reduction occurs in parallel with a decline in the vulnerability difference between men and women, but despite these advances, the risk of death remains high for respiratory diseases, and particularly for women.

Research paper II ***(Q1-4, H1-4, O1-4)***

In Achebak et al. (2019), the PhD candidate comprehensively assess the impact of the 1°C increase in annual 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 candidate analyses a dataset from 48 provinces in mainland Spain and the Balearic Islands between 1980 and 2016, which includes daily temperatures and 4,576,600 cardiovascular disease deaths stratified by sex an age group. He applies a quasi-Poisson regression model for data subsets of 15-year moving periods in all Spanish provinces, controlling for seasonal and long-term trends, to estimate the temporal changes in the province-specific temperature-mortality associations with a distributed lag non-linear model. Heat-attributable and cold-attributable fractions of death are computed by separating the contributions from days with temperatures warmer and colder than the

MMT, respectively. Results show that 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), differs by sex and age group and decreases over the study period for both sexes and across all age groups. This supports the hypothesis that the global warming observed in recent decades has been accompanied by substantial adaptation to both warm and cold temperatures in Spain.

Research paper III ***(Q1-4, H1-4, O1-4)***

In Achebak et al. (2020), the PhD candidate examines trends in the seasonality of temperature-attributable mortality from respiratory diseases by sex, age group and province of residence between 1980 and 2016 in Spain. The candidate analyses a dataset from 48 provinces in mainland Spain and the Balearic Islands between 1980 and 2016, which includes daily temperatures and 1,306,283 respiratory diseases deaths stratified by sex an age group. Province-specific temperature-mortality associations are estimated for data subsets of 15-year moving periods using a quasi-Poisson regression combined with distributed lag nonlinear model. Monthly temperature-attributable fractions of mortality are computed under different centring temperature assumptions. Results show the complete reversal of the seasonality of temperature-attributable mortality, with a significant shift of the maximum monthly incidence from winter to summer, and the minimum monthly incidence from early and late summer to winter. The reversal in the seasonal distribution of the attributable deaths is not driven by the observed warming in both winter and summer temperatures, but rather by the very large decrease in the risk of death due to cold temperatures and the relatively much smaller reduction due to hot temperatures. The study concludes that the projected decrease in the number of moderate and extreme cold days due to climate warming will not contribute to a further reduction of cold-attributable respiratory deaths.

PART II
ORIGINAL PUBLICATIONS

4. RESEARCH ARTICLE I

Title
Heat-related mortality trends under recent climate warming in Spain: A 36-year observational study[52]

Authors
Hicham Achebak, Daniel Devolder, Joan Ballester

Journal
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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.

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PLOS | MEDICINE

RESEARCH ARTICLE

Heat-related mortality trends under recent climate warming in Spain: A 36-year observational study

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Abstract

Background

Anthropogenic greenhouse gas emissions have increased summer temperatures in Spain by nearly one degree Celsius on average between 1980 and 2015. However, little is known about the extent to which the association between heat and human mortality has been modified. We here investigate whether the observed warming has been associated with an upward trend in excess mortality attributable to heat or, on the contrary, a decrease in the vulnerability to heat has contributed to a reduction of the mortality burden.

Methods and findings

We analysed a dataset from 47 major cities in Spain for the summer months between 1980 and 2015, which included daily temperatures and 554,491 deaths from circulatory and respiratory causes, by sex. We applied standard quasi-Poisson regression models, controlling for seasonality and long-term trends, and estimated the temporal variation in heat-related mortality with time-varying distributed lag nonlinear models (DLNMs). Results pointed to a reduction in the relative risks of cause-specific and cause-sex mortality across the whole range of summer temperatures. These reductions in turn explained the observed downward trends in heat-attributable deaths, with the only exceptions of respiratory diseases for women and both sexes together. The heat-attributable deaths were consistently higher in women than in men for both circulatory and respiratory causes. The main limitation of our study is that we were not able to account for air pollution in the models because of data unavailability.

Conclusions

Despite the summer warming observed in Spain between 1980 and 2015, the decline in the vulnerability of the population has contributed to a general downward trend in overall heat-attributable mortality. This reduction occurred in parallel with a decline in the vulnerability difference between men and women for circulatory and cardiorespiratory mortality. Despite

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Data Availability Statement: The climate data can be downloaded for free from the website of the European Climate Assessment and Dataset (ECA&D, www.ecad.eu/dailydata/predefinedseries.php). The mortality data can be obtained from the Spanish National Statistics Institute (INE) under request*. Unfortunately, we cannot publish the mortality data because several restrictions imposed by the Spanish National Statistics Institute (INE) apply. Specifically, the INE stipulates in the contract for the supply of the data the following clause: "No distribuir los datos a terceros" ("Do no distribute the data to third parties" in English). *Customised

information and special files, customised requests: www.ine.es/ss/Satellite?c=Page&p=1254735550786&pagename=ProductosYServicios%2FPYSLayout&cid=1254735550786&L=1.

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Competing interests: The authors have declared that no competing interests exist.

Abbreviations: BLUP, best linear unbiased prediction; CI, confidence interval; DLNM, distributed lag nonlinear model; ECA&D, European Climate Assessment and Dataset; INE, Spanish National Statistics Institute; MMT, minimum mortality temperature; RR, relative risk; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

these advances, the risk of death remained high for respiratory diseases, and particularly in women.

Author summary

Why was this study done?

- The Euro-Mediterranean region arises as a major climatic hot spot because of global warming.
- Warmer temperatures should in principle contribute to an increase in the number of deaths because of heat.
- We do not know yet if and to what extent societal adaptation and/or socioeconomic development is modifying this expected increase.

What did the researchers do and find?

- We analysed daily mortality records from 47 major cities in Spain.
- There has been a general and sustained decline in the vulnerability of the population since 1980.
- Despite the observed warming, the decline of the vulnerability has generally contributed to a progressive reduction in the number of deaths attributed to heat since 1980.

What do these findings mean?

- It is generally believed that climate change will cause an increase in heat-related mortality.
- Societal adaptation and/or socioeconomic development contributed, up to now, to a general decline in heat-related mortality.
- It is still uncertain if this decline in heat-related mortality will also occur at higher future levels of climate warming.

Introduction

Anthropogenic climate change represents a major threat for human health and a challenge for public health services [1]. One of its most important effects is the potential increase in heat-related mortality resulting from rising temperatures and the associated increase in the frequency, intensity, and duration of extreme heat events [2,3]. However, the extent of this impact will not only depend on the increase in the level of exposure to heat but also on any underlying change in the vulnerability of the exposed population [4].

Several factors have the potential to modify population vulnerability over time and, therefore, the eventual incidence of increasing temperatures on heat-related mortality. In ageing societies such as Europe, the rising elderly population is expected to increase vulnerability to high ambient temperatures, given that the elderly have diminished physiological capacity for the regulation of body core temperature under heat stress conditions [5]. On the contrary, general improvements in housing conditions (e.g., wider use of air conditioning systems in retirement homes) and healthcare services (e.g., improved treatment of heat-related morbidity) [6,7] as well as some planned adaptive measures to reduce the exposure and vulnerability to heat (e.g., implementation of effective heat health warning systems) [8] could all contribute to reducing the negative health consequences of temperatures and warming trends.

The Euro-Mediterranean region arises as a major climatic hot spot as a result of global warming [9], and, particularly, Spain was the country with the largest relative number of excess deaths during the record-breaking summer 2003 heat wave [10], even if interannual temperature anomalies were twice as large in France during the episode [11]. Some authors have shown that there has been a decline in heat-mortality associations during the last decades in some, albeit not all, of the countries [12–15], and especially since this event in a subset of locations [16–18]. In the case of Spain, the vulnerability associated with heat was found to decrease for the range of extreme summer temperatures [12], suggesting an adjustment response of the Spanish society to rising temperatures despite the ageing of the population. However, evidence about the risk attributable to heat, either as absolute or relative excesses or its temporal evolution, is lacking, with no clear upward or downward trend in the number of deaths. Furthermore, changes by cause of death and sex have not been described for Spain, nor for the rest of the countries.

In the present work, we assess the impact of the summer warming observed in Spain during the period 1980–2015 on cause-specific mortality by sex. The main objective was to determine whether warmer summers were associated with an upward trend in excess mortality attributable to heat. Addressing the early impacts of increased ambient temperatures on human health is a relevant question that could translate into more effective public health adaptation strategies to current and future climate change conditions.

Methods

Study design and data

The Spanish National Statistics Institute (INE) provided daily death counts from circulatory (ICD-9: 390–459, ICD-10: I00–I99) and respiratory (ICD-9: 460–519, ICD-10: J00–J99) diseases, disaggregated by sex and covering the period from 1 January 1980 to 31 December 2015 in 47 major Spanish cities. Daily mortality data had no missing value. We derived daily mean 2-meter temperature observations from the European Climate Assessment and Dataset (ECA&D), which were computed as the average between daily maximum and minimum values from meteorological stations. About 1% of the temperature time series was missing data.

Statistical analysis

The analysis was restricted to the warm season from June to September, and it was performed in two stages. In the first part, standard quasi-Poisson regression models allowing for overdispersion were individually applied in each of the 47 cities included in the analysis in order to estimate location-specific temperature-mortality associations, summarised in terms of relative risk (RR) values by cause of death and sex. The seasonal trend was controlled for in the models by using a natural cubic B-spline of day of the season, with 2 degrees of freedom per year/summer and equally spaced knots, and it was allowed to vary from one year to another through the specification of an interaction between the B-spline and indicators of summer/year. The models also included a natural cubic B-spline of time, with 1 degree of freedom per decade and equally spaced knots to control for the long-term trend, as well as a categorical variable to control for the day of the week.

The complex nonlinear and delayed dependencies found for temperature and mortality were captured by using a distributed lag nonlinear model (DLNM), a flexible methodological framework widely used to investigate the health effects of air pollution and temperature. This model is based on the definition of a cross-basis function, obtained by the combination of two functions describing the exposure-response association and the lag-response association [19]. Specifically, the exposure-response curve was modelled through a natural cubic B-spline, with one internal knot placed at the 15th percentile of the daily temperature distribution, and the lag-response curve was modelled through a natural cubic B-spline, with an intercept and two internal knots placed at equally spaced values in the log scale, with a lag period extended up to 10 days to account for the lagged effects of heat and short-term harvesting. In this way, the overall effect of a given summer day temperature on mortality was defined as the sum of the effect on that day and the 10 subsequent days. These modelling choices were thoroughly tested in sensitivity analyses, which are shown in the Supporting information (S1 Fig). The Poisson regression model for the whole study period was given as follows:

$$\mathrm{Log\ E}\ (\mathrm{Y_t}) = \mathrm{intercept} + \mathrm{cb} + \mathrm{dow} + \mathrm{S1}(\mathrm{dos},\ \mathrm{df} = 2) : \mathrm{factor}(\mathrm{year}) + \mathrm{S2}(\mathrm{time},\ \mathrm{df} = 1\ \mathrm{per\ decade})$$

where $\mathrm{Y_t}$ denotes the series of daily mortality counts, cb the cross-basis matrix produced by DLNM, dow the day of the week, S1 the natural cubic B-spline of the day of the season, and S2 the natural cubic B-spline of time.

To model temporal variations in the bidimensional exposure-lag-response associations between temperature and mortality, the DLNM model described above was extended to a time-varying DLNM, specified through a linear interaction between the cross-basis and time variables [20]. This extension allowed us to predict the temperature-mortality relationship for each summer in the series, by centring the time variable in the central day of the respective summer season.

$$\mathrm{Log\ E}\ (\mathrm{Y_t}) = \mathrm{intercept} + \mathrm{cb} + \mathrm{dow} + \mathrm{S1}(\mathrm{dos},\ \mathrm{df} = 2) : \mathrm{factor}(\mathrm{year}) + \mathrm{S2}(\mathrm{time},\ \mathrm{df} = 1\ \mathrm{per\ decade}) + \mathrm{int}(\mathrm{time}{*}\mathrm{cb})$$

In the second stage, a simple multivariate random-effects meta-analysis [21] was used to estimate the average temperature-mortality association across cities for the whole study period (estimates provided by the model without interaction) and for each year in the series (estimates provided by the model with interaction). The fitted meta-analytical model was also used to derive the best linear unbiased predictions (BLUPs) of the temperature-mortality relationships and the related point of minimum mortality temperature (MMT) in each location. Uncertainty in estimated MMTs was investigated through the method described in Tobías et al. [22].

To assess the temporal evolution in the effect of heat on mortality, the pooled RR curves from the time-varying DLNMs with interaction terms were compared between years. The temporal variations in the RR curves were analysed by means of a multivariate Wald test on the pooled coefficients of the interaction terms, which represent the change in the average temperature mortality curves. The null hypothesis of the test is that no change in the temperature-mortality association ocurred throughout the study period. We also summarised the results by calculating the pooled RR at the 90th and 99th temperature percentiles from year-specific curves between 1980 and 2015.

The mortality burden attributable to heat across the whole study period, reported as relative excess (i.e., attributable fraction) of deaths, was estimated by using the methodology developed by Gasparrini and Leone [23]. First, the RR of mortality corresponding to each day and city was used to calculate the attributable fraction of deaths on that day and the next 10 days. Then, the daily attributable number of deaths was computed by multiplying the daily attributable fraction by the daily number of deaths. The overall number of attributable deaths caused by heat was given by the sum of the contributions from all days of the series with temperatures higher than the value of MMT derived from the BLUP of the model with no interaction in each city, and its ratio with the total number of deaths provided the total heat-attributable fraction. This attributable component was separated further into the contributions of moderate and extreme heat. Moderate heat was defined as the range of temperatures between the city-specific MMT and the city-specific 97.5th daily temperature percentile, and extreme heat as the range of temperatures warmer than this threshold. We also computed the attributable risk of heat for each summer from time-varying DLNMs (model with interaction) to investigate temporal variations in heat-attributable deaths. Confidence intervals (CIs) of attributable risk were obtained empirically through Monte Carlo simulations.

All statistical analyses were performed with R software (version 3.4.3) using functions from the packages *dlnm* (first-stage regression) and *mvmeta* (second-stage meta-analysis).

No data-driven changes were done during the analyses. The development of the statistical analysis plan, including changes inspired by referees, is described in S1 Analysis Plan. This study is reported as per the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (S1 STROBE Checklist).

Results

We analysed data from 47 major cities representing about 32% of the total Spanish population, which includes 544,491 summer deaths, corresponding to the period 1980–2015. Circulatory counts represented 78.9% of the total cardiorespiratory mortality (here the word 'cardiorespiratory' is used to refer to deaths from circulatory and respiratory deaths together), while respiratory deaths accounted for the remaining 21.1%. The temporal pattern of each cause of death was similar in men and women (S2 Fig), with a decline in the number of deaths from circulatory diseases and an increase in the number of deaths from respiratory diseases. Nevertheless, mortality decreased at a slower pace in women for circulatory diseases, therefore increasing the magnitude of the difference between women and men. Moreover, for respiratory diseases, mortality increased at a faster pace in women, therefore reducing the magnitude of the difference between women and men. The geographic distribution of the cities included in the analysis, along with the corresponding evolution in overall summer mean temperature, are displayed in Fig 1. As expected, summer temperatures have been increasing, on average, at a rate of 0.32˚C per decade.

