Contrasting patterns of temperature related mortality and hospitalization by cardiovascular and respiratory diseases in 52 Spanish cities

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ABSTRACT

Background: Climate change is a severe public health challenge. Understanding to what extent fatal and non-fatal consequences of specific diseases are associated with temperature may help to improve the effectiveness of preventive public health efforts. This study examines the effects of temperature on deaths and hospital admissions by cardiovascular and respiratory diseases, empathizing the difference between mortality and morbidity.

Methods: Daily counts for mortality and hospital admissions by cardiovascular and respiratory diseases were collected for the 52 provincial capital cities in Spain, between 1990 and 2014. The association with temperature in each city was investigated by means of distributed lag non-linear models using quasi-Poisson regression. City-specific exposure-response curves were pooled by multivariate random-effects meta-analysis to obtain countrywide risk estimates of mortality and hospitalizations due to heat and cold, and attributable fractions were computed.

Results: Heat and cold exposure were identified to be associated with increased risk of cardiovascular and respiratory mortality. Heat was not found to have an impact on hospital admissions. The estimated fraction of mortality attributable to cold was of greater magnitude in hospitalizations (17.5% for cardiovascular and 12.5% for respiratory diseases) compared to deaths (9% and 2.7%, respectively).

Conclusions: There were noteworthy differences between temperature-related mortality and hospital admissions regarding cardiovascular and respiratory diseases, hence reinforcing the convenience of cause-specific measures to prevent temperature-related deaths.

1. Introduction

The association between daily temperature and mortality or hospitalization has been well-documented in the scientific literature (Song et al., 2017; Gasparrini et al., 2015). Most of the studies have reported increased risk associated with non-optimum temperature (Song et al., 2017; Gasparrini et al., 2015). Specific causes mortality and hospitalization have been studied to a lesser extent and rarely the two endpoints have been compared (Gasparrini et al., 2015; Moghadamnia et al., 2017). From our knowledge only three local studies addressed properly this comparison (Kovats et al., 2005; Hanzlikova et al., 2015; Mastrangelo et al., 2006), all restricted to heat effects. The contrast between temperature-related mortality and hospitalization by specific causes would be extremely useful for better understanding the mechanisms by which ambient temperatures trigger fatal and non-fatal health consequences.

The Southern Mediterranean region arises as a significant climatic hot spot as a result of global warming (Vicedo-Cabrera et al., 2018). In particular, Spain is one of the countries mainly affected by rising temperatures and heat waves (Vicedo-Cabrera et al., 2018). Previous countrywide studies conducted in Spain have examined how temperature is associated with cause-specific mortality (Achebak et al., 2019; Analitis et al., 2008) and hospital admissions (Martinez-Solanas and Basagana, 2019; D’Ippoliti et al., 2010), although using different study periods, model specifications, and definitions for cold and heat effects.

To our knowledge, no study has yet examined at the local, regional or national level the relative impact of ambient temperature on both simultaneously, cause-specific mortality and morbidity, during the same
study period under a standardized study protocol. In this study, we compare the associations between ambient temperature and daily mortality and emergency hospital admissions for cardiovascular and respiratory diseases for the 52 provincial capital cities in Spain between 1997 and 2014.

2. Data and methods

2.1. Mortality and hospital admissions data

Data on daily mortality by cardiovascular causes (International Classification of Diseases, 9th Revision (ICD-9) codes 390–459; and 10th Revision (ICD-10) codes 100–199) and respiratory causes (ICD-9: 460-519, ICD-10: J00-J99) for the 52 capital cities was provided by the Spanish National Institute of Statistics for the study period, between 1st January 1997 to 31st December 2014.

Daily counts of urgent (non-scheduled) hospital admissions registered in Spain during the study period were obtained from Conjointo Mínimo Básico de Datos (CMBD) of the Spanish Ministry of Health. The CMBD includes data from all hospitals from the National Health System, where approximately 92% of the hospitalizations are collected in this register. We aggregated hospitalization counts by city and selected cardiovascular and respiratory as admission causes for the study period.

2.2. Weather station temperature data

Average daily air temperature for the 52 capital cities was provided by the European Climate Assessment & Dataset (ECAD) project (http://ecad.eu). We collected the observed temperature data from ECAD for the study period.