Fig 2 depicts the pooled RR values associated with the temperature-mortality relationships by cause of death and sex from the model with no interaction, interpreted as the average relation throughout the whole study period (1980–2015). The temperature-mortality relationships computed as BLUPs for the 47 cities and the corresponding MMTs are provided in the Supporting information, S3 Fig and S4 Fig. All these curves are J shaped, indicating a monotonically increasing mortality risk for temperatures above and below the MMT. The slope of the curve above this point varied greatly among cases, being generally larger for respiratory than circulatory diseases, and for women than for men. Thus, in each of these two groups of causes, taken either individually or together, women showed systematically higher values of RR for the whole range of warm temperatures, with generally lower MMT than men. For the ensemble of

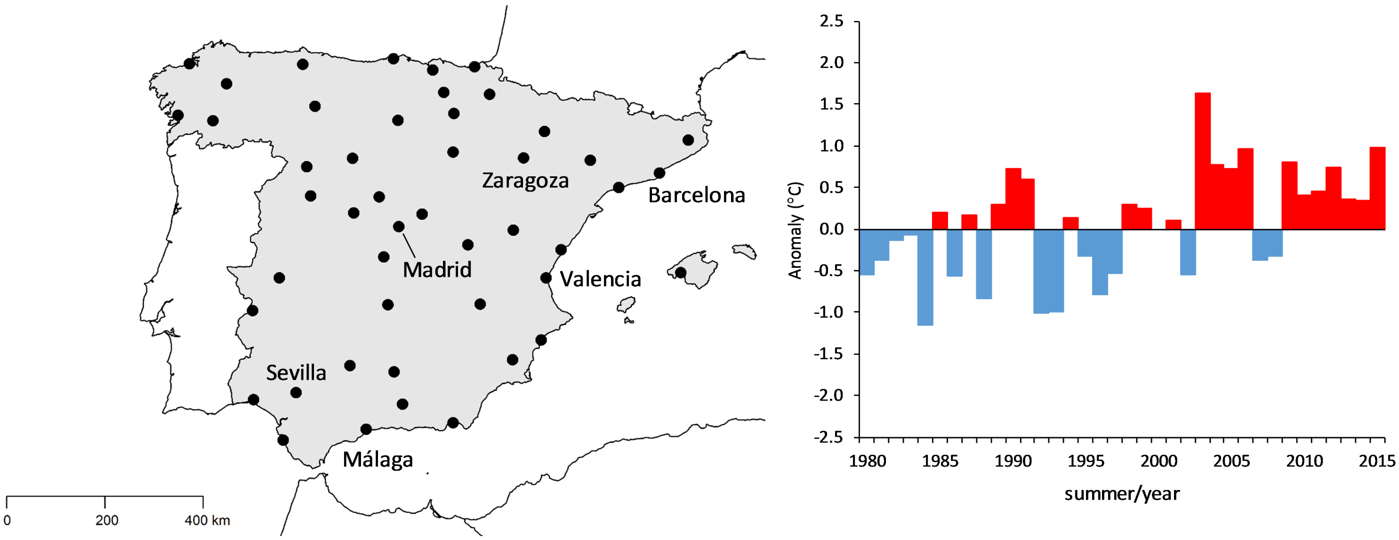


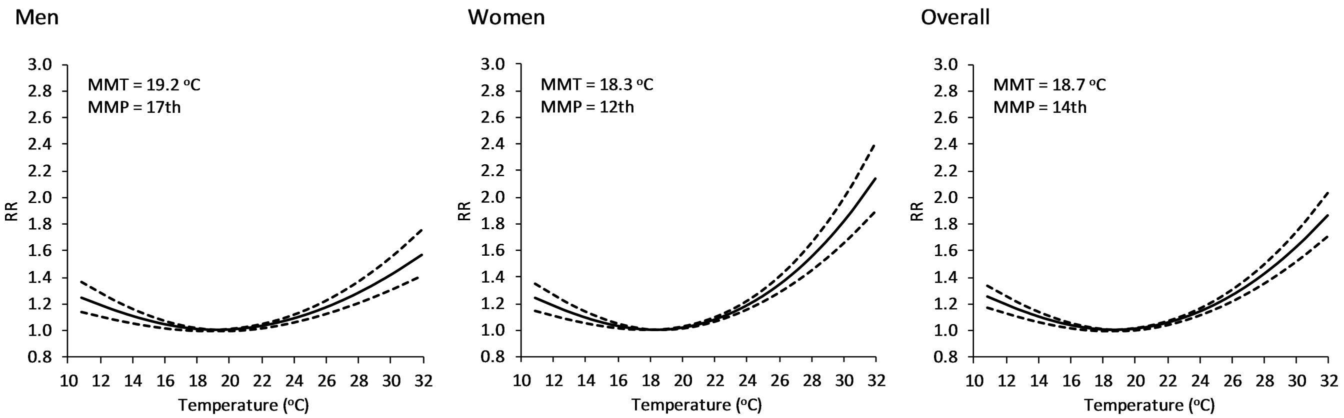
Fig 1. Geographic distribution of the 47 major Spanish cities (left) and the corresponding evolution of overall summer mean temperature (expressed as the difference relative to the average of the 1981–2010 period, right).

https://doi.org/10.1371/journal.pmed.1002617.g001

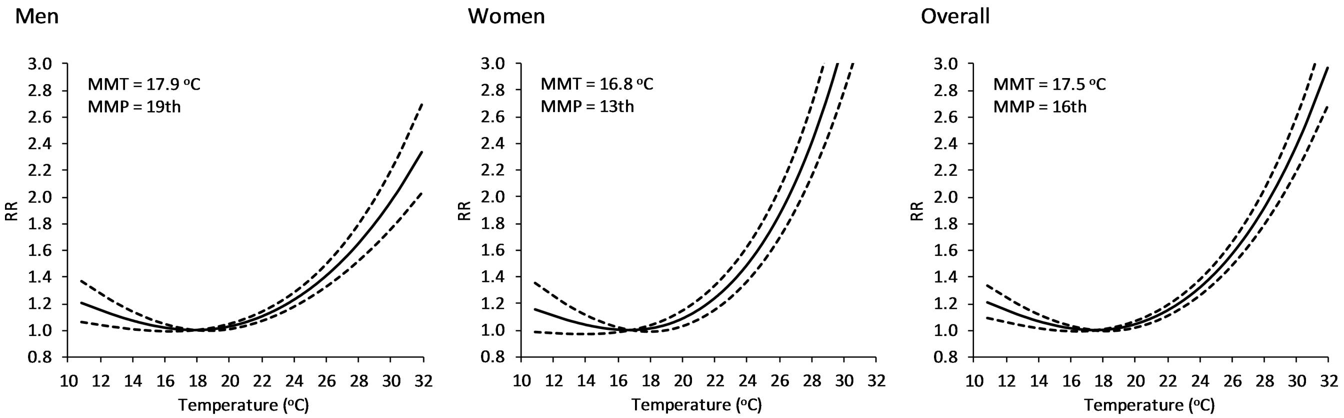
cities, the values of the MMT and the summer mean temperature are largely correlated, with a spatial dependency of between 0.81 and 0.96˚C in MMT per 1˚C in summer mean temperature (Student *t* test/*p*-value < 0.001, S5 Fig).

Results from the analysis of the temporal evolution of the temperature-mortality associations predicted from the model with interaction (time-varying DLNM) are summarised by cause of death and sex in Figs 3 and 4. On the one hand, Fig 3 displays the comparison of the pooled RR curves for representative years (i.e., every 5 years; see also S6 Fig for estimates in each of the 47 cities for years 1980 and 2015). On the other hand, Fig 4 shows the temporal evolution of the pooled RR corresponding to the 99th temperature percentile of the whole time period (left panels) and corresponding to the time-varying 99th temperature percentile computed from data of each individual summer (right panels; find equivalent results for the 90th percentile in S7 Fig). Temporal changes suggest a strong and progressive reduction in the RR of heat-related mortality during the whole study period for the pooled analysis and generally for the ensemble of cities, but despite these advances, the RR to extreme warm temperatures remained high for respiratory diseases, and particularly in women. The significance test (S1 Table) indicates strong evidence for significant temporal changes in the RR curves, with the only exception being respiratory mortality for women. As a result of all these results, differences in mortality risk between men and women from both circulatory and cardiorespiratory diseases generally declined during the study period.

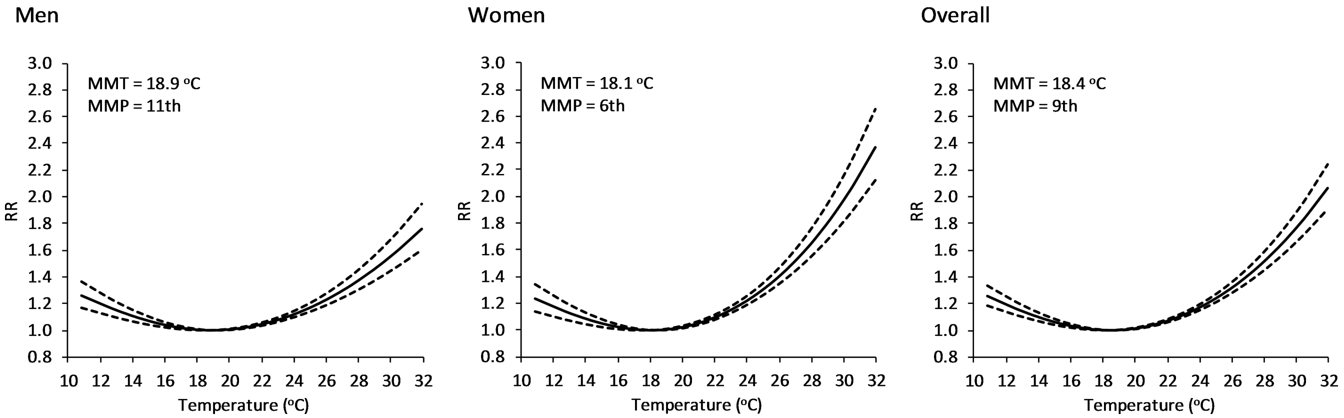
Table 1 summarises the estimates of mortality deaths attributable to heat during the whole study period. The overall fraction of deaths caused by summer heat was 10.65% (95% CI 9.93–11.33), with moderate heat being responsible for almost nine times as many deaths as extreme heat. This was explained by the fact that the days with moderate temperatures occur more frequently in the series, and, therefore, they have a higher absolute impact on the total number of deaths. The attributable fraction due to respiratory causes (17.60%, 95% CI 16.00–18.95) was twice as high as that from circulatory causes (8.94%, 95% CI 8.22–9.61), although in absolute terms circulatory deaths accounted for most of the mortality burden. When considering these two groups of causes by sex, both the attributable fractions and numbers were substantially higher for women. The same pattern was separately observed for moderate and extreme heat.



A. Circulatory causes



B. Respiratory causes



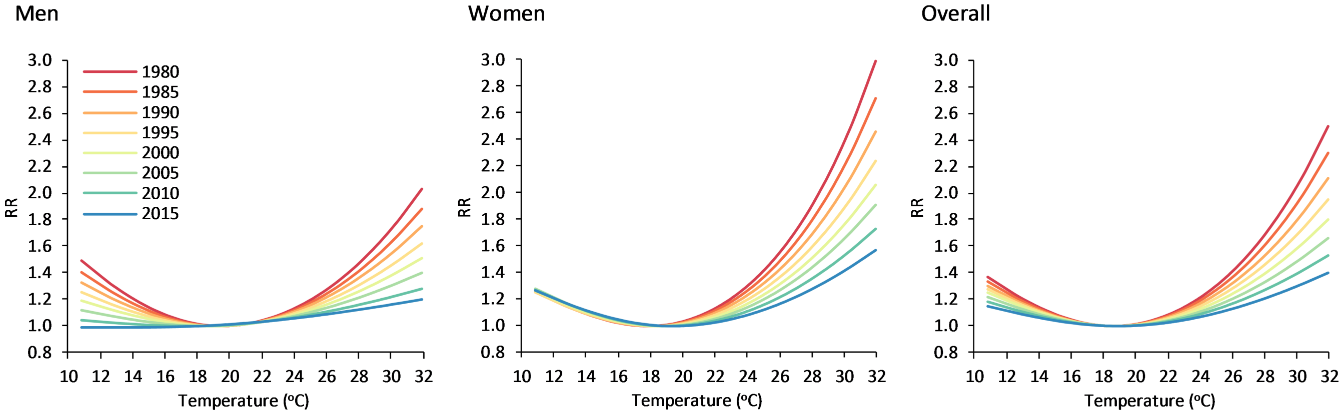
C. Circulatory and respiratory causes

Fig 2. Temperature-mortality relationships from the model with no interaction for the period 1980–2015. The dashed lines represent the 95% empirical confidence interval. MMP, minimum mortality percentile; MMT, minimum mortality temperature; RR, relative risk.

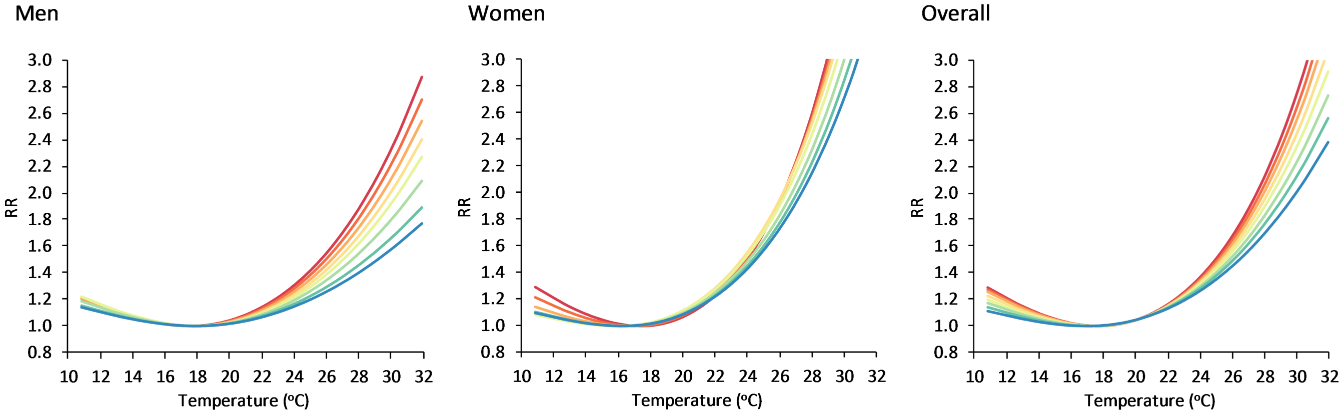
https://doi.org/10.1371/journal.pmed.1002617.g002

The black curves in Fig 5 depict the temporal evolution of the attributable fraction by cause of death and sex (see S8 Fig for the relative contribution of moderate and extreme heat). Regardless of the interannual variability and warming trend associated with the year-to-year changes in summer temperature, the heat-attributable fraction shows no clear and generalised upward trend during the study period. The only exception is found for respiratory diseases

A. Circulatory causes



B. Respiratory causes



C. Circulatory and respiratory causes

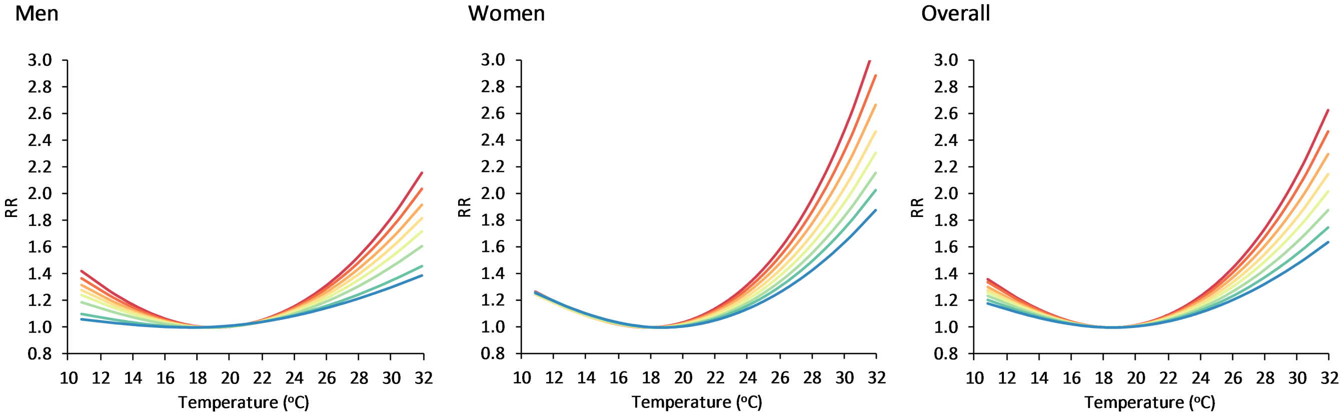
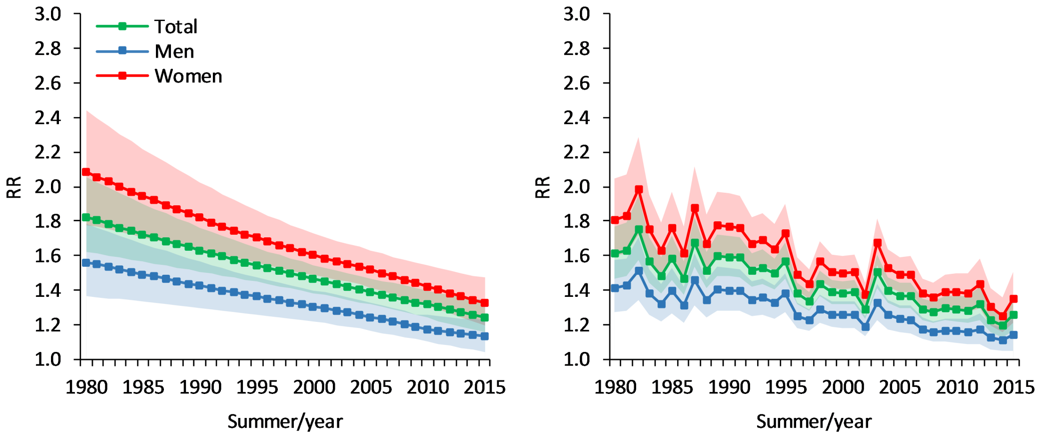


Fig 3. Temperature-mortality relationships from the model with interaction (time-varying DLNM) for representative years. DLNM, distributed lag nonlinear model; RR, relative risk.

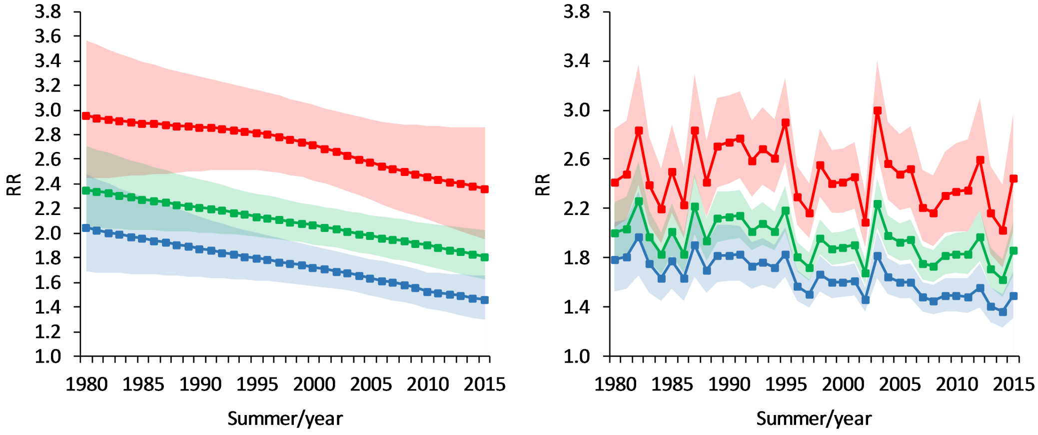
https://doi.org/10.1371/journal.pmed.1002617.g003

(for men and women together, and for women only), in which case the rather small reduction in RR only partially contributed to reducing the negative impact of increasing summer temperatures. Apart from these few exceptions, however, the general evolution shows that, regardless of the summer warming trend shown in Fig 1, the general lack of increasing trends in the

A. Circulatory causes



B. Respiratory causes



C. Circulatory and respiratory causes

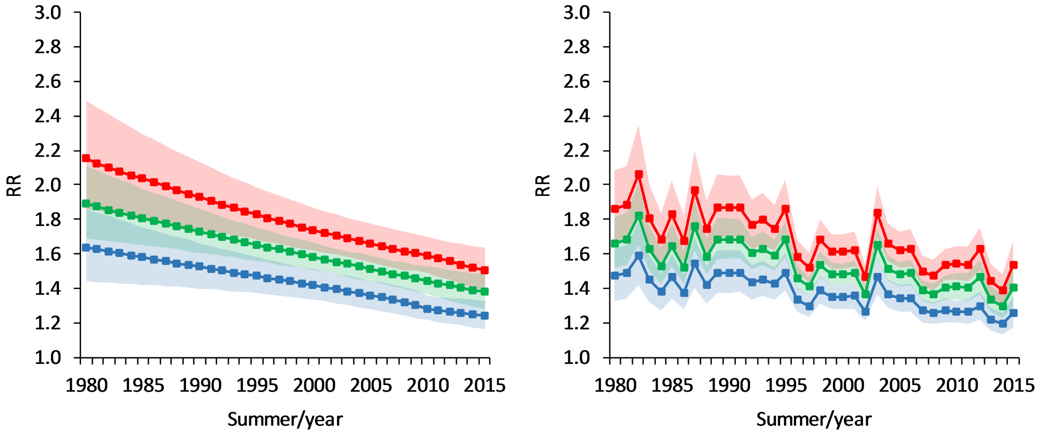


Fig 4. Temporal evolution of mortality RR at the 99th temperature percentile from the model with interaction (time-varying DLNM). In the left column panels, RR estimates correspond to the 99th temperature percentile of the summer time series for the whole study period, while in the right column graphs, they correspond to the 99th temperature percentile of the summer days of the given year (i.e., the 99th percentile of the 122 daily summer values of the year, computed separately for each year). The shaded areas represent the 95% empirical confidence interval. DLNM, distributed lag nonlinear model; RR, relative risk.

https://doi.org/10.1371/journal.pmed.1002617.g004

Table 1. Mortality attributable fraction and number because of moderate and/or extreme heat, together with the 95% empirical confidence interval. Attributable fractions and numbers were predicted from the model without interaction and, therefore, are interpreted as values representing the whole study period (1980–2015).

A. Attributable fraction of deaths

		Heat		Moderate heat		Extreme heat	
		AF	**95% CI**	**AF**	**95% CI**	**AF**	**95% CI**
Circulatory causes		8.94%	(8.22–9.61)	8.00%	(7.34–8.62)	0.94%	(0.87–0.99)
	Men	5.60%	(4.62–6.50)	4.96%	(4.07–5.79)	0.64%	(0.55–0.71)
	Women	11.71%	(10.75–12.64)	10.54%	(9.66–11.41)	1.17%	(1.09–1.23)
Respiratory causes		17.60%	(16.00–18.95)	15.88%	(14.36–17.17)	1.73%	(1.64–1.79)
	Men	13.80%	(12.28–15.20)	12.44%	(11.05–13.76)	1.35%	(1.23–1.44)
	Women	24.26%	(20.75–26.57)	22.02%	(18.63–24.26)	2.24%	(2.12–2.31)
Circulatory and respiratory causes		10.65%	(9.93–11.33)	9.55%	(8.88–10.18)	1.10%	(1.05–1.15)
	Men	7.54%	(6.68–8.31)	6.72%	(5.94–7.43)	0.82%	(0.74–0.89)
	Women	13.50%	(12.44–14.42)	12.15%	(11.17–13.02)	1.34%	(1.27–1.40)

B. Attributable number of deaths

		Heat		Moderate heat		Extreme heat	
		AN	**95% CI**	**AN**	**95% CI**	**AN**	**95% CI**
Circulatory causes		38,287	(35,192–41,174)	34,281	(31,453–36,935)	4,006	(3,738–4,239)
	Men	10,693	(8,826–12,428)	9,472	(7,784–11,064)	1,221	(1,042–1,363)
	Women	27,790	(25,498–29,995)	25,021	(22,921–27,075)	2,769	(2,577–2,920)
Respiratory causes		20,120	(18,288–21,664)	18,147	(16,410–19,623)	1,972	(1,878–2,041)
	Men	9,117	(8,117–10,046)	8,222	(7,302–9,093)	895	(814–953)
	Women	11,704	(10,011–12,818)	10,624	(8,987–11,703)	1,080	(1,024–1,115)
Circulatory and respiratory causes		57,814	(53,866–61,479)	51,844	(48,192–55,251)	5,971	(5,674–6,228)
	Men	19,377	(17,174–21,379)	17,273	(15,272–19,100)	2,104	(1,902–2,279)
	Women	38,543	(35,519–41,162)	34,705	(31,898–37,162)	3,838	(3,621–4,000)

Abbreviations: AF, attributable fraction; AN, attributable number; CI, confidence interval.

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attributable fraction is explained by the large decrease in the mortality RR shown in Figs 3 and 4.

The red and blue curves in Fig 5 show the temporal evolution of the attributable fraction to heat if the effect of long-term warming temperatures were removed. This hypothetical evolution is constructed by replacing the temperature time series by the daily time series of a given summer (i.e., 122 values corresponding to the four summer months here considered) that is repeated by construction for all the years in the study period. Thus, the blue and red lines result from predicting the attributable fraction by applying the time-varying annual RR curves (1980–2015) to the daily time series of temperatures for summers 1984 (i.e., the coldest during the study period) and 2003 (the warmest), respectively. In this way, given that more moderate summer temperatures were observed in 1984 and more extreme temperatures in 2003, the magnitude of the corresponding trends in the attributable fraction results to a large extent from the decreasing magnitude in the RR for the moderate or extreme temperature percentiles, respectively (cf. with Fig 4). In this way, the range between these lines as well as differences with regard to the central curves show the relative contribution of interannual temperature anomalies and year-to-year climate variability to the evolution of the attributable fraction; they also show a rough estimation of the potential impact range of near-future summer temperatures. For example, compared with the attributable fraction observed in 2003, the estimated

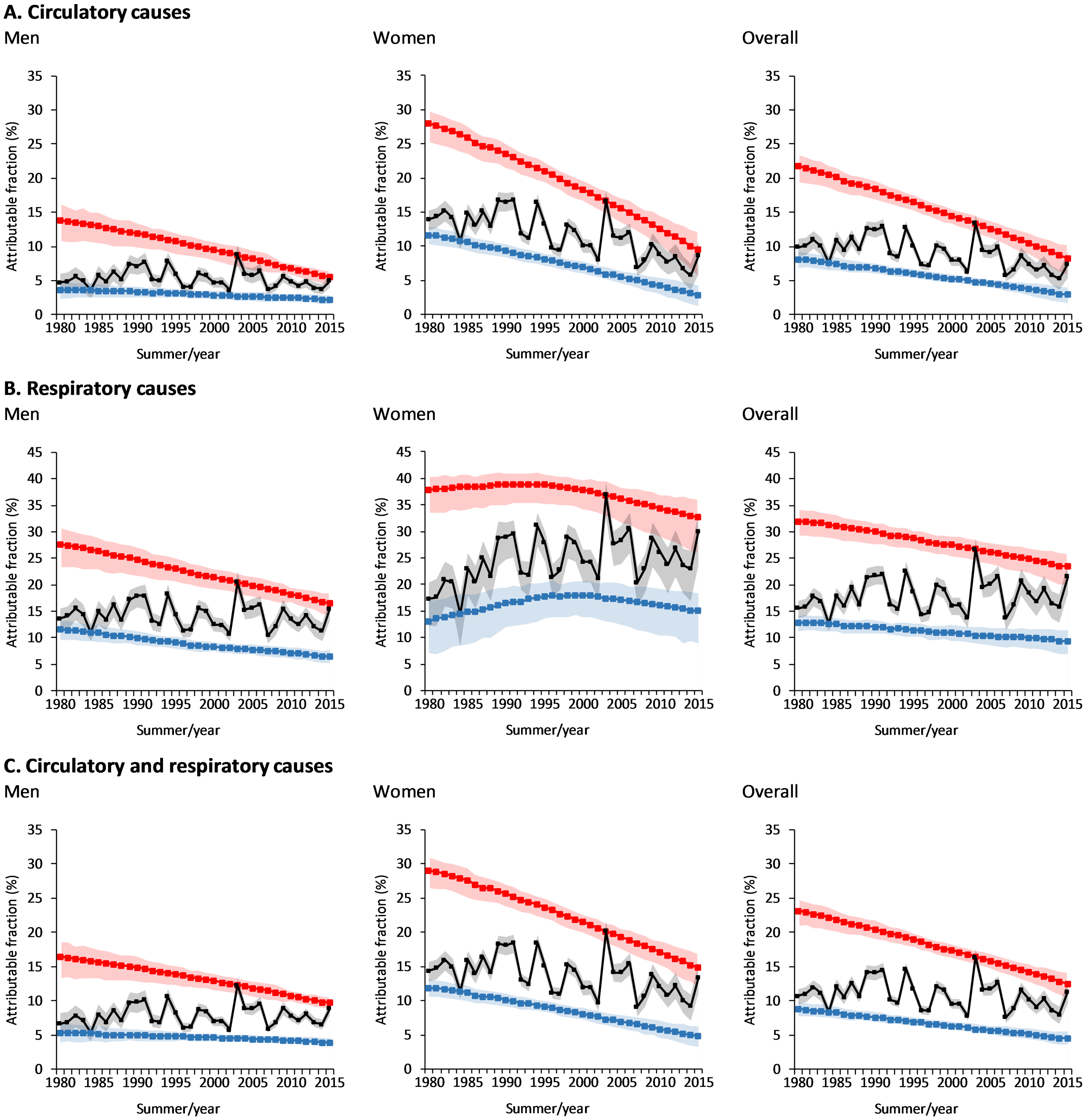

Fig 5. Temporal evolution of the mortality fraction attributable to heat (black). The blue and red lines result from applying the time-varying annual RR curves (1980–2015) to the daily time series of temperatures for summers 1984 and 2003, respectively. The shaded areas represent the 95% empirical confidence interval. RR, relative risk.