2.3. Statistical analysis

A standard time-series quasi-Poisson regression was applied to each city and outcome. The model included a natural cubic spline of time with 10 degrees of freedom per year to control for long-term trend and seasonality and indicator variables for weekdays, influenza epidemics (except for respiratory diseases), and summer holidays. The mortality-temperature association was modeled by using distributed lag-nonlinear models, able to describe complex nonlinear and lagged dependencies (Gasparrini et al., 2015). Explicitly, we modeled the exposure-response curve with a natural cubic spline with three internal knots placed at the 10th, 75th, and 90th percentiles of city-specific temperature distributions. We modeled the lag-exposure curve with a natural cubic spline with three internal knots equally spaced in the log scale. The lag period was extended to 21 to capture the long delay in the effects of cold. Modelling choices have been thoroughly tested by sensitivity analyses in our previous studies (Gasparrini et al., 2015).

As a summary at the country level, the city-specific curves were pooled using multivariate meta-regression models to represent the overall cumulative exposure-response relationship (Gasparrini et al., 2015). As the natural scale for temperature makes for difficulties when combining curves across cities with non-overlapping temperature ranges, we used a relative scale (percentiles). The results were expressed in terms of country temperature percentiles, which correspond to different city-specific absolute temperatures. For each outcome, we calculated a country average minimum mortality or morbidity percentile of temperature (MMP) and their empirical confidence interval by using a semi-parametric bootstrap (Tobías et al., 2017). Then, we estimated the overall cumulative relative risks of death associated with cold and heat, respectively, defined as the risk increment at percentiles 2.5th and 97.5th of the joint temperature distribution relative to MMP.

We also examine the lagged pattern of associations at the country level, for cold and heat. Finally, for each outcome, calculated the attributable fractions (AF) by cold and heat from all the days of a temperature below and above the MMP (Gasparrini et al., 2015).

Statistical analyses were performed in R software (Version 3.6.2). Effect estimates are reported as Relative Risks (RR), with their 95% confidence intervals (95%CI).

3. Results

Overall, 732,851 and 262,493 deaths were registered for cardiovascular and respiratory diseases, respectively. Regarding hospital admissions, were 504,230 and 472,544, respectively. Outcomes and temperature are summarized by city at Appendix 1.

The pooled overall cumulative exposure-response curves for temperature and cause-specific mortality and hospital admissions are presented in Fig. 1. The temperature-mortality relationships were V-shaped for both causes, showing a larger cold effect for cardiovascular than respiratory diseases. The temperature-hospitalizations relationship was V-shaped for respiratory diseases and linear for cardiovascular diseases. The MMP was displaced to warmer temperatures in hospital admissions compared to mortality, moving the MMP from 81st to the last percentile for cardiovascular diseases, and 31st to 89th for respiratory diseases. Table 1 reports the risk estimates and attributable fractions for both cold and heat effects. The estimated pooled overall cold effect (percentile 2.5th) kept of similar magnitude for cardiovascular mortality (RR = 1.32, 95%CI = [1.22,1.42]), cardiovascular hospitalizations (RR = 1.27, 95%CI = [1.16,1.40]), and respiratory hospitalizations (RR = 1.33, 95%CI = [1.19,1.49]) while slightly decreased for respiratory mortality (RR = 1.16, 95%CI = [1.05,1.27]). The estimated pooled overall heat effect (percentile 97.5th) for cardiovascular mortality (RR = 1.15, 95%CI = [1.08,1.23]) sensibly increased for respiratory mortality (RR = 1.63, 95%CI = [1.45,1.83]), null for cardiovascular hospitalizations, and statistically not significant for respiratory hospitalizations (RR = 1.04, 95%CI = [0.97,1.11]). The 17.5% of hospital admissions by cardiovascular causes and the 12.6% of hospital admissions by respiratory causes were attributed to cold. In addition, a higher fraction of cardiovascular mortality was attributed to cold (9.0%) than to heat (1.2%). While for respiratory mortality the opposite pattern was observed (2.7% and 9.4%, respectively).