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impact of a 2003-like summer with the RR of 2015 would be 21.13% smaller for men, 28.16% for women, 38.31% for cardiovascular diseases, and 12.34% for respiratory diseases (i.e., decrease of the red curves between years 2003 and 2015).

Discussion

To the best of our knowledge, this is the first study that comprehensively addresses the eventual impact of recent climate warming on summer mortality in Spain by cause of death and sex. The study pointed to a strong reduction in cause-specific and cause-sex mortality RR associated with summer temperatures for the last three and a half decades and, with the exception of respiratory diseases (for men and women together, and for women only), downward trends in heat-attributable deaths. These results strongly support the hypothesis that the observed warming trend in summer temperatures in Spain has not been paralleled by a general increase in the mortality fraction attributable to heat, as a result of substantial decline in population vulnerability to warm temperatures [11].

In this study, the effect of heat on mortality largely varied by cause of death. We observed a greater impact of heat on respiratory rather than circulatory mortality. This is in agreement with previous studies [24–27] and probably reflects the large health vulnerability among people with pre-existing or chronic respiratory diseases during hot periods [28]. It should be remembered that respiratory mortality accounted for only 21.1% of cardiorespiratory deaths during the study period, but the observed rise in the relative prevalence of respiratory diseases over recent decades might continue in the near future and keep increasing the relative percentage of the population susceptible to heat-related respiratory mortality. The underlying physiological mechanisms behind the effect of heat on mortality from circulatory and respiratory causes are not well known yet, but they seem to be largely mediated by a thermoregulatory pathway.

We assessed circulatory- and respiratory-specific mortality by sex, and we found that women were systematically more at risk of dying from heat. This finding has been reported in many previous articles analysing the effect through the whole range of hot temperatures [27,29–31] and in many studies based on extreme heat events [16,32–35]. These quantitative differences between men and women may partially arise from physiological characteristics in body temperature regulation between males and females [36]. However, most of these differences could simply be attributed to existing sociodemographic characteristics of the society (e.g., differences between men and women in age pyramid, life expectancy, or social isolation). Previous studies have actually shown that this type of difference can in some cases result in gender being an important variable to predict the mortality risk; i.e., 64% of the deaths were women during the 2003 heat wave in France [33]. The gender gap was, however, found to be reduced by the group of planned adaptation measures implemented just after this record-breaking episode [16]: while 60% of the deaths were expected to be women during the following major heat wave in 2006, gender differences in observed mortality were significantly lower; i.e., 53% of the deaths were women.

The heat attributable fractions reported in our study are higher than those presented, for example, in Gasparrini et al. [37] and somewhat different, for example, from those reported by Carmona et al. [38]. However, these results are not comparable, because in our study, mortality data are analysed only for circulatory and respiratory causes, which are two of the main groups associated with ambient temperatures (see, for example, Basagaña et al. [39]). Instead, in Gasparrini et al. [37], mortality data for Spain are analysed for all causes of death together, and in Carmona et al. [38] for natural causes, including many causes of death that are not largely associated with ambient temperatures. As a result, the attributable fraction (i.e., the ratio between attributable deaths and total deaths) is understandably higher in our study than in Gasparrini et al. [37] and Carmona et al. [38]. We note that other methodological differences might explain (to a lower extent) these differences; e.g., the time period of data is different (taking into account that the relative risk decreases with time).

The temporal evolution of heat-related mortality risks here found is, in general, consistent with those reported by previous studies in some other countries [12–15], which provide evidence for a decrease in vulnerability to climate warming despite the ageing of societies. For example, in Spain, the proportion of people aged over 64 years increased from 11.6% to 15.0% in men and from 15.9% to 19.6% in women between 1991 and 2011 [40]. The general downward trend in mortality risks has been attributed by some investigators to socioeconomic development and structural transformations, such as improvements in housing and healthcare services [12–15], or even to specific public health interventions [16–18]. The large socioeconomic advances that occurred in Spain during the last decades might have also contributed to this response, thus reducing the effect of mortality risks over time. For example, the gross domestic product (from €8,798 per capita in 1991 to €22,813 in 2009), the life expectancy at birth (from 77.08 years to 81.58), the expenditure in healthcare (from €605 per capita to €2,182) and social protection (from €1,845 per capita to €5,746), and the number of doctors (from 3,930 per million inhabitants to 4,760 per million inhabitants) have all largely increased in Spain [41]. In addition, the use of air conditioning, which has been postulated as a major contributor to the reduction in heat-related mortality in the United States [13], has also experienced a strong increase in Spanish households within the analysed period (from 5.3% to 35.5%) [42].

Another potential contributing factor to the reduction of the mortality risks might have been the 'National plan for preventive actions against the effects of excess temperatures on health' from the Spanish Ministry of Health [43], which was implemented in 2004, just after the 2003 summer heat wave, in order to minimise the negative effects of summer extreme temperatures on the population's health, particularly among vulnerable groups such as the elderly, children, people with chronic disease, and disadvantaged persons. Nonetheless, we do not see a change in the slope of the generally linear declining trend of RR and attributable fraction in the mid-2000s, which seems to indicate that this measure had at most a minor beneficial impact (specific analyses will be performed elsewhere). The cause-specific and cause-sex attributable numbers all showed a rather linear downward trend during the study period as a result of the strong decrease in RR, which was largest for the warmest temperatures. Although the range corresponding to moderate hot temperatures had a comparatively lower RR, it included the majority of days in the series, accounting for most of the overall deaths caused by heat. In that regard, public health interventions should also be directed towards non-extreme temperatures, to include the whole range of moderate conditions above the MMT [37].

Finally, some limitations of the study deserve to be mentioned. First, we were not able to control for air pollution because of data unavailability. However, previous studies showed that effects of hot temperatures on mortality in the US were only slightly reduced after adjusting for air pollution [24]. Secondly, the study did not take into account the long-term changes in the age structure of the population, which will be analysed when a more complete dataset by age is available.

Supporting information

S1 STROBE Checklist. STROBE checklist.
(PDF)

S1 Fig. Sensitivity analysis for modelling choices.
(PDF)

S2 Fig. Temporal evolution of summer (June–September) deaths for 1980–2015.
(PDF)

S3 Fig. Temperature-mortality relationships for the 47 provincial capital cities in Spain.
(PDF)

S4 Fig. Estimated minimum mortality temperature for the 47 provincial capital cities in Spain.
(PDF)

S5 Fig. Relationship for the ensemble of the cities between MMT and summer mean temperature. MMT, minimum mortality temperature.
(PDF)

S6 Fig. Temperature-mortality relationships predicted for 1980 (green) and 2015 (blue) in the 47 provincial capital cities.
(PDF)

S7 Fig. Temporal evolution of mortality RR at the 90th temperature percentile from the model with interaction (time-varying DLNM). DLNM, distributed lag nonlinear model; RR, relative risk.
(PDF)

S8 Fig. Temporal evolution of mortality attributable to moderate and extreme heat for 1980–2015.
(PDF)

S1 Analysis Plan. Analysis plan.
(PDF)

S1 Table. Results of the multivariate Wald test for mortality RR curves. RR, relative risk.
(PDF)

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Supervision: Daniel Devolder, Joan Ballester.

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Writing – original draft: Hicham Achebak.

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5. RESEARCH ARTICLE II

Title
Trends in temperature-related age-specific and sex-specific mortality from cardiovascular diseases in Spain: a national time-series analysis[53]

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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.

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

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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.

Funding None.

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.

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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:

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

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

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

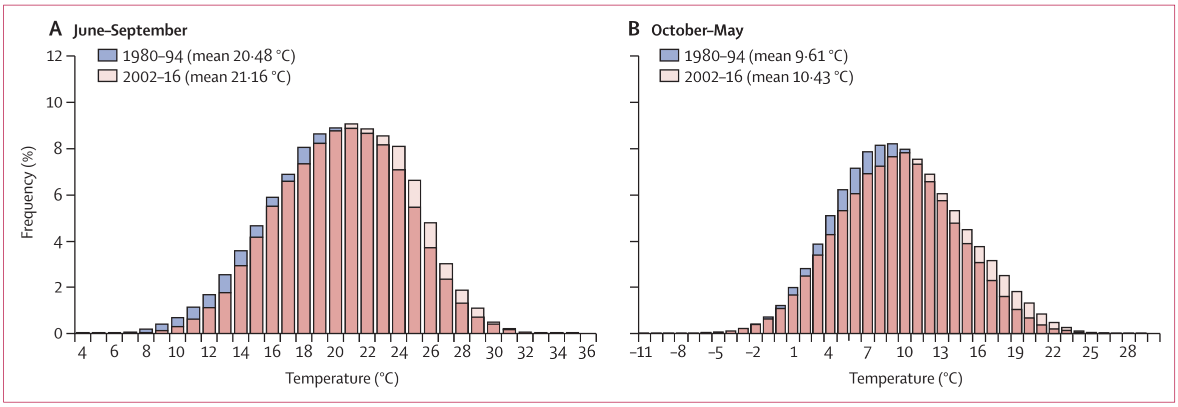

Figure 1: **Distribution of daily mean temperatures in Spain between 1980 and 1994 and 2002 and 2016**
Daily mean temperatures between June and September (A) and between October and May (B).

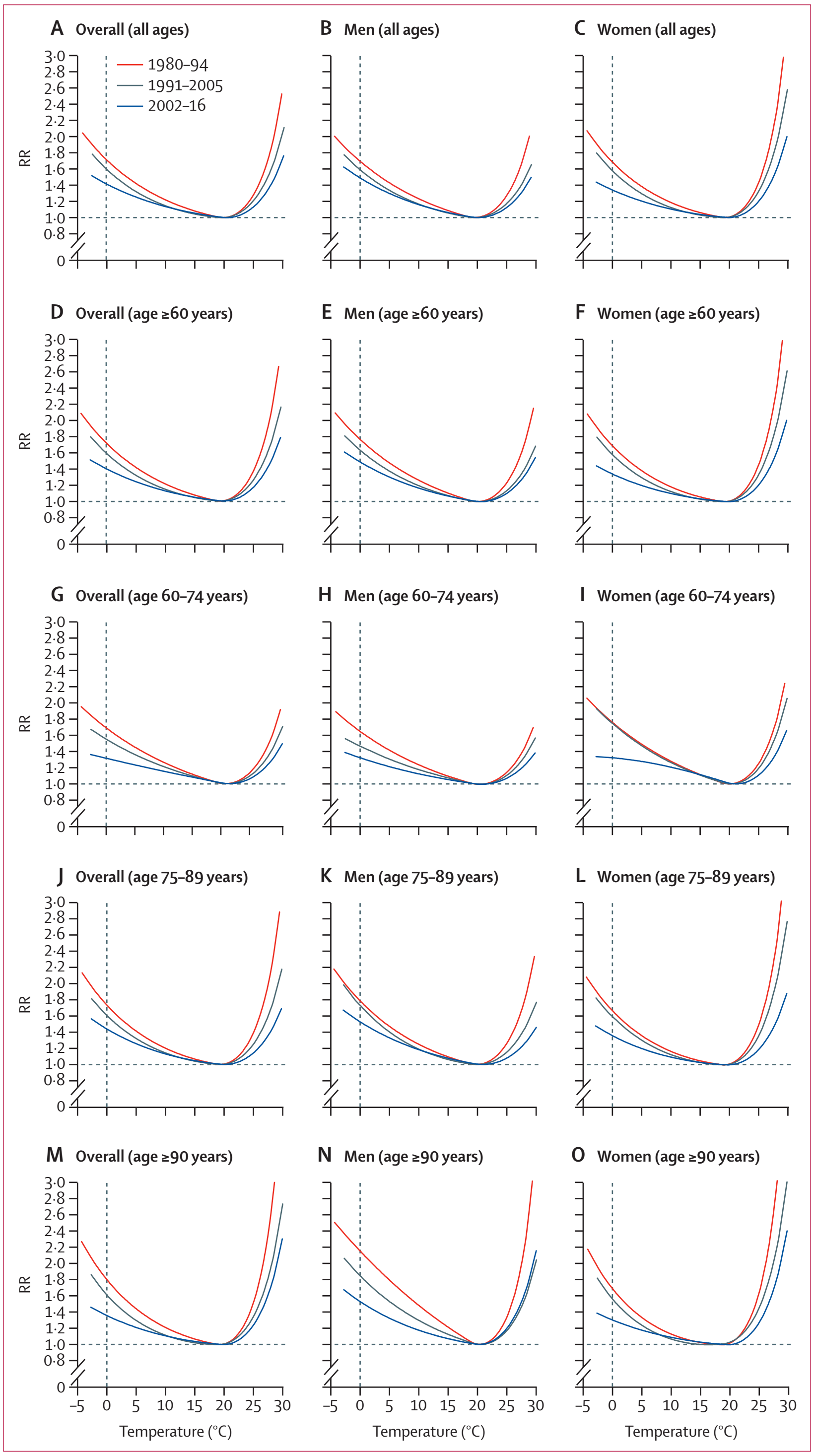

Figure 2: **RR of death from cardiovascular diseases in Spain for 15-year time periods between 1980 and 2016**
95% empirical CIs are shown in the appendix (pp 9, 10). RR=relative risk.

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

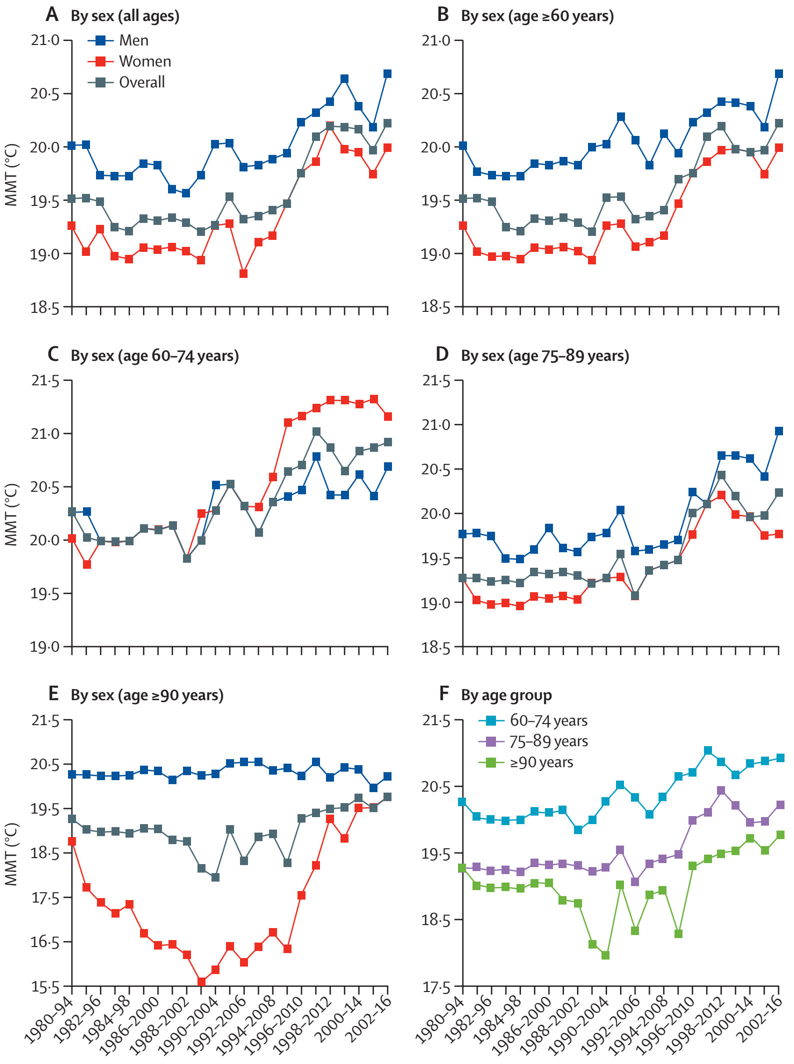

Figure 3: **Minimum mortality temperature for cardiovascular diseases by sex and age, 1980–2016**
MMT=minimum mortality temperature.

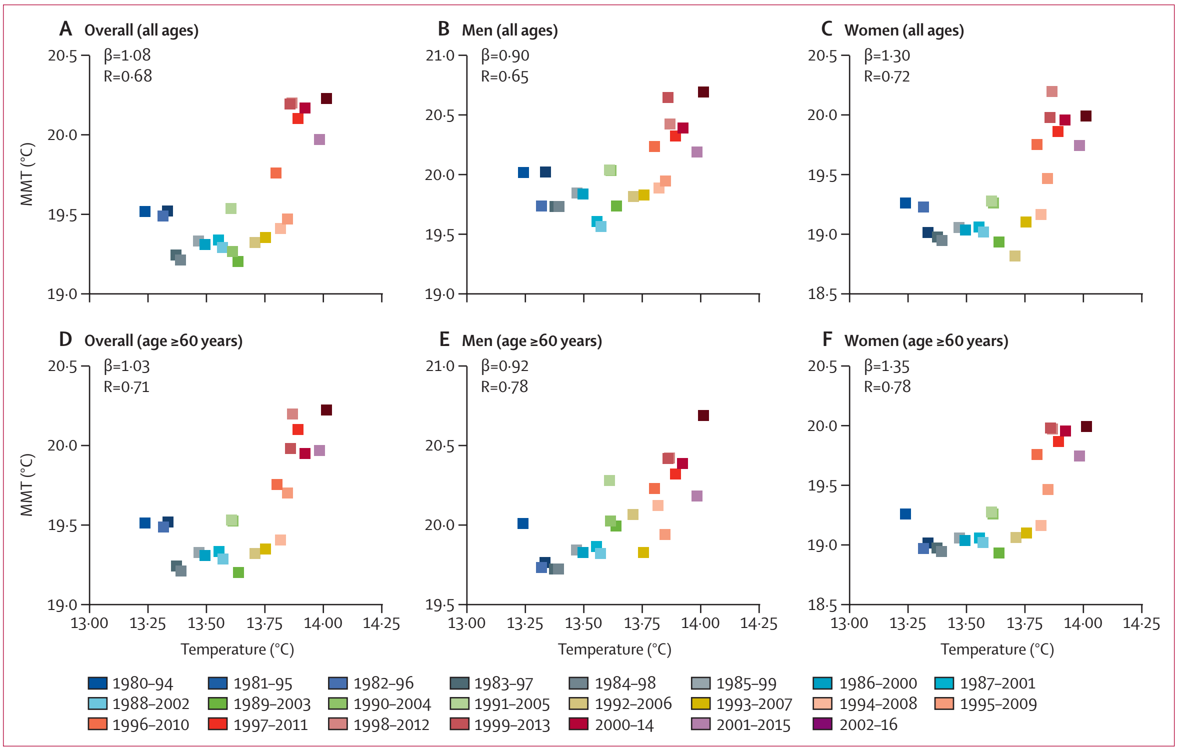

Figure 4: **Association between the mean temperature and minimum mortality temperature by time period**
MMT=minimum mortality temperature. β=slope. R=Pearson correlation.

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 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

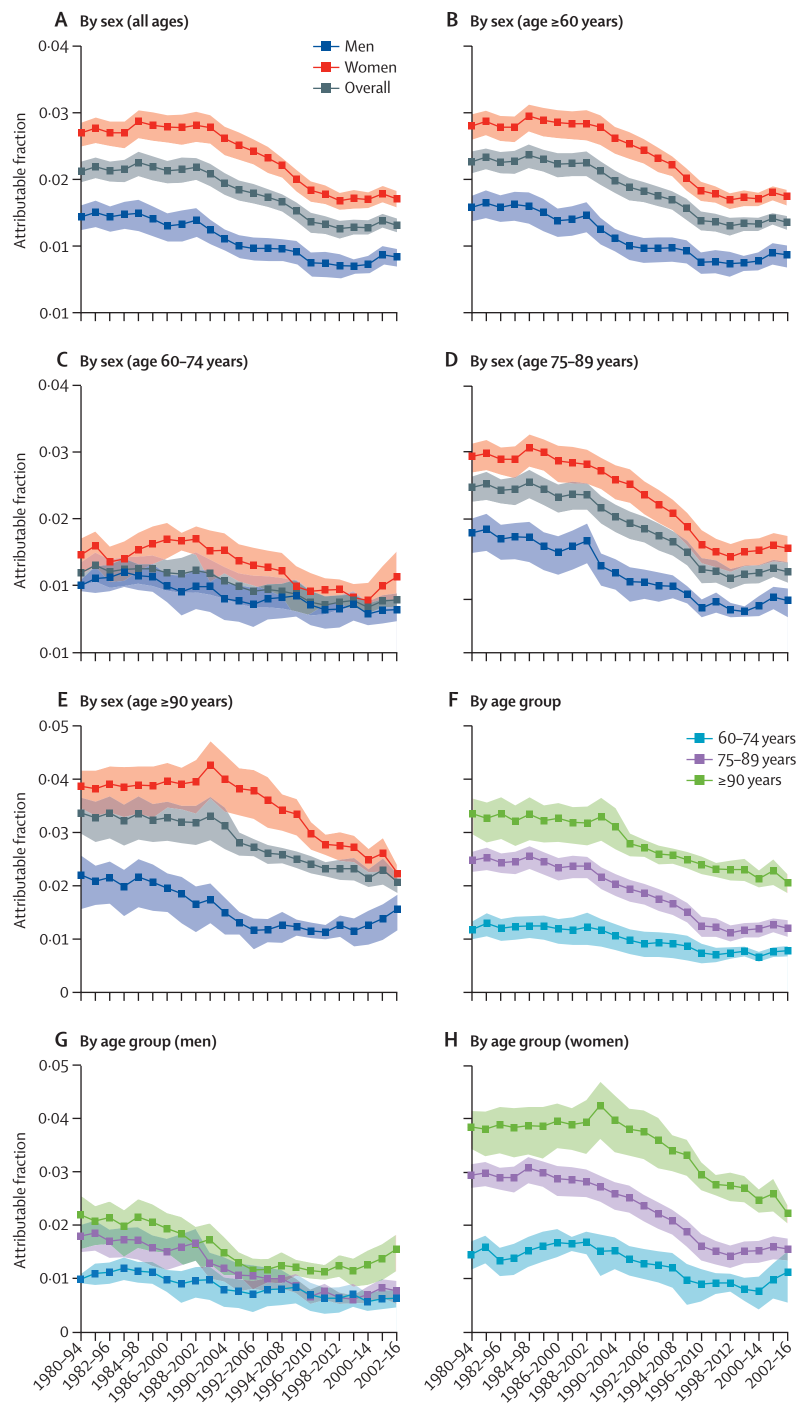

Figure 5: **Heat-attributable fraction of cardiovascular disease mortality in Spain by age and sex, 1980–2016**
Shaded areas represent the 95% empirical CIs.

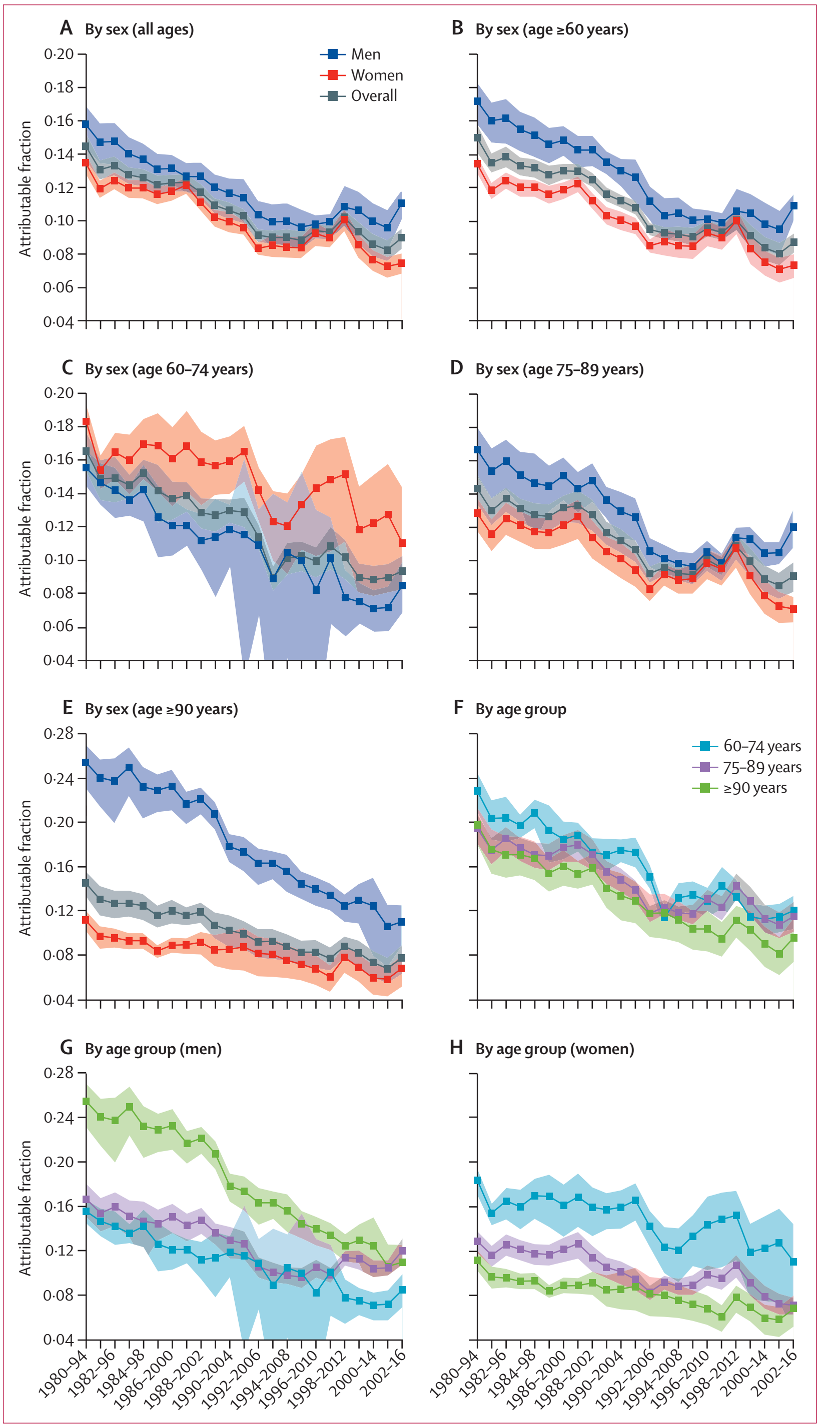

Figure 6: **Cold-attributable fraction of cardiovascular disease mortality in Spain by age and sex, 1980–2016**
Shaded areas represent the 95% empirical CIs.

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.

Acknowledgments

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6. RESEARCH ARTICLE III

Title
Reversal of the seasonality of temperature- attributable mortality from respiratory diseases in Spain[54]

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Reversal of the seasonality of temperature-attributable mortality from respiratory diseases in Spain

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A growing number of epidemiological studies have recently assessed temporal variations in vulnerability and/or mortality attributable to hot and cold temperatures. However, the eventual changes in the seasonal distribution of temperature-attributable mortality remain unexplored. Here, we analyse countrywide daily time-series of temperature and mortality counts from respiratory diseases by sex, age group and province of residence during the period 1980–2016 in Spain. We show the complete reversal of the seasonality of temperature-attributable mortality, with a significant shift of the maximum monthly incidence from winter to summer, and the minimum monthly incidence from early and late summer to winter. The reversal in the seasonal distribution of the attributable deaths is not driven by the observed warming in both winter and summer temperatures, but rather by the very large decrease in the risk of death due to cold temperatures and the relatively much smaller reduction due to hot temperatures. We conclude that the projected decrease in the number of moderate and extreme cold days due to climate warming will not contribute to a further reduction of cold-attributable respiratory deaths.

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Human-driven climate change has become a major concern for public health worldwide[1]. Its direct impacts on health expand across a range of sectors[2], including changes in mortality and morbidity rates associated with the general rise in temperatures and the related increase in the frequency, intensity and duration of extreme heatwaves[3].

Projections of the impact of rising temperatures on mortality consistently indicate a progressive increase in heat-attributable mortality and a decrease of cold-attributable mortality during the next decades, resulting in a substantial positive or negative net effect in temperature-attributable mortality depending on the location and magnitude of the warming[4]. However, this scenario is subject to a high level of uncertainty, given that it will also depend on the future capacity of the societies to reduce their vulnerability to both warm and cold temperatures[5]. Trends in the health impact (i.e. heat-attributable and cold-attributable deaths) essentially arise from the combination of variations in both exposure and vulnerability. A decrease in vulnerability, often expressed as relative risk (RR)[6], can be largely linked to adaptation processes, either occurring by means of a physiological acclimatisation response of the population to changing temperature (intrinsic or causal adaptation)[7], or independently from the warming through a range of non-climate driven factors (extrinsic adaptation), such as socioeconomic development or improved healthcare services[8].

A growing number of epidemiological studies have recently assessed temporal variations in the vulnerability and/or mortality attributable to hot and cold temperatures, reporting evidence of a reduction in population vulnerability to both heat and cold in some, albeit not all, of the analysed countries[7,9–12]. However, even though it is well established that the impact of temperature on mortality varies by season in extratropical countries, being higher in winter than during other parts of the year[13], mainly for cardiovascular and respiratory diseases, the possible change in the seasonal distribution of temperature-attributable mortality remains unexplored.