The effects of cold temperatures were delayed and lasted for at least ten days while the effect of hot temperature was immediate and lasted less, by about five days (Fig. 2). Comparing by cause, cold effects persisted more in respiratory diseases and heat effects showed the same lag-structure on both respiratory and cardiovascular diseases.

The lag-response relationship for cold was nearly the same in both mortality and hospital admissions for cardiovascular diseases. For respiratory diseases, the cold effect for deaths peaked up before (two days) than for hospital admissions (10 days), but was of lesser magnitude, with non-overlapping confidence intervals in the central band until the loss of statistical significance.

The lag-response relationship for heat showed an immediate effect experienced a sharp decrease from deaths to hospital admissions, with some suggestion of effect displacement or harvesting for respiratory admissions.

4. Discussion

We compared patterns of mortality and emergency hospital admissions related to ambient temperature in Spain. 1) This study provides evidence that both mortality and hospital admissions increased with cold. However, heat did not increase the risk of hospital admissions in Spain. 2) Although the highest relative risk was estimated for heat-related deaths by respiratory diseases, the estimated risk of cold-related deaths by respiratory diseases was of lower magnitude than that of hospitalizations. 3) The impact of non-optimun temperature, in terms of estimated attributable fractions, was of higher magnitude in hospitalizations compared to deaths.

Several systematic reviews have examined the association between ambient temperature and cause-specific mortality (Song et al., 2017;
Moghadamnia et al., 2017) or morbidity (Song et al., 2017) around the world. Only two of them included simultaneously results from both mortality and morbidity, being the oldest included in the most recent (Song et al., 2017). According this last one, when looking at cause-specific diseases, heat has been more studied than cold, and cardiovascular more than respiratory diseases (Song et al., 2017).

In Spain, a previous countrywide study reported an association between temperature and cause-specific mortality (Achebak et al., 2019), with similar risk estimates than us. In our study, the estimated pooled overall heat effect was lower on cardiovascular than on respiratory mortality. This pattern was also observed countrywide, and by the EuroHeat project (D’Ippoliti et al., 2010), which included two Spanish cities (Barcelona and Valencia). Oppositely, we found the pooled overall cold effect to be slightly higher for cardiovascular than for respiratory deaths. This pattern was also observed in the PHEWE Project (Analitis et al., 2008), again including Barcelona and Valencia. Oppositely, we found the pooled overall cold effect to be slightly higher for cardiovascular than for respiratory deaths. This pattern was also observed in the PHEWE Project (Analitis et al., 2008), again including Barcelona and Valencia. Also influenced by the MMP location, which defines the number of days contributing to each (cold or heat) impact, heat showed a lower impact on cardiovascular mortality (1.2%) than cold (9%), but a higher impact on respiratory mortality (9.4%) than cold (2.7%). The magnitude of these estimates are in agreement with those reported by Achebak et al. (2019) in which the heat-attributable cardiovascular mortality ranged between 1 and 2% and the cold-attributable cardiovascular mortality ranged between 8 and 11%.

The lack of heat effects on cardiovascular hospitalizations is in agreement with the current evidence, globally (Song et al., 2017; Michelozzi et al., 2009) and locally in Spain (Martinez-Solanas and Basagana, 2019). Song et al. (2017) and Dominici et al. (Michelozzi et al., 2009) reported that heat was associated with an increased risk of respiratory hospitalizations only for the elderly population. Regarding respiratory hospitalizations, the countrywide study in Spain reported a significant heat effect (Martinez-Solanas and Basagana, 2019). This might be due to a higher statistical power raised in that study because, in spite of using provincial capital cities as exposure sites for temperature (Tobias et al., 2017), provincial instead city counts were analyzed. The three studies (Kovats et al., 2005; Hanzlikova et al., 2015; Mastrangelo et al., 2006) properly contrasting patterns between heat-related mortality and morbidity confirmed the same pattern; emergency hospital admissions were comparatively less affected by heat than mortality, and absent from cardiovascular hospital admissions.