In the present work, we examine trends in the seasonality of temperature-attributable mortality from respiratory diseases by sex and age group between 1980 and 2016 in Spain. Ambient temperatures are mainly correlated with cardiovascular and respiratory diseases, and the mechanisms behind these associations, as well as their recent evolution, are substantially different[6]. We here specifically analyse mortality from respiratory causes, and discuss differences with regard to recent findings on cardiovascular diseases[12]. Results show a very strong reduction in the temperature-attributable fraction (AF) during the coldest months of the year and only a small decrease during the hottest ones, resulting in the redefinition of the seasonality of mortality, with a shift of the maximum monthly AF from winter to summer, and the minimum monthly AF from early and late summer to winter. We conclude that the projected decrease in the number of moderate and extreme cold days will not contribute to a further reduction of cold-attributable respiratory deaths in Spain, which opens a new avenue towards a more realistic estimation of future mortality under climate change scenarios.

Results

Evolution of mortality and temperatures. We analysed data from 48 provinces in mainland Spain and the Balearic Islands (Supplementary Fig. 1), which included 1,306,283 deaths from respiratory diseases (10.9% of total mortality due to natural causes), covering a period of 37 years from 1980 to 2016. The number of deaths from respiratory causes showed an important increase over the study period for both men (+66.5%) and women (+77.3%), except for the age group 60–74 years (Supplementary Fig. 2). The proportion of mortality due to respiratory causes (i.e. ratio between respiratory and total deaths) has risen from 9.9% in 1980 to 11.9% in 2016, representing a relative increase of 20.2%. In parallel, the distribution of temperatures has shifted towards higher values, generally with more moderate and extreme warm days and less moderate and extreme cold days in 2002–2016 compared with 1980–1994 (Supplementary Fig. 3).

Risk of death due to temperatures. The RR values associated with the temperature–mortality relationships by sex and age group for the whole study period indicate that both low and high temperatures are associated with increased risk of mortality, especially in the case of the extreme temperatures (Supplementary Fig. 4). The heat slope was in all cases much steeper than the cold one, and varied greatly by sex and age group. Thus, the heat slope of women and the older age groups was higher than the ones for men and the younger age groups, respectively. By contrast, the cold slope was slightly more pronounced for men than for women, and for younger age groups than for older ones for cold temperatures. The point of MMT decreased with age, and it was higher for men than for women.

Temporal changes in the pooled exposure-response relationships between temperature and mortality are displayed in Fig. 1 (see province-specific estimates in Supplementary Figs. 5–10). The RR curves, which are all centred at the MMT value of the 1980–1994 subperiod (i.e. *invariant centring temperature assumption*, see the red vertical line in the panels), suggest a very strong reduction in the effects of cold on mortality for all the sex and age groups, while the reductions in the mortality risk associated with heat were generally smaller. Specifically, the RR corresponding to the 1st temperature percentile of the whole study period fell from 1.805 (95% empirical CI: 1.670–1.952) in 1980–1994 to 1.047 (0.973–1.126) in 2002–2016, and the RR corresponding to the 99th percentile from 1.885 (1.696–2.095) to 1.610 (1.520–1.705). Overall, very small differences in the RR due to cold temperatures are found among sex and age groups in the last subperiod, showing an almost complete process of adaptation to cold, while differences are still significant in summer.

Trends in minimum mortality temperature. The curves in Fig. 2 depict the estimates of minimum MMT extracted from exposure–response curves computed from the 23 subperiods of 15 consecutive years. MMT largely cooled both for men and women, as well as for all the age groups. The overall MMT fell from 21.0 °C in 1980–1994 to 7.2 °C in 2002–2016, which corresponds to a displacement from percentiles 83 (i.e. in summer) to 18 (in winter) of the daily temperature distribution of the whole study period. Furthermore, the shift in the MMT occurred earlier in women than in men, and in the older age groups than in the younger ones. However, given that the RR curves changed from an asymmetric V-shape to a hockey stick, with flat values for all non-summer temperatures (Fig. 1), the confidence interval of the MMT largely expanded towards the coldest values, and therefore, the temporal changes in the MMT are not statistically significant in most of the cases (Supplementary Figs. 11–22).

Reversal of the seasonality of temperature-attributable mortality. Figure 3 shows the AF by month of the year for the first and last 15-year subperiods of the series (see Supplementary Fig. 23 for other subperiods, and Supplementary Figs. 24–29 for province-specific estimates). Strikingly, the results reveal a complete change in the seasonality of the AF between 1980–1994 and 2002–2016 for both sexes and all the age groups, with a displacement of the maximum monthly AF from winter to summer,

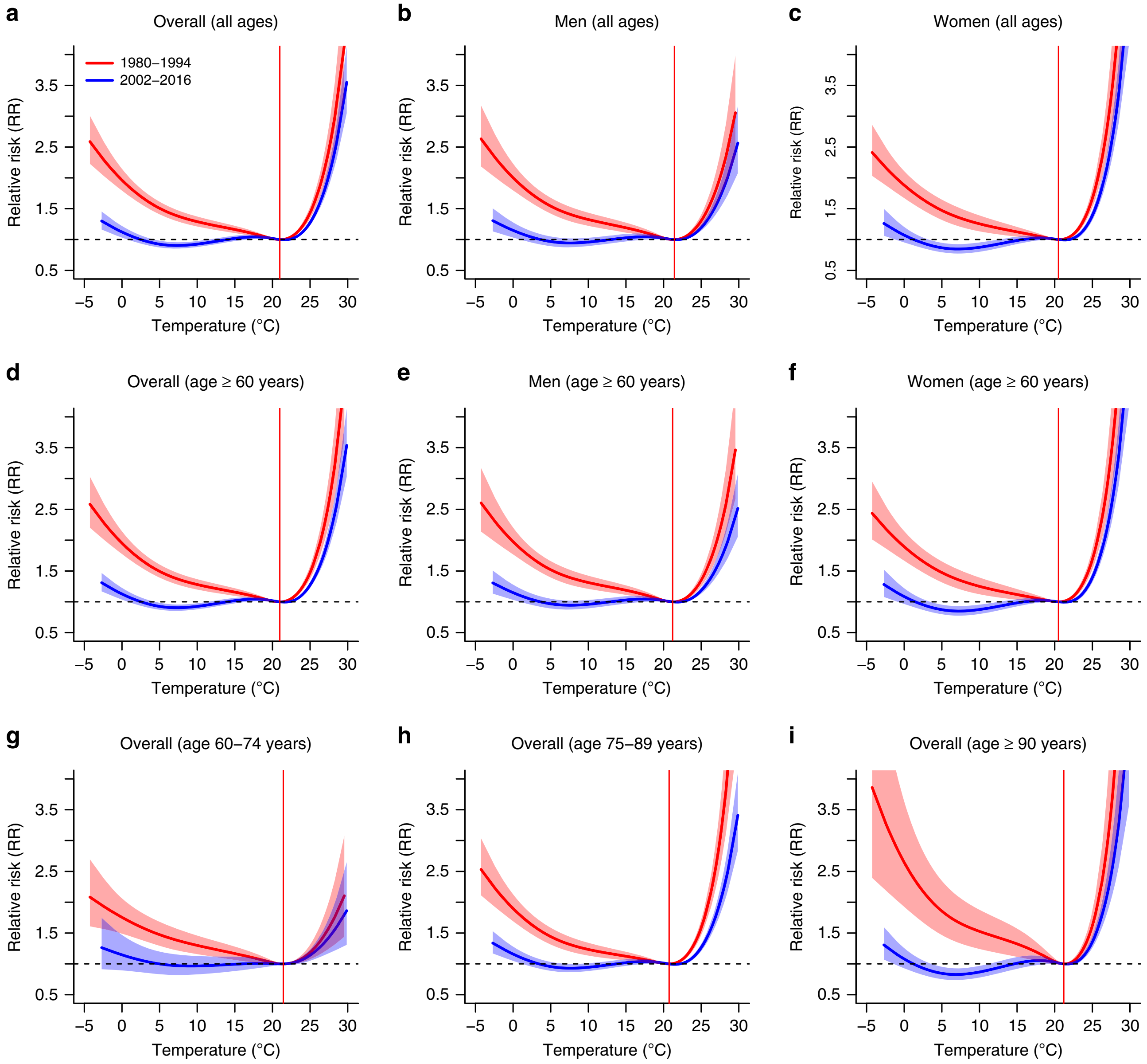

Fig. 1 Relative risk (unitless) of death from respiratory diseases in Spain. The minimum mortality temperature in 1980–1994 is used as the centring temperature for the two subperiods (i.e. *invariant centring temperature assumption*, see red vertical lines).

and the minimum monthly AF from early and late summer to winter. This statistically significant reversal of the seasonality has been essentially driven so far by the very large decrease in the RR due to cold temperatures and the modest decrease due to hot temperatures, and not by the observed warming in both winter and summer (Supplementary Fig. 30).

The trends in overall monthly AF are summarised in Fig. 4, and indicate a steep decrease in the AF during the cold months of the year, especially in winter (December–March), and only a slight reduction during the summer months (June–September). For instance, the value of the trend in AF for the coldest month of the year (i.e. January) was −0.19 per decade (95% empirical CI: −0.17 to -0.21), whereas for the hottest one (i.e. August) was −0.02 per decade (−0.01 to −0.03) (Fig. 5). It is also noteworthy that, in line with the changes in the MMT, the monthly AF generally declined at a faster pace for women than for men, and for the older age groups than for the younger ones (Fig. 5).

Invariant and varying centring temperature. All the results shown here have been reported under the *invariant centring temperature assumption*, that is, the RR at the MMT of the first subperiod does not change over time and is equal to 1 in all the subperiods. Please note that a similar assumption is implicitly used with time-varying distributed lag non-linear model[7,10,11]. Given the very strong decrease of the slope of the RR for the cold temperatures, this implicitly implies that the RR is in some cases smaller than 1 for some cold temperatures in the most recent subperiods (Fig. 1), and therefore, the AF can become negative (Fig. 3). This negative value should only be understood as a way to evaluate the trend (or more precisely, the relative inter-subperiod change) in the AF by taking the first subperiod as the reference baseline (Fig. 4), and not to quantify the actual absolute burden in a given subperiod. In the Supplementary Information (Supplementary Figs. 31–39), the same analyses are provided under the *varying centring temperature assumption*, that is, the centring temperature is allowed to change over time, and

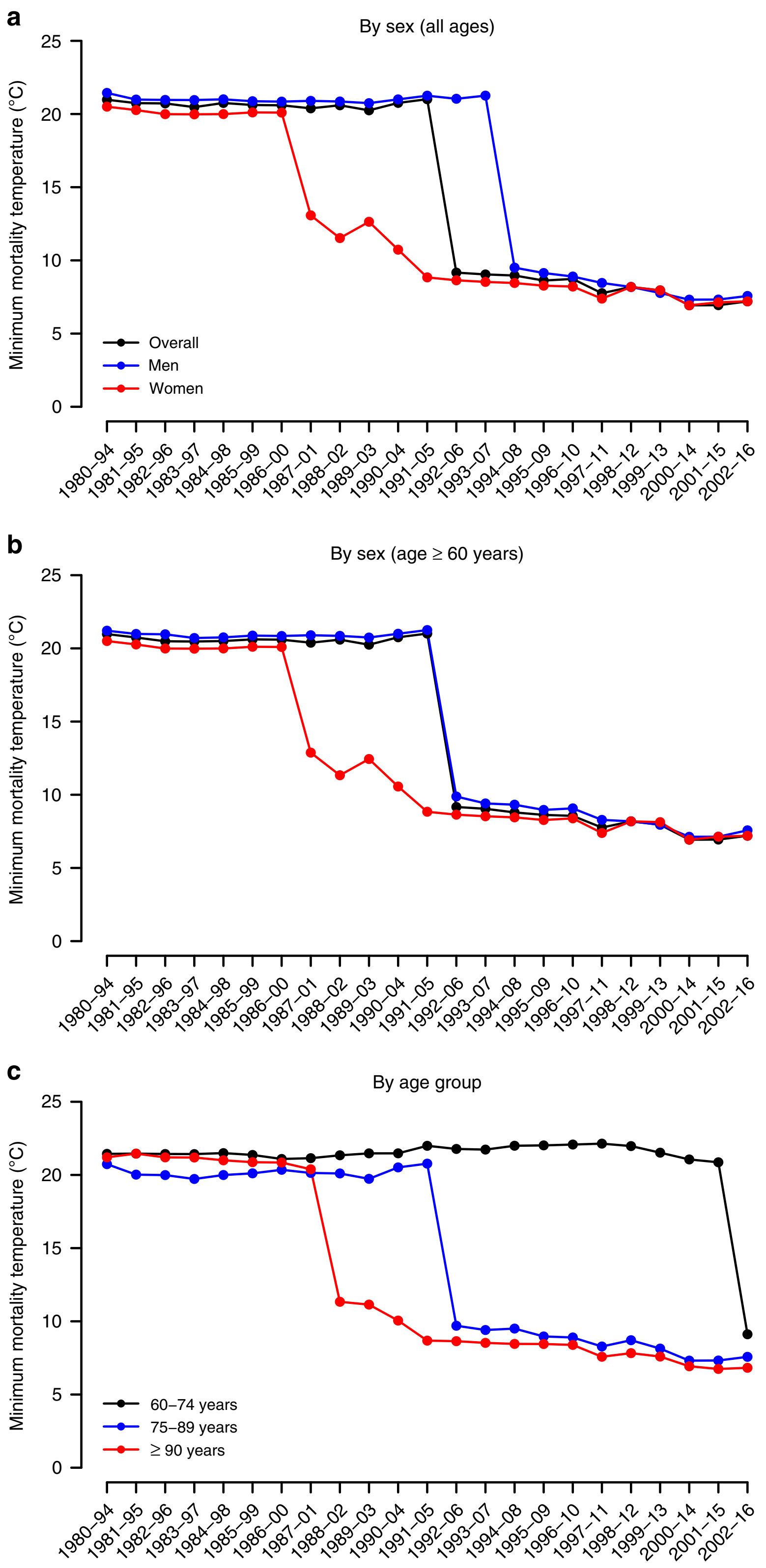

Fig. 2 Minimum mortality temperature (°C) corresponding to respiratory diseases.

therefore, the RR is never smaller than 1 and the AF is never negative. This implicitly implies that the RR at the MMT of the first subperiod and the AF in summer have both increased. This scenario is here considered to be unrealistic because it results to be an artefact of the modelling procedure, which implicitly assumes an increase of the RR for some temperatures that is contrary to the available literature[6].

All sensitivity analyses suggested that the reported results were not dependent on modelling assumptions (Supplementary Fig. 40).