A possible reason for this contrast between heat related admissions and deaths may be that extreme heat has an acute effect, likely causing the fast death of the vulnerable population, the elderly, or people with chronic pathology (Mastrangelo et al., 2006), before they get to medical attention (Kovats et al., 2005; Martinez-Solanas and Basagana, 2019; Michelozzi et al., 2009). This explanation would be in coherence with the absent slope for heat on cardiovascular admissions, given that acute events are more common within this big diagnostic group and the lag-structure of heat effects, showing an immediate effect on admissions to be two or three times lower in magnitude and less prolonged in time. At last, the higher fraction of hospitalizations than deaths attributed to non-optimum temperature, mathematically resulted from the higher relative risk for cold at longer lags (peaking 10–12 days after exposure) together with the MMP displacement to warmer temperatures.

### Table 1
Cold and heat effects and attributable fraction on cause-specific (cardiovascular and respiratory) mortality and hospital admission for the 52 provincial capital cities in Spain, 1997–2014.

<table>
<thead>
<tr>
<th>Cause/outcome</th>
<th>MMP (%) (95% CI)</th>
<th>Cold RR (95% CI) AF (%) (95% CI)</th>
<th>Heat RR (95% CI) AF (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>81 (65, 84)</td>
<td>1.32 (1.12, 1.42) 9.0 (0.9, 16)</td>
<td>1.15 (1.08, 1.23) 1.2 (0.1, 2.2)</td>
</tr>
<tr>
<td>Hospital admissions</td>
<td>100 (100, 100)</td>
<td>1.27 (1.16, 1.4) 17.5 (9.7, 24.8)</td>
<td>1.02 (1.00, 1.04) 0.0 (0.0, 0.0)</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>31 (24, 42)</td>
<td>1.16 (1.05, 1.27) 2.7 (-1.9, 6.6)</td>
<td>1.63 (1.45, 1.83) 9.4 (3.1, 15)</td>
</tr>
<tr>
<td>Hospital admissions</td>
<td>89 (85, 100)</td>
<td>1.53 (1.19, 1.49) 12.6 (5.7, 27.5)</td>
<td>1.04 (0.97, 1.11) 0.2 (-0.3, 0.6)</td>
</tr>
</tbody>
</table>

![Fig. 1. Pooled cumulative exposure-response curves for associations between daily temperature and cause-specific cardiovascular and respiratory mortality and hospital admissions.](image-url)
experienced in admissions, mainly for respiratory diseases. We do not have any biological explanation or previous evidence supporting our results on the mismatch between patterns of cold related hospitalizations and cold related deaths, although we believe that an analysis on more specific subgroups of diseases or by age-group could throw some light. Unfortunately, such analysis was unavailable for this countrywide study, due to low numbers in some cities.

We have to realize some additional limitations, mainly derived from the use of hospital records. First, as in other health routine datasets, there are some uncertainties over their completeness that could have an effect on estimates accuracy, but unlikely differential. Secondly, emergency room admissions are limited by the hospital beds availability, which can exhibit short and medium-term dependences (for instance, beds availability is expected to have more pressure in winter). To this respect, the seasonal control and inclusion of day of week and summer holidays should provide at least some adjustment. Finally, hospitalization criteria are prone to change across cities or even between hospitals within the same city. To this respect, heterogeneity across cities in our study kept moderate. Differences between hospitals in the city are expected do not affect results since they tend to be averaged out when data are pooled over the whole of each city (Kovats et al., 2005).

The main strength of our study is the ability to perform a proper contrast between temperature-related mortality and morbidity by specific diseases, during the same period and population. To our knowledge, this is the first countrywide study addressing this comparison and also the first study addressing this comparison for cold effects.

In conclusion, our results may have important implications for public health. The high risk of mortality by respiratory causes due to heat may enhance public health efforts towards avoiding isolation of vulnerable people and providing better information on the early symptoms of heat stress. The large attributable fraction of hospitalizations due to cold should strengthen health systems to assume the burden associated explicitly with low temperatures, as in a climate change scenario, extreme cold, as heat, are predicted more frequent in the future.

**Author statement file**

All of authors participated in the conceptualization and methodology for this study and in writing-review and editing the final version of this manuscript. The corresponding author (Carmen Iníguez) performed the formal analysis and wrote the original draft. Aurelio Tobías provided resources, was on charge of the supervision and was on charge of the project administration. Dominic Royé was on charge of Visualization.

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**Declaration of competing interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

**Appendix A. Supplementary data**

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2020.110191.

**References**


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