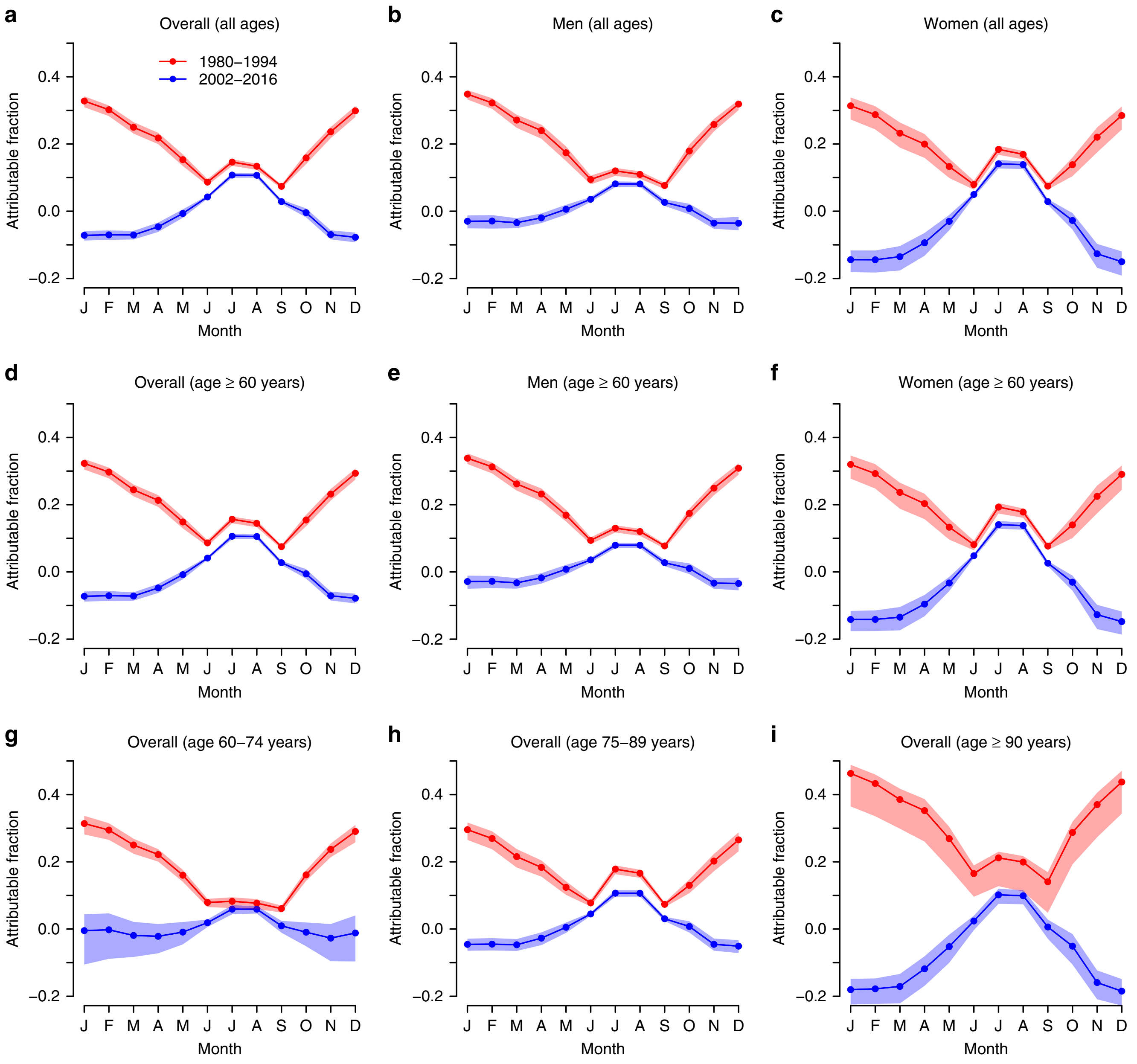

Fig. 3 Monthly attributable fraction (unitless) of respiratory disease mortality in Spain. The minimum mortality temperature in 1980-1994 is used as the centring temperature for the two subperiods (i.e. *invariant centring temperature assumption*). The attributable fractions (AF) are estimated with the corresponding 95% empirical CI.

Discussion

This study reports a complete reversal of the seasonality of temperature-attributable mortality from respiratory diseases over the last four decades in Spain. Results of this investigation showed a very strong reduction in the AF during the coldest months of the year and only a small decrease during the hottest ones, resulting in the redefinition of the seasonality of mortality, with a shift of the maximum monthly AF from winter to summer, and the minimum monthly AF from early and late summer to winter. These findings have major implications for climate change health adaptation policies. We conclude that the projected decrease in the number of moderate and extreme cold days will not contribute to a further reduction of cold-attributable respiratory deaths in the country.

In this study, the decline in the vulnerability (expressed as RR) to cold temperatures was so large that the MMT associated with respiratory diseases moved from very warm to very cold temperatures. This cooling in the MMT contrasts with the warming trend found in previous studies for other causes of death[14,15]. For instance, in Spain, the MMT for cardiovascular diseases rose from 19.5 °C in 1980–1994 to 20.2 °C in 2002–2016, a warming that was similar in magnitude, and occurred in parallel with, the recorded average warming of 0.77 °C between these two periods[12]. Moreover, the MMT, which typically ranges between the 60th and the 90th temperature percentile, is commonly used as the reference point to separate between heat- and cold-attributable mortality[16]. Given the abrupt cooling of the MMT here observed, a definition of heat and cold from a health perspective, i.e. based on this optimum point, does not seem a good choice for the characterisation of trends in attributable mortality, and therefore we favoured the description of trends by monthly attributable values.

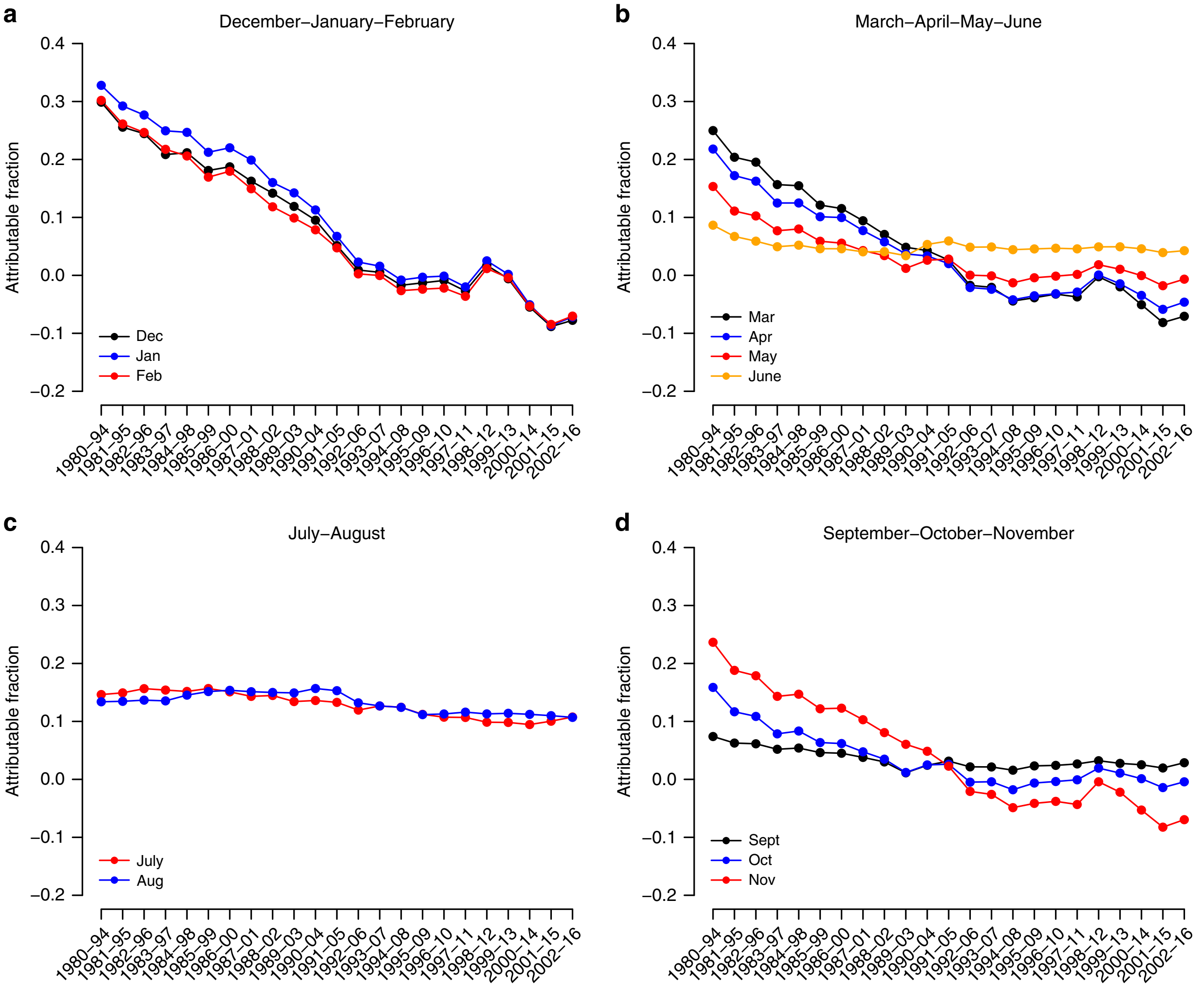

Fig. 4 Evolution of the monthly attributable fraction (unitless) of respiratory disease mortality in Spain. The minimum mortality temperature in 1980–1994 is used as the centring temperature for all the subperiods (i.e. invariant centring temperature assumption).

We found a change in the seasonal distribution of temperature-attributable mortality from respiratory diseases. This was essentially explained by the large differences in the reduction of the RR for the cold and hot temperatures. The large decline in the RR associated with cold temperatures contributed to a steep decrease in the AF in the coldest moths of the year, while the smaller reduction in the RR associated with warm temperatures only contributed to a limited reduction in the AF in the hottest months. In earlier investigations conducted in the United States[9] and Japan[17], the rate of decline in heat-related respiratory mortality during summer was larger than in our study, whereas a comparison for cold temperatures is not possible due to the lack of enough evidence in the literature.

The general reduction in the vulnerability and/or impact due to heat has been attributed in many studies to socioeconomic development and structural transformations, such as improvements in housing conditions and healthcare systems (e.g., improved treatment of heat-related morbidity)[11,17], the reduction in risk factors (e.g. smoking and healthier diet)[9], or even to planned adaptation policies led by governments and public health agencies[18,19]. In Spain, the large socioeconomic advances experienced during the study period might have widely contributed to the declining vulnerability to heat and, especially, cold temperatures. For example, the gross domestic product increased from €8789 per capita in 1991 to €22,813 in 2009, and the expenditure in healthcare system from €605 per capita to €2182 (ref. [20]). In addition, the percentage of households with air conditioning increased from 4.16% in 1991 (ref. [21]) to 35.5% in 2008 (ref. [22]), and with central heating from 25.83% in 1991 to 56.86% in 2011 (ref. [21]).

This study also revealed differences in the effects of hot and cold temperatures on respiratory deaths by sex and age. Mortality risks due to heat were higher for women than for men and increased with age, while, on the contrary, the effects of cold were lower for women than for men and decreased with age. Findings of previous studies on sex and age differences have been mixed. Some articles have shown that men were more sensitive to heat than women[23,24], while other studies reported the opposite result[6]. This heterogeneity may arise from socioeconomic, cultural and health-related factors. With respect to the effect modification by age, the elderly has been described as the most vulnerable population group for heat[17,23,25], while differences by age for cold temperatures are not homogeneous[26]. For instance, an acute effect of cold on respiratory mortality was observed for subjects aged less than 65 years in the United States[27]. One possible explanation for that pattern is that the elderly tend to stay indoors more often than younger people, with more limited social contact, and thus avoid direct exposure to cold

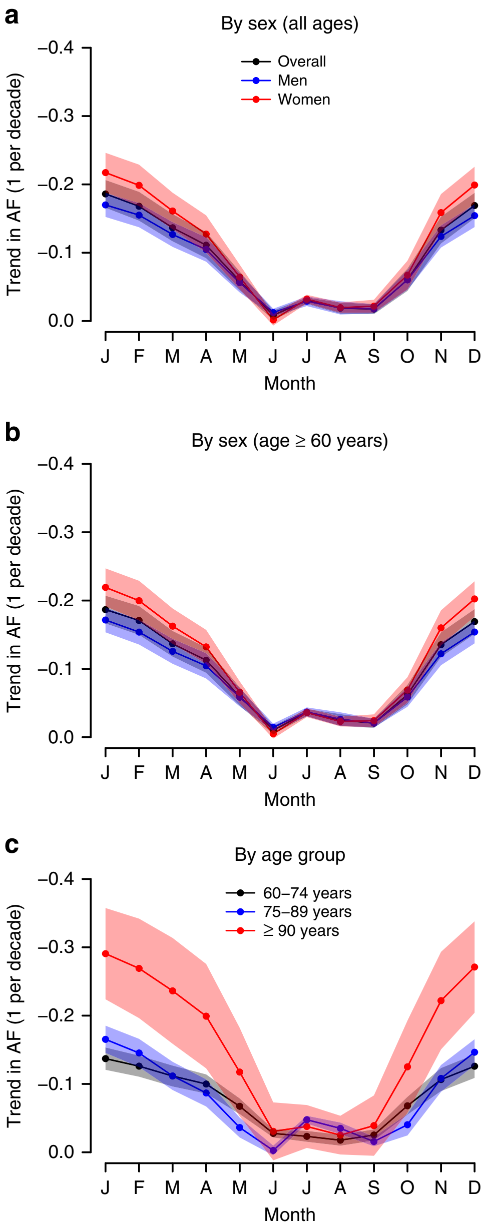

Fig. 5 Trends in monthly attributable fraction (1 per decade) of respiratory disease mortality in Spain. The minimum mortality temperature in 1980–1994 is used as the centring temperature for all the subperiods (i.e. invariant centring temperature assumption). Data are presented as mean values ± 95% empirical CI.

temperatures and infectious diseases. The underlying physiological mechanisms by which heat and cold trigger respiratory mortality are not well understood, but they seem to be largely mediated by a thermoregulatory pathway[28].

Finally, this study has three main limitations that need to be mentioned. First, we were not able to control for ambient air pollution in the models because of data unavailability, and therefore, we do not know the extent to which this would have affected mortality trends here reported. However, the available literature on the confounding effect of air pollution on temperature–mortality associations shows modest[27,29] or no modifying effect[30,31]. Second, the multivariate random-effect meta-analysis used in our study to drive and pool estimates from the multi-location DLNM does not consider the non-random spatial dependence of mortality, which could produce biased estimates. However, demographic and socio-economic characteristics related to mortality in Spain do not differ greatly between regions. Third, the present work did not describe the drivers of the observed change in the seasonality of temperature-attributable respiratory mortality in Spain, which will be addressed in a future study including socioeconomic and demographic data.

Methods

Data collection. Countrywide time-series of daily mortality counts from respiratory diseases as primary cause of death disaggregated by sex, 15-year age groups (0–14, 15–29, …, 75–89, ≥90 years) and province of residence between the years 1980 and 2016 were provided by the Spanish National Statistics Institute (INE). Note that the coding of death certificates changed during the study period from ICD-9 (460–519) in 1980–1998 to ICD-10 (J00–J99) in 1999–2016, although both classifications contained the same disaggregation of causes of death. In addition, daily high-resolution gridded (0.25° × 0.25°) observations of daily mean 2-m temperature were derived from E-OBS v16 of the European Climate Assessment and Dataset (ECA&D), and transformed into regional estimates using the average temperature for each province[32]. Both mortality and temperature datasets had no missing values.

First-stage time-series model. The statistical analysis was performed in two stages. In the first stage, standard quasi-Poisson regression models allowing for overdispersion were individually applied to the whole study period (1980–2016) and data subsets of 15-year moving periods (1980–1994, 1981–1995, …, 2002–2016) 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 the seasonality and the long-term trend, as well as a categorical variable to control for the day of the week. The temperature–mortality dependency was captured by using a distributed lag non-linear model (DLNM), which is based on the definition of a cross-basis function combining exposure–response and lag–response associations[33]. On the one hand, the exposure–response curve was modelled through a natural cubic B-spline with three internal knots placed at the 10th, 75th and 90th percentile of the daily temperature distribution. On the other hand, the lag-response curve was modelled through a natural cubic B-spline, with an intercept and three internal knots placed at equally spaced values in the log scale, and a lag period extending up to 21 days to account for the long-delayed effects of cold and short-term harvesting (i.e. deaths brought forward by only a few days due to temperature)[16]. In this way, the overall effect of a given day temperature on the RR of death was defined as the sum of the effects on that day and the 21 subsequent days. The quasi-Poisson regression model was given as follows:

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

where Y denotes the series of daily mortality counts; cb the cross-basis matrix produced by DLNM; dow the day of the week; and S the natural cubic B-spline of time. The modelling choices were thoroughly 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 seasonality and the long-term trend (Supplementary Fig. 40). We did not assess the associations between temperature and respiratory mortality specifically for individuals younger than 60 years because of the small number of daily deaths counts recorded for those age ranges in most provinces, which did not guarantee model convergence and optimal fitting. We did not include relative humidity into the analyses because its potential confounding effect was very small in past studies[34–36]. Furthermore, the use of combined indices of temperature and humidity, such as apparent temperature, did not predict mortality better than the single measure of temperature[37,38], and the assessment of the effect of temperature and humidity separately showed that humidity plays a small and inconsistent role in affecting mortality[39].

Second-stage meta-analysis. In the second stage, a multivariate random-effects meta-analysis was used to estimate the mean RR values associated with the temperature–mortality curves across provinces[40], and to derive the best linear unbiased prediction of the temperature–mortality associations in each location. We then extracted the minimum mortality temperature (MMT) from the country-level and province-specific exposure-response curves as the temperature with minimum RR.

Centring temperature assumptions. Temporal changes in the exposure-response curves between 15-year subperiods were presented under two different centring temperature assumptions. Note that the centring temperature refers to the reference temperature value in which the RR is imposed to be equal to 1, and it does not need to coincide with the MMT. In the first case, here referred to as "*invariant centring temperature assumption*", the value of the MMT obtained in the first 15-year subperiod (1980–1994) was chosen as the centring point of the exposure–response relationship in all the 15-year subperiods. This scenario therefore assumes that the RR at the MMT of the first subperiod does not change over time, and it therefore allows for RR values smaller than one. In the second case, shown in Supplementary Information (Fig. 31), the value of the MMT obtained in a given 15-year subperiod was automatically chosen as the centring temperature of the subperiod. This alternative scenario, here referred to as "*varying centring temperature assumption*", assumes that the centring temperature changes over time, and therefore, the RR is never smaller than one. Note that the choice of the centring temperature only displaces the curve along the vertical RR axis, and therefore, it does not modify the shape of the model fit. However, the choice does modify the magnitude of the estimates in each subperiod, and therefore, the one of the long-term trends.

Attributable risk. The mortality burden attributable to ambient temperatures, reported as the AF of deaths, was estimated by using the methodology developed by Gasparrini and Leone[41]. First, the overall RR corresponding to each day of the series was used to calculate the AF of deaths on that day and the next 21 days. Then, the daily attributable number (AN) of deaths was computed by multiplying the daily AF by the daily number of deaths. The number of AN in each month was separately aggregated from the daily series, and its ratio with the corresponding total number of deaths provided the monthly AF. We calculated 95% empirical CIs (eCIs) of attributable mortality using Monte Carlo simulations.

Statistical software. All statistical analyses were done with R software (version 3.6.1) using functions from the packages *dlnm* (for the first-stage regression) and *mvmeta* (for the second-stage meta-analysis).

Reporting summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request. The climate data can be obtained from the European Climate Assessment and Dataset (ECA&D, www.ecad.eu). The mortality data can be obtained from the Spanish National Statistics Institute (INE) under request. Unfortunately, we cannot publish the mortality data because several restrictions imposed by the INE apply. Specifically, the INE stipulates in the contract for the supply of the data the following clause: "No distribuir a terceros" ("Do not distribute the data to third parties" in English).

Code availability

The code is available on request.

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Author contributions

H.A. designed the study, did the statistical analysis, interpreted the results and wrote the original draft. J.B. provided the data and contributed to the statistical analysis, the interpretation of the results and the drafting of the paper. D.D. and V.I. contributed to the interpretation of the results and the drafting of the paper. All authors contributed to the development of the paper and approved the final draft.

Competing interests

The authors declare no competing interests.

Additional information

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PART III

FINAL COMMENTS

7. CONCLUSIONS

This section answers/contrasts the research questions/hypotheses posed by the PhD candidate at the beginning of the thesis in accordance with the results obtained in the empirical studies published in academic journals (Part II).

Q1: *Has the observed rise in temperatures contributed to an increase in heat-related mortality during the last decades in Spain or, instead, the changes in vulnerability to heat have completely offset the negative contribution of the warming? Are there differences by sex, age and cause of death?*

H1: *Heat-related mortality has decreased in Spain during the last decades despite the observed rise in temperatures.*

Overall, the results reported in the empirical studies showed that, despite the observed warming in Spain over the last decades, the decline in the vulnerability (i.e., mortality risk) of the Spanish population to high temperatures has led to a downward trend in sex and age-specific mortality attributed to heat since 1980, both for cardiovascular and respiratory diseases. However, the degree of causation between the increase in temperatures and the decrease in the risk of dying from heat (i.e., adaptation) remains unknown. This is because, in practice, it is difficult to separate the part of adaptation to heat that is linked to rising temperatures (i.e., physiological acclimatization of the population, or planned interventions to tackle the negative effects of climate change) from that occurring independently from the warming (e.g., socioeconomic development). Nonetheless, it is likely that the observed adaptation to heat in Spain has mainly occurred as a result of the large socioeconomic development that took place over the study period, since the physiological acclimatisation of the population to warmer conditions involves timescales longer than the few decades and climate change health adaptation policies were scarce in the country.

The risk associated with heat decreased at a rather slower pace in respiratory than in cardiovascular mortality, but it was enough, up to now, to outweigh the negative impact of rising temperatures on attributable mortality. This could have to do with the temporal evolution of each cause of death over the study period, with a decrease in cardiovascular deaths and an increase in respiratory deaths.

In absence of the warming there would have been a big drop of mortality attributable to high temperatures in Spain. However, there is high uncertainty on whether the observed adaptation will be enough to compensate future increases of temperature and population ageing.

Q2: *Has cold-related mortality decreased during the last decades in Spain? And if so, was this decrease dominated by the contribution of the warming or by the changes in vulnerability to cold? Are there differences by sex, age and cause of death?*

H2: *Cold-related mortality has decreased in Spain during the last decades because of population adaptation to cold.*

The findings of the empirical studies indicated a strong reduction in sex- and age-specific mortality attributed to cold during the period 1980-2016 in Spain, both for cardiovascular and respiratory diseases. The results also pointed out that this temporal evolution was not driven by the observed warming in winter temperatures, but rather by the substantial decrease in the risk of mortality due to cold temperatures. The decrease in vulnerability to cold temperatures in this context of rising temperatures could only be explained by mechanisms of adaptation that are not associated with climate change such as a progressive socioeconomic development and the associated improvements in housing conditions (e.g., higher use of heating) and health-care system (e.g., improved treatment of cold-related morbidity) among other factors.

In contrast to the results obtained for heat, the decline in vulnerability to cold temperatures was much greater for respiratory than circulatory diseases, showing an almost complete process of adaptation to cold in more recent years in spite of the upward trend in the number of respiratory deaths over the study period (figure 6b). One possible explanation for this difference could be the improvement in the medical treatment and prevention of infectious respiratory diseases (e.g., seasonal influenza vaccination), which could prevent a large fraction of cold-related death.

Q3: *Is climate warming affecting the seasonal distribution of temperature-related mortality? Is this different by sex, age and cause of death?*

H3: *There was no change in the seasonality of temperature-related mortality in Spain during the last decades.*

The analyses showed the complete reversal of the seasonality of temperature-attributable mortality for respiratory diseases, but not for cardiovascular ones, with a significant shift of the maximum monthly incidence from winter to summer, and the minimum monthly incidence from early and late summer to winter. The reversal in the seasonal distribution of the attributable deaths from respiratory diseases was not driven by the observed warming in both winter and summer temperatures, but rather by the very large decrease in the risk of death due to cold temperatures (only extreme cold days represents a risk for mortality in recent years) and the relatively much smaller reduction due to warm temperatures. By contrast, the seasonal pattern in temperature-related mortality for cardiovascular causes remained stable over the study period because, unlike respiratory diseases, the mortality risk associated to heat and cold decreased at similar rate and remained significantly high in recent years. As noted above in the answer to Q2, the almost complete adaptation process to cold in the case of respiratory mortality could be related to the progress achieved in the treatment and prevention of infectious respiratory diseases (e.g., seasonal influenza vaccination), which might make people less susceptible to cold-related death.

These findings lead to the conclusion that the projected decrease in the number of moderate and extreme cold days due to climate warming could contribute significantly to the reduction of cold-related mortality from cardiovascular diseases, but not from respiratory causes.

Q4: *Has the MMT shifted towards warmer values over time? Is this shift different by sex, age and cause of death?*

H4: *The MMT increased in parallel with the temperature rise observed in Spain over the last decades.*

The evolution of the MMT was found to be different for each group of causes of death. The MMT for cardiovascular diseases increased in parallel with the mean increase in annual temperature observed during the study period, which was consistent with earlier findings from other countries for all-cause mortality. Specifically, the MMT rose from 19.5 °C in 1980–1994 to 20.2 °C in 2002–2016, a warming that was similar in magnitude, and occurred in parallel with, the recorded average warming of 0.77 °C between these two periods. The concurrent timing of the increase in MMT (used as a reference point to attribute mortality burden to heat and cold) 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 (level of vulnerability) above and below the MMT, rather than on the warming itself. The increase in MMT also implies a time-evolving definition of warm and cold temperatures, which parallels the shift in the temperature distribution towards warmer temperatures. Moreover, there was a strong positive spatial correlation between mean temperature and MMT, which has been widely reported elsewhere, but additionally, this association has also remained stable with time.

On the other side, the warming trend in the MMT for cardiovascular diseases contrasts with the large cooling observed in the MMT for respiratory diseases (from a warm [83th] to a cold [18th] temperature percentile between 1980–1994 and 2002–2016), which was explained by a much stronger adaptation to cold (almost complete in recent years) than warm ambient temperatures. This finding is particularly important because it questions the validity of the MMT as a reference point to separate between heat-related mortality (temperatures above the MMT) and cold-related mortality (temperatures below the MMT). Given the abrupt cooling of the MMT here observed, a definition of heat and cold from a health perspective, i.e. based on this optimum point, does not seem a good choice for the characterisation of attributable mortality, and therefore, an alternative description based on calendar months or seasons should be favoured.

8. LIMITATIONS AND FUTURE RESEARCH

8.1. LIMITATIONS

The empirical studies that constitute the main core of the PhD project (Part II) share some common limitations that need to be acknowledged:

On the one side, a systematic control for ambient air pollution and relative humidity in the statistical models was not possible due to paucity of data, and therefore, the extent to which trends in temperature-related mortality are affected by temporal variation in these factors remain unknown. However, the available literature on the confounding effect of air pollution shows modest[11,55] (slightly lowering the effects of heat) or not modifying effect[56] by this environmental factor, while the effects of warm and cold temperatures remained unchanged when relative humidity is accounted for[12,29,57]. In addition, 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[22], and the assessment of the effect of temperature and humidity separately showed that humidity does not affect mortality[58].

On the other side, although the spatial unit of analysis was relatively large (at the provincial level), a further assessment of the association between temperature and mortality for cause-specific cardiorespiratory diseases and for population groups younger than 60 years was not feasible because of the small number of daily deaths counts recorded for those causes of death and age groups in most provinces, which did not guarantee model convergence and optimal fitting. This limitation could be overcome by using Bayesian spatio-temporal models, an alternative study design to time-series regression models especially designed to reduce the noise associated with data sample in areas with fewer cases, borrowing strength across administrative units and estimating the effect in each administrative unit from its own data and those in its neighbours. The Bayesian framework would also allow the inspection of the temporal changes in vulnerability and attributable mortality at a finer geographical or administrative scale (e.g., municipalities), differentiating, for example, between urban a rural areas.

8.2. FUTURE RESEARCH

The present PhD thesis has advanced knowledge of the evolution in cardiorespiratory risk and burden associated with ambient temperatures in Spain during the last four decades, showing a substantial societal adaptation to hot and cold ambient temperatures in a context of notable climate warming. However, questions remain about the drivers of such adaptation to ambient temperatures and the contribution of socioeconomic factors (non-causal or spontaneous adaptation) and planned interventions (causal adaptation), which are hitherto unknown. Moreover, the evidence on the eventual changes in morbidity outcomes such hospital admissions has been limited[59].

Future research should focus on the mechanisms explaining the recent trends in vulnerability and attributable mortality/morbidity, and differences among populations and social groups adopting a multi-scale spatial perspective. There is a body of literature describing the relation between a range of socioeconomic variables and the vulnerability of the populations to heat and cold[27,28,60], but up to date, there is no study describing the factors that explain spatiotemporal differences in vulnerability, and particularly in the context of rising temperatures and the implementation of adaptation measures. This analysis should implicitly separate the processes of spontaneous adaptation from the effect of planned interventions, which have been increasingly implemented in recent years in Spain.

After the record-breaking heat wave in summer 2003, which caused an unprecedented increase in premature deaths across Spain, several Heat Health Warning Systems (HHWS) have been implemented at the national (Spanish Ministry of Health) and regional (e.g., Catalan Public Health Agency) levels in order to minimise the negative effects of extreme heat on mortality and morbidity outcomes (e.g., hospital admissions), and particularly among vulnerable groups such as the elderly, children, people with pre-existent or chronic diseases, and people at risk of poverty or social exclusion. HHWS are the only available measure of adaptation to climate warming in Spain, but the evaluation of its effectiveness in reducing morbidity and mortality is still inconclusive, with no evidence on the causal relation between this public health intervention and the decreasing vulnerability to heat[59,61].

A detailed understanding the factors behind the temporal trends and spatial differences in vulnerability to temperature is key to develop effective climate change health adaptation policies in the country.

